CHEMICAL REVIEWS

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Review

Polymeric Nanoparticles for Drug Delivery

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Cite This: *Chem. Rev.* 2024, 124, 5505−5616

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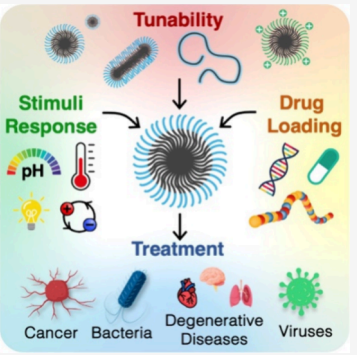
ABSTRACT: The recent emergence of nanomedicine has revolutionized the therapeutic landscape and necessitated the creation of more sophisticated drug delivery systems. Polymeric nanoparticles sit at the forefront of numerous promising drug delivery designs, due to their unmatched control over physiochemical properties such as size, shape, architecture, charge, and surface functionality. Furthermore, polymeric nanoparticles have the ability to navigate various biological barriers to precisely target specific sites within the body, encapsulate a diverse range of therapeutic cargo and efficiently release this cargo in response to internal and external stimuli. However, despite these remarkable advantages, the presence of polymeric nanoparticles in wider clinical application is minimal. This review will provide a comprehensive understanding of polymeric nanoparticles as drug delivery vehicles. The biological barriers affecting drug delivery will be outlined first, followed by a comprehensive description of the various nanoparticle designs and preparation methods, beginning with the polymers on which they are based. The review will meticulously explore the current performance of polymeric nanoparticles against a myriad of diseases including cancer, viral and bacterial infections, before finally evaluating the advantages and crucial challenges that will determine their wider clinical potential in the decades to come.



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Published: April 16, 2024

1. INTRODUCTION

Nanoparticles have the potential to drastically improve the therapeutic efficacy of drugs by providing superior protection and facilitating drug delivery at specific sites of action. There are many different types of nanoparticles that have shown promise for drug-delivery applications, including polymeric-, inorganic-, and lipid-based particles.[1−4] This review will focus on polymeric nanoparticles, which are nanoparticles derived from polymer building blocks. Among other drug-delivery systems, these nanoparticles are unique in that their polymeric composition allows for diverse and highly sophisticated designs. A controllable size, shape, and surface charge are three of the principal advantages associated with polymeric nanoparticles for drug delivery. Just as beneficial, however, is the enormous variety of chemical and biological functionality that can be incorporated into polymeric nanoparticle designs. Such sophisticated functionality has yielded nanoparticles with the potential to target specific sites throughout the body and within individual cellular compartments, as well as the ability to respond to stimuli associated with specific biological environments, resulting in highly efficient drug release. As a result of these advantages, polymeric nanoparticles are attracting significant attention for intelligent drug-delivery designs and will become increasingly vital as more innovative therapeutic cargo and treatments develop.

Effective polymeric nanoparticles must be designed to migrate a myriad of biological roadblocks throughout both the extracellular and intracellular environments. These roadblocks are often specific to a particular drug, delivery route, disease, or endogenous target. For example, the challenges associated with delivering low molecular weight drugs, which include solubility, toxicity, and controlled release, are significantly different to the delivery of larger therapeutics such as proteins or nucleic acids, which generally require enhanced stability and targeted release at specific regions within a cell.[5−7] Thus, understanding how nanoparticles interact with each biological barrier, and which barriers are necessary to mitigate for a given disease/treatment, is crucial to designing highly efficient polymeric nanoparticles for drug delivery. There has been an immense research effort over the last twenty years to develop polymeric nanoparticles that can more effectively respond to these biological challenges and thus optimize therapeutic efficacy. This research has yielded many success stories, one of which is Abraxane, an albumin-bound paclitaxel formulation that was approved by the FDA in 2005.[8] This nanoparticle is based on the conjugation of paclitaxel, an anti-cancer drug, with albumin, and yields superior pharmacokinetics, improved tumor inhibition and reduced side effects compared to free paclitaxel. More recently, injectable formulations have been approved to prolong the release of drugs for treatment of HIV (Apretude) and Osteoporosis (Zilretta).[9] Furthermore, Genexol-PM, a paclitaxel-loaded polymeric micelle, was approved in Korea in 2007 for the treatment of breast, lung and pancreatic cancer.[10] As well as these commercial products, polymeric nanoparticles represent many drug-delivery designs currently in early- and late-stage clinical trials.[10−12]

Despite the extensive research in this area, there are only a handful of polymeric nanoparticle designs currently used in wider clinical applications.[13] There are a number of reasons for this, one of which is that nanoparticle design is hampered by a lack of understanding of the series of inherent (endogenous) barriers that particles need to migrate before reaching a target site.[14] This is a significant design challenge, as the properties that enhance interactions with some barriers can often impact negatively on others. To address this problem, more recent research has focused on designing nanoparticles with a multi-staged response to biological stimuli. Another problem impacting the wider application of polymeric nanoparticles is the translation gap between animal and human studies, as well as the inherent heterogeneity between and within patient populations.[15,16] These two problems highlight the need to better understand the relationship between nanoparticle

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Chem. Rev. 2024, 124, 5505−5616

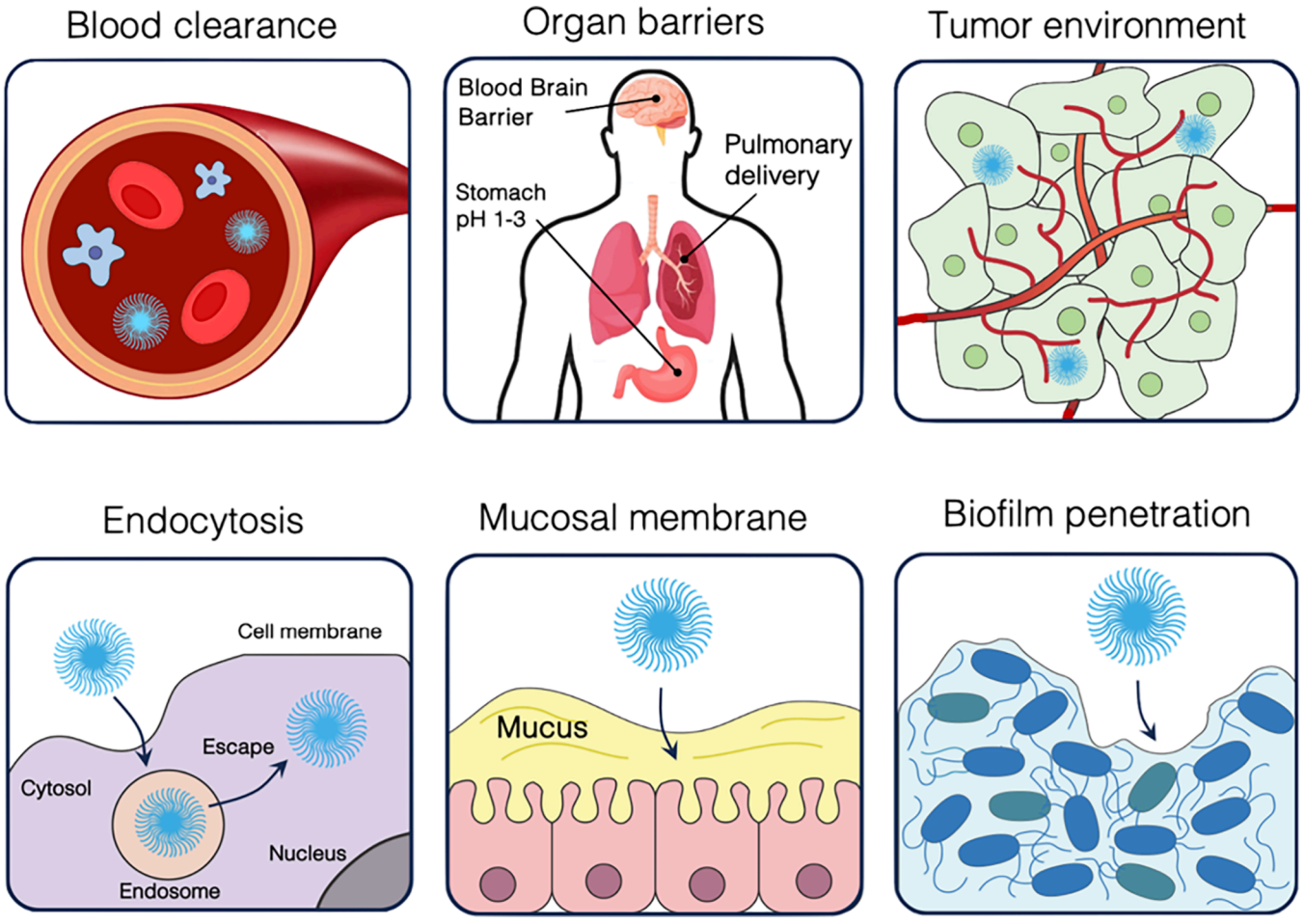

Figure 1. The principal biological environments and barriers polymeric nanoparticles must overcome in order to achieve efficient therapeutic delivery.

function and the varied and complex biological environments they will inevitably encounter.[17] Such knowledge must work in combination with advances in controlled polymer synthesis to design nanoparticles with more sophisticated architecture and bio-responsive functionality tailored for specific applications. This review will provide a comprehensive understanding of the current state of polymeric nanoparticles for drug delivery, highlighting the critical delivery pathways and biological barriers that need to be considered for designing effective polymeric nanoparticles. The review will then comprehensively outline both the simple and advanced nanoparticle designs, beginning with the polymers on which they are based, and their preparation methods. The bulk of the review will appraise the performance of polymeric nanoparticles against cancers, viral and bacterial infections, and other diseases over the last decade, before concluding with a summary and evaluation of the present challenges and future potential of polymeric nanoparticles as widely applicable drug-delivery vehicles.

2. BIOLOGICAL BARRIERS TO NANOPARTICLE DELIVERY

The biological barriers applicable to polymeric nanoparticles depend on a number of factors, including how the nanoparticles are administered, the therapeutic cargo being delivered, and the disease type. In this review we will focus on understanding the biological barriers relevant to the most common systemic delivery routes, which are intravenous injection, oral delivery and inhalation. The ability to evade the immune system is one significant challenge consistent across all nanoparticle delivery routes. However, there are also specific physical barriers that need to be overcome for particular delivery routes such as oral delivery or inhalation, as well as barriers associated with specific target regions of interest such as tumors or the blood−brain barrier. There are many highly specialized reviews that cover these biological barriers in great detail.[7,14,18−20] In this review we will give a brief overview of each particular barrier, and how polymeric nanoparticles can be tailored to overcome them (Figure 1).

2.1. Clearance and Delivery in the Blood

To optimize delivery to a treatment site, it is necessary to design a nanoparticle that enables extended circulation in the blood stream, thus increasing the probability of localization at a target site while minimizing off-target effects. The mononuclear phagocytic system (MPS) begins sequestering nanoparticles immediately after ingestion and thus provides the first barrier to nanoparticle delivery. The MPS consists of populations of phagocytic cells—a type of white blood cell capable of ingesting foreign particles—such as macrophages that are present in the liver, spleen, lymph nodes, bone marrow, and skin. The elimination of nanoparticles by the immune system is initiated by opsonization, whereby the particles are coated with plasma proteins including serum albumin, apolipoproteins, complement components, and

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Chem. Rev. 2024, 124, 5505−5616

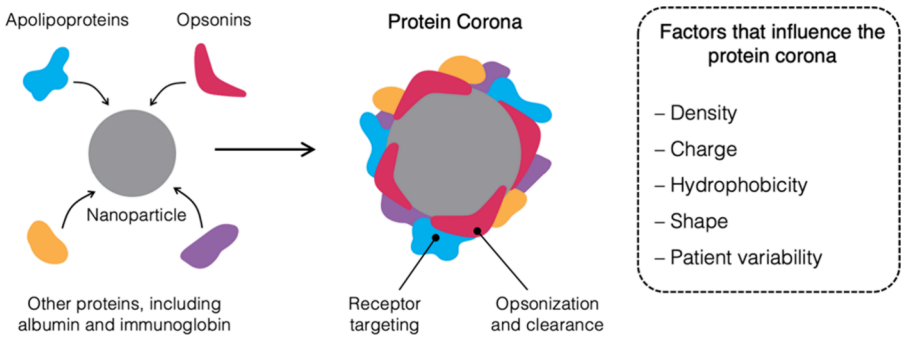

Figure 2. A corona is generated around the nanoparticle surface via the attachment of a variety of proteins to its surface. This protein corona affects how rapidly particles are cleared by the immune system, and is highly dependent on particle size, shape, and charge.

immunoglobulins. This generates a protein corona on the surface of the particle, impacting its interactions with the environment from that point onward (Figure 2). The composition of the protein corona is impacted by the initial surface coating of the nanoparticle and is also subject to inherent variations in the blood due to patient variability. The corona composition has been shown to impact nanoparticle trafficking and clearance, with coronas containing apolipoprotein E (ApoE) acting as targeting moieties for low-density lipoprotein receptors, leading to nanoparticle delivery to hepatocytes and in some instances across the blood–brain barrier.[18] In other cases, coronas, which include opsonins or pattern recognition receptors, result in clearance by immune cells as part of the complement cascade. Controlling the composition of the protein corona and thus the biological fate of nanoparticles remains poorly understood.[18,21] The presence of this protein corona is also problematic for nanoparticles with specific targeting capability, as following protein corona generation, their targeting functionality is no longer accessible.[22] Most importantly, a protein corona facilitates the attachment of the nanoparticle to a phagocytic cell, within either the MPS or the reticuloendothelial system (RES). This process drastically reduces circulation time, and results in the clearance and elimination of the nanoparticle. Understanding how the protein corona can be controlled or tuned to facilitate specific cellular localization is an important area of fundamental study and is likely to be critical to optimizing nanoparticle delivery. There are also strategies to avoid protein coronas from impacting targeting by designing nanoparticles with releasable layers, as discussed in Section 2.2.6.

The size, shape, and surface chemistry of nanoparticles significantly influences circulation time through their respective effects on the nature of the protein corona and cell (Figure 3). The ideal particle size is typically reported between 10 and 200 nm. Nanoparticles below 10 nm are subject to elimination by the kidneys, while particles bigger than 200 nm are recognized by the complement cascade. One of the most prominent mechanisms of liver accumulation is cell uptake by Kupffer cells.[23] These cells are located in the liver, specifically on the surface of the liver sinusoid, a discontinuous capillary with openings (fenestrations) to facilitate endocytosis. Kupffer cells are the largest population of tissue-resident macrophages in the body.

Recognition by the immune system can be modified by tuning the surface chemistry of polymeric nanoparticles. Typically, cationic particles are cleared most rapidly by the immune system, followed by anionic particles and then uncharged particles, which have the longest circulation times

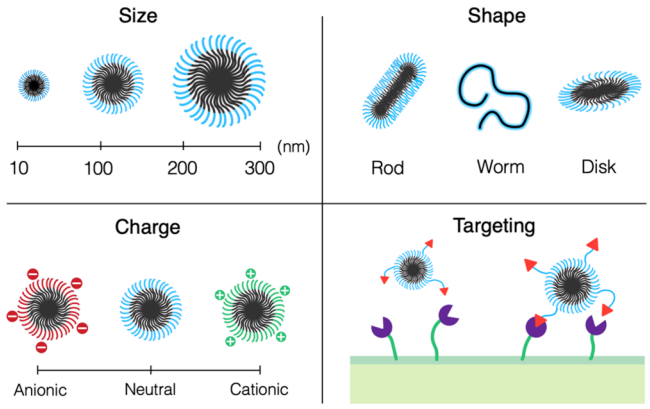

Figure 3. A selection of the physicochemical properties of polymeric nanoparticles that can impact circulation time. They encompass size, shape, and surface chemistry, including surface charge and the incorporation of targeting moieties.

in vivo.[14] To control these interactions, many nanoparticles incorporate surface coatings to enhance their "stealth", i.e., their ability to avoid detection by the immune system and biological species such as enzymes and antibodies, which facilitate degradation, secretion, and clearance. Poly(ethylene glycol) (PEG) is a hydrophilic polymer highly valued for its stealth properties. PEG is employed on the surface of nanoparticles to enhance circulation, but it cannot completely shield the particle from macrophages or other cells in the immune system. In addition, there is a significant collection of literature that describes how the body can produce anti-PEG antibodies, which can induce clearance of nanoparticles despite PEG functionalization. Consequently, polymers such as poly(2-oxazaline) (POx), polypeptides, and zwitterionic polymers have received attention as possible alternatives to PEG.[14] Another strategy to imbue polymeric nanoparticles with stealth properties is to employ biological functionality that inherently has a longer circulation time. Abraxane, for example, utilizes human serum albumin, likely prolonging immune recognition time.[15] Peptide-modified nanoparticle surfaces have also been investigated to enhance stealth. For example, a polystyrene based nanoparticle was modified with a "don't eat me" glycoprotein sequence (hCD47) and a synthetic self-peptide.[24] These nanoparticles displayed significantly improved circulation, as macrophages recognized the peptides on the particle surface as "self" minimizing opsonization. Another biomimetic strategy that has shown the potential to increase circulation time by reducing opsonization and phagocytosis is the use of cell membranes to coat nanoparticle

https://doi.org/10.1021/acs.chemrev.3c00705
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surfaces. These stealthy cell membranes can include white blood cell or leukocyte membranes.[25]

Nanoparticle shape is another important factor that influences clearance. In Section 6.2, we will discuss the impact of nanoparticle shape on drug delivery in detail. Generally speaking, previous work has shown that worm-like micelles with a high aspect ratio (the proportional relationship between a particle's height and width) can reduce circulation time in the body and result in higher localization in the liver and spleen, suggesting greater particle uptake by the MPS and RES systems.[26] Rigidity has also been shown to impact clearance. Red blood cells (RBCs), for example, are biconcave disks approximately 8 μm in size. They are highly deformable and thus can migrate through barriers that are impenetrable to objects less than one tenth their size.[27] These properties allow red blood cells to have lifetimes of over three months.

2.2. Physical Barriers for Nanoparticle Localization in Target Regions

Upon intravenous administration, nanoparticles disperse throughout the circulatory system, and extravasate/accumulate in different tissues over time. Their concentration in the blood decreases due to a combination of factors such as elimination and excretion via the liver and kidneys as discussed above, as well as partitioning and diffusion into tissue. Extravasation is impacted by nanoparticle properties including size, whereby smaller particles generally cross capillary walls more easily than large particles.[13] Nanoparticles are capable of extravasation into all areas of the body; however, they are often found in high concentrations in the liver or spleen. Apart from uptake by the immune system, this accumulation is also caused by the fact that particles can become trapped by the size of openings (fenestrations) in capillaries within major organs such as the spleen. Research has shown that the size of splenic fenestrations is in the order of 200−500 nm.[28] The ability of nanoparticles to avoid being trapped by these barriers depends on both their size and rigidity. DeSimone and co-workers investigated the impact of nanoparticle rigidity in an interesting study involving a library of red blood cell mimicking nanoparticles (∼6 μm) with variable rigidity. This change in rigidity was achieved by tuning the nanoparticle's cross-linking density. Their work showed that an 8-fold decrease in Young's modulus was correlated with a >30-fold increase in the elimination half-life. This was likely due to the particle's ability to deform and thus migrate fenestrations in the lung more effectively.[29]

2.2.1. Gastrointestinal Tract. Oral delivery is the most attractive route for therapeutic delivery, given it is simple, convenient, and minimally invasive. However, successful delivery of cargo using this method requires nanoparticles to migrate through multiple aggressive environments before accessing the blood stream. This begins when nanoparticles enter the stomach, where gastric juices are highly acidic (pH 1.5−3), and contain hydrochloric acid (HCl), potassium chloride (KCl), and sodium chloride (NaCl). The stomach also contains enzymes that can break down foreign materials such as pepsin, which cleaves peptide bonds. Following migration from the stomach, nanoparticles then reach the duodenum in the gastrointestinal (GI) tract, which has a pH of 5.5. The pH further increases in later regions of the GI tract, from pH 6 in the jejunum, to pH 7.2−8 in the ileum, and finally pH 6.4−7 in the colon.[30] Due to the inherent pH variation of these regions, pH has been commonly used to tune nanoparticle stability and cargo release.[31] The GI tract is coated with a brush-like layer of microvilli. This brush-like layer contains sucrase and several peptidase enzymes that cleave a broad range of peptide bonds. The enzyme activity is generally greater in the duodenum than the jejunum or ileum.

Mucus also plays a critical role in the absorption and bioavailability of orally administered drugs. The mucosal barrier encompasses the entire GI tract, including the stomach, small intestine and the colon, and contains multiple protective components. The first is a compact epithelial lining containing tight junctions that limit the permeation of foreign species such as nanoparticles. The second is a mucus blanket composed of 95% water, 0.2−5% mucin, 0.5% globular proteins, 0.5−1.0% electrolytes, 1−2% lipids and DNA. Mucin is a key component of mucus and controls its ability to form cross-linked and entangled fibrous networks, thus impacting the ability of nanoparticles to migrate within this layer. Mucin is excreted from the surface of foveolar and goblet cells. This insoluble mucus forms a gel-like coating over the surface of the gastric mucosa. Bicarbonate ions secreted from the surface of epithelial cells are a third protective element. To deliver cargo in this environment, it is critical that nanoparticles achieve efficient trafficking through the mucus layer to the epithelial cells that lie beneath. Such trafficking is a challenge, as the mucus contains many pathways for clearance of foreign material. Numerous studies report a size range necessary to pass through the mucus layer based on the mesh-pore spacing of the mucus, which is between 50 and 1800 nm.[32] Due to the properties of the mucus layer, positively charged or lipophilic materials also have limited permeability through this environment. Thus, to penetrate this mucus matrix, nanoparticles should ideally possess a hydrophilic, nearly electrically neutral surface with a size small enough to avoid unfavorable interactions with the mucin network. While the addition of PEG to the surface of nanoparticles (PEGylation) is commonly used to provide such a surface, another strategy is the use of zwitterionic surfaces. Shan et al. recently showed that zwitterionic surfaces were as efficient at trafficking through mucus as PEGylated systems, but had superior internalization into epithelial cells.[33] Rigidity is another nanoparticle property that has been shown to impact penetration through mucus. In one important study, a series of nanoparticles based on a poly(lactic-*co*-glycolic acid) (PLGA) core and a lipid shell were designed with three different rigidities. The data showed that the system with the intermediate rigidity had the fastest penetration. This was thought to be due to efficient deformation that allowed migration through the mucus matrix, leading to a higher drug release *in vivo*.[34]

To achieve successful delivery, nanoparticles also have to navigate the compact epithelial layer in the gastrointestinal tract. There are two possible pathways for trafficking across the epithelial layer into surrounding tissue. The paracellular pathway involves trafficking between the tight junctions of the epithelial cells, which is only applicable to small materials due to the size of these junctions. In contrast, the transcellular pathway involves migration through the epithelial layer by cellular uptake, followed by exocytosis into the blood stream. This process is based on either specific uptake mechanisms such as receptor-based endocytosis, or non-specific methods including clathrin or caveolin-mediated endocytosis, macropinocytosis, and, in the case of larger particles, phagocytosis.[35] However, there is still little understanding of how different internalization approaches can be used to tune exocytosis, thus

https://doi.org/10.1021/acs.chemrev.3c00705
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there is clearly a need for fundamental studies to support improving oral delivery efficiency.

2.2.2. Pulmonary Delivery. Pulmonary drug delivery has generated significant interest for the treatment of respiratory diseases. This is due to the extremely high surface area within the lung, which enhances the absorption of cargo, as well as its relatively thin epithelial layer.[36] Nanoparticles can be delivered into the respiratory tract using a range of techniques such as nebulizers, metered-dose inhalers, and dry powder inhalers. In order to reach systematic circulation in the blood stream, nanoparticles must be delivered sufficiently deep into the lung, and migrate a number of biological barriers into systemic circulation. There are two main regions within the lung, the conducting airways, and the respiratory region. The conducting airways region is the upper area of the airway, and includes the nose, mouth, trachea, bronchi, bronchioles, and terminal bronchioles (bronchial tree). The respiratory region comprises the lower areas of respiratory bronchioles, alveolar ducts, and alveolar sacs. The fate of inhaled nanoparticles depends on where they are deposited.[37] Two different epithelial cells are present in the lungs, ciliated epithelial cells, and goblet cells.[37] A mucus layer covers the epithelia of the trachea and bronchial tree, and this mucus layer can easily entrap inhaled nanoparticles and sweep them out of the lungs. This mucus is predominately water (95%), but also contains mucins (2%) and other components (DNA, proteins, cells, and cellular debris).[38] These mucins are high molecular weight glycoproteins that are cross-linked with cysteine, and create a physical barrier that restricts nanoparticles according to size. The mucus layer is also anionic, which facilitates electrostatic interactions with positively charged nanoparticles. Shape and rigidity are also important parameters that impact penetration through mucus as highlighted in the discussion on oral delivery above. Importantly, this physiological barrier in the respiratory tract is highly variable in pathological conditions. For example, mucus viscoelasticity increases in lung diseases such as cystic fibrosis, chronic obstructive pulmonary disease, and asthma, and this change in elasticity increases the ability of mucus to trap nanoparticles.[38]

The epithelial cells present in the lower respiratory region consist of alveolar epithelial type I (AT-I) cells and alveolar epithelial type II (AT-II) cells. AT-I cells are larger and thinner than AT-II cells and comprise 90% of the alveolar surface area. AT-II cells are much smaller, and their role is to produce pulmonary surfactants, which protect the surface of the lungs. The lungs also contain immune cells, specifically alveolar macrophages and dendritic cells, which provide a barrier to delivery by internalizing nanoparticles. These cells phagocytose nanoparticles based on their size and surface chemistry. Pulmonary surfactants are another endogenous material that represent a barrier to efficient nanoparticle delivery. These surfactants, which serve to lower the energy required for inhalation by reducing air−liquid surface tension, form specific protein coronas on the surface of nanoparticles.[38] As well as interacting with nanoparticles in an undesirable manner, these coronas also impact nanoparticle uptake and clearance, and can even negatively affect lung function. Ultimately, nanoparticles require trafficking through epithelial cells to reach systematic circulation in the blood or be trafficked to lymph nodes.

2.2.3. Biofilms. Bacterial infections affect 17 million people annually in the United States, resulting in approximately 550,000 deaths, and costing billions of dollars every year.[39] Up to 80% of these infections are caused by bacteria that form biofilms.[40] Biofilms are a heterogenous structure that often contain a large population of rapidly growing cells and a small population of dormant or slowly growing bacteria (termed persister cells). Biofilms render bacteria far more resistant to antibiotic treatment and thus are a critical biological barrier to improving therapeutic efficacy. Extracellular polymeric substances (EPS) comprise a key component of biofilms (Figure 4). The composition of the EPS depends on the type of

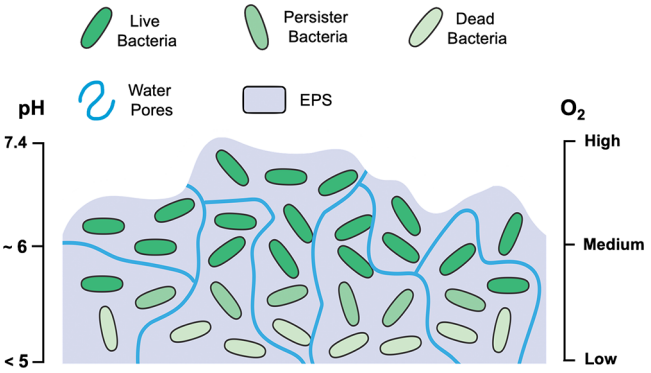

Figure 4. A schematic representation of a biofilm and the properties that affect bacteria targeting. These properties include pH and oxygen gradients throughout the film, as well as the protective extracellular polymeric substances (EPS) matrix and intrafilm water channels.

bacteria, the local mechanical shear forces, the substrate availability and the host environment. However, commonalities in the EPS exist across different kinds of biofilms. The EPS typically contains exopolysaccharides as well as fibrous and globular proteins including extracellular enzymes, lipids and extracellular nucleic acids.[41] The EPS provides a scaffold for mechanical stability and creates a compartmentalized microenvironment for the bacteria within its structure. This provides a physical barrier that prevents nanoparticles from easily accessing and eliminating bacteria. Thus, polymeric nanoparticles tailored to combat biofilms need to migrate the EPS network before antimicrobial agents can be efficiently delivered. There are a number of strategies that have been developed to disrupt the EPS matrix and thus allow more efficient killing of the bacteria within the biofilm, including nitric oxide or enzymes such as deoxyribonuclease (DNAse).[41] The biofilm also contains water-filled pores that allow for the transport of nutrients into the film. Nanoparticle transport has been shown to occur either through the biofilm or through these water-filled pores, but is strongly dependent on charge, with cationic materials favored due to the anionic nature of the biofilm.[42] It is critical that strategies to treat biofilms target persister cells, as to leave some bacteria alive results in the continued spread of infection as well as antimicrobial resistance (the generation of bacteria that are resistant to antimicrobial treatment). Biofilms also develop a gradient in pH, oxygen, and nutrient concentration as a result of the metabolic activity of the microorganisms contained within the film. While the pH of the blood stream is approximately 7.4, it has been reported that the pH of a biofilm is as low as pH 5.0.[43]

2.2.4. Blood−Brain Barrier. Neurological disorders that impact the brain and spinal cord are one of the leading causes of morbidity and disability globally.[44] Devising efficient treatments for neurological diseases is challenging, due to the strength of the blood−brain barrier (BBB), which drastically

https://doi.org/10.1021/acs.chemrev.3c00705
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limits the ability of therapies, including polymeric nanoparticles, to access the brain. The BBB precisely controls the transport of ions, nutrients and cells between the blood and the brain. It consists of a compact layer of cerebral epithelial cells with extremely tight junctions between each cell. The inter-endothelial space is characterized by transmembrane complexes containing occludin, claudin and other junction adhesion molecules. This barrier is critical for safeguarding the highly specific environment required for proper brain function, and ensures the maintenance of brain fluids and the protection of neurons. These transmembrane complexes create homophilic interactions with each other to form an intricate tight barrier. This barrier is supported by a basement membrane (30−40 nm thick) composed of collagen type IV, laminin, heparin sulfate proteoglycans, fibronectin, and other extracellular matrix proteins.[45] There are also two other important cell types that are associated with this barrier. Pericytes are smooth muscle cells spanning several endothelial cell lengths. They serve to regulate endothelial cells and also act as macrophages during inflammation. Astrocytes play a critical role in enhancing the BBB integrity by excreting soluble factors that upregulate the expression level of tight junction proteins on epithelial cells.[19]

There are two pathways by which nanoparticle transport can occur from the blood into the brain: paracellular and transcellular transport. Paracellular delivery relies on transport through the miniscule intracellular spaces in the BBB, and hence is severely limited for polymeric nanoparticles, which are often larger than these tiny spaces. Thus, only nanoparticles that release their cargo in the BBB environment, whereby their small cargo is tiny enough to diffuse, can successfully harness this mechanism. Transcellular delivery, on the other hand, is more promising, and can be divided into three distinct categories. Carrier-mediated transcytosis involves utilizing transporter protein pumps based on the external (luminal) side of the endothelial cells. There are also pumps located on the side of endothelial cells closest to the brain (abluminal) to efflux unwarranted materials. Receptor-mediated transcytosis involves transport through a specific receptor-mediated pathway. The three most well studied receptors include insulin, transferrin, and low-density cholesterol. In receptor-mediated endocytosis, the nanoparticle is commonly internalized into an endo/lysosomal compartment and then must escape this compartment and be exocytosed from the cell on the abluminal side of the BBB. A number of interesting studies have shown that cleavable targeting ligands can be employed to yield more efficient transport across the BBB. These targeting groups enhance transport efficiency by impacting escape from endosomal/lysosomal compartments, or by dictating exocytosis onto the abluminal side of the BBB. One such study involved the use of a pH cleavable transferrin that led to the deshielding of a *p*-aminophenyl-alpha-D-mannopyranoside, allowing more effective exocytosis on the abluminal side of the BBB endothelial membrane to target glioma.[46] Later work used a similar approach to treat Alzheimer's disease.[47] Endocytosis can also occur via absorptive-mediated transcytosis. This is based on the electrostatic interaction between positively charged nanoparticles and the negatively charged surface of endothelial cells.[19]

The significant barriers preventing passive delivery of drug-delivery vehicles to the brain necessitates more sophisticated polymeric nanoparticle designs. These designs involve size, shape and surface charge modification, as well as the incorporation of specific functionality such as targeting ligands. A 2013 study investigated PEGylated polystyrene nanoparticles with sizes ranging from 20 to 500 nm in comparison to non-PEGylated controls.[48] *In vivo* studies showed that accumulation in the brain was significantly improved for nanoparticles below 200 nm. This accumulation was further enhanced when the nanoparticles were coated with PEG. Such improved uptake was thought to be due to the variable size and surface coating, which reduced the interaction of the particles with the RES system, thus facilitating transport across the BBB. Importantly, though the properties of the particles were kept consistent in order to observe this trend, it is likely that other size-dependent clearance mechanisms contributed to this observed biodistribution. For BBB transport, it is very challenging to isolate one clear structure−property relationship, and it is likely that small variations in nanoparticle structure may significantly alter performance. Shape is another tunable nanoparticle property that offers the ability to enhance BBB transport. For example, in one study, rod-like nanoparticles conjugated to an anti-transferrin receptor antibody showed an approximately 7-fold higher accumulation in the brain compared to their spherical counterparts.[49] Positive charge is also thought to impact transport through the BBB due to the negative charge on the luminal side of the BBB, resulting in favorable electrostatic interactions. However, these interactions are likely balanced out by the higher immune system clearance of positively charged nanoparticles, as well as higher toxicity.[19]

2.2.5. Tumors. Tumors are collections of abnormal or defective cells that, when their growth is unchecked by the immune system, lead to cancer. The ability to successfully target and delivery drugs to and throughout tumors is vital for effective anti-cancer therapy. To reach targets within a tumor environment, nanoparticles must first translocate the vascular endothelium and accumulate within tumor tissue. This can be achieved via a number of mechanisms including diffusion, passing through fenestrations, and transcytosis through endothelial cells.[21] The tumor environment is inherently heterogenous, and comprises variations in the vascular density throughout the tumor, with areas of unstructured branching of vasculature as well as a dense extracellular matrix. These issues act to restrict interstitial fluid drainage and thus increase inter-tumor interstitial pressures, ultimately reducing perfusion (penetration) of the nanoparticles. Tumor vasculature is generally maximized at the tumor−host interface, while lower vascular density tends to occur closer to the core of the tumor. Due to this reduced blood flow, the core of a tumor also tends to have poor oxygen supply, resulting in necrosis. In solid tumors, high structural rigidity is supported by extracellular matrix components such as collagen, fibronectin, hyaluronan, fibrin, and proteoglycans. Tumors are made up of different cell types such as stroma (non-malignant cells such as fibroblasts and immune cells) and parenchyma (malignant cells).[21] The physiological conditions within a tumor environment are also highly variable. For example, the pH within a tumor is in the range 6.4−6.8, due to cancerous cells metabolizing glucose through a reaction that produces lactate, an acidic compound.[50] There are also enzymes overexpressed in tumor environments such as matrix metalloproteinases (MMPs). Many polymeric nanoparticles are designed to take advantage of these variations in order to induce site-specific and highly targeted drug release.

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

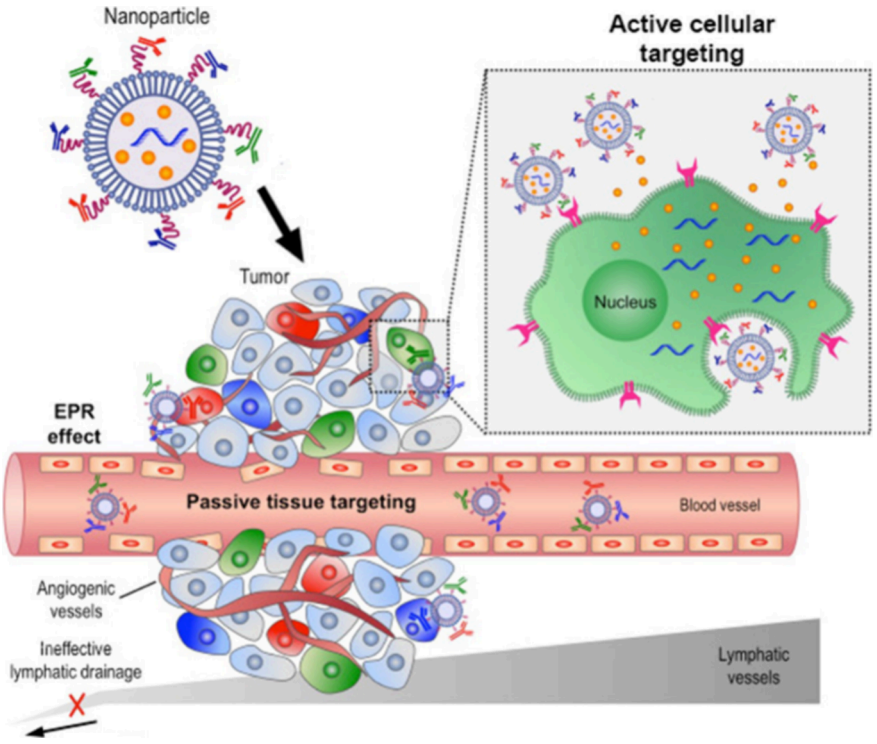

Figure 5. A schematic representation of the tumor microenvironment, and two different mechanisms, passive and active targeting, by which nanoparticles deliver drugs to tumors. Passive tumor targeting is achieved through the EPR effect, which results from the increased permeability of tumor vasculature and ineffective lymphatic drainage. Active tumor targeting is achieved by functionalizing nanoparticles with targeting ligands that can bind to specific cellular receptors present in the tumor mass. Reproduced with permission from ref. 56. Copyright 2019, American Chemical Society.

Tumors are highly heterogenous, and their entire composition varies widely depending on tumor type and stage. Some of the important tumor characteristics that impact the migration of nanoparticles through this environment are vasculature density, interstitial pressure and the extracellular matrix (ECM) density. To optimize drug delivery in a tumor, it is necessary for nanoparticles to permeate from the periphery of the tumor into the central regions, which have a lower blood supply, higher interstitial pressure, and a denser ECM matrix. This deep permeation is still a central challenge to efficient drug delivery. A recent study demonstrated four key nanoparticle indicia that yield higher tumor accumulation: particle sizes above 100 nm, rod-shaped architectures, near neutral charges, and inorganic material compositions.[51] It has been shown that cationic nanoparticles have reduced diffusivity in tumors due to non-specific interactions with the ECM network, making neutral or anionic particles a superior design for deeper penetration.[52] These trends, however, are by no means hard and fast rules, and there remains a significant disagreement in the literature regarding the trends and the contexts in which they apply. For each seemingly clear rule, there are papers that have observed opposing trends.[52,53] This disagreement is probably due to the interconnected nature of many nanoparticle properties, as well as the variety of biological parameters that affect nanoparticle performance, including circulation, extravasation, and permeation. Therefore, to consider one parameter central to highly efficient nanoparticle anti-tumor performance in isolation is limiting. Furthermore, inherent variations in biological models used across different studies also need to be carefully considered.

It has been postulated that nanoparticles can more efficiently extravasate in the leaky vasculature of the tumor, and thus preferentially accumulate in tumor tissue over time. This phenomenon is known as the enhanced permeability and retention (EPR) effect (Figure 5). However, recent studies have cast some doubt on the effectiveness of the EPR effect. In a meta-study of 232 independent research papers, it was found that an average of 0.7% of nanoparticles reach the tumor site.[51] That same study investigated the impact of targeting on tumor localization, whereby 0.9% of targeted nanoparticles reached the tumor, as opposed to 0.6% of untargeted (passively accumulating) nanoparticles. Later work showed these numbers can change dramatically based on the way in which accumulation is measured, and this is an important consideration when comparing such studies.[54] The composition of the tumor, and thus the efficacy of the EPR effect, is also impacted by individual patient factors such as age, genetics, and lifestyle factors. Previous literature has investigated functionalizing nanoparticles to target tumor tissue using a number of different targeting ligands, including small molecules, polysaccharides, and peptides, which target tumors generally, through to antibodies or aptamers, which yield more specific targeting toward certain cell types (Figure 5).[55,56] Moreover, our understanding of how to target cells more specifically continues to improve, leading to an increase in personalized treatment approaches based on individual tumors. Recent strategies include a patient's own tumor-associated antigens (TAAs) being infused back into their body to enhance T cell activation and tumor killing. An alternative strategy is the use of tumor expressing mutated proteins (neoantigens) as

https://doi.org/10.1021/acs.chemrev.3c00705
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these proteins arise from mutations in an individual tumor and thus are highly specific for targeted immunotherapy.[57]

2.2.6. Strategies to Intelligently Migrate Biological Barriers. As we gain an increased understanding of the varied and complex interactions between nanoparticles and endogenous environments, it is becoming clear that a more structured approach to the design of nanoparticles provides significant benefits; in other words, designing a particle that has a multi-staged response to biological stimuli to allow specific response to different biological barriers. Such nanoparticle designs can combine the ability to be stealthy with targeted uptake into cells via surface chemistries that are switchable.[58] The following section discusses some advanced nanoparticle designs that incorporate a multi-staged response to biological stimuli. One strategy involves designing nanoparticles functionalized with a PEG surface that can be released through changes in physiological conditions such as pH or enzyme concentration. A recent study showed that PEG modified with 2,3-dimethyl maleic anhydride (DMMA) could be electrostatically associated to a cationic nanoparticle containing a cell penetrating (TAT) peptide.[59] This PEG layer protected the nanoparticle and gave it stealth capabilities until the pH was decreased (to mimic the lower pH in a tumor). The DMMA functionality was hydrolyzed, causing the TAT peptide to be visible on the nanoparticle surface and thus the nanoparticle became capable of efficiently internalizing within cells. The results showed a highly tunable association based on the pH of the particles with high association only when the pH was low (pH 6.8). This approach had the added benefit of noticeably reducing toxicity, which is usually a significant problem for highly cationic materials. Systems capable of releasing PEG in a tumor environment have also been designed in response to the overexpressed enzymes MMP2 and MMP9, by including cleavable peptide sequences such as Pro-Leu-Gly-Leu-Ala-Gly (PLGLAG) within their structure.[60]

Moieties such as DMMA can also be used to transition nanoparticles from anionic to cationic in the presence of a low pH environment. In a recent study, dual-responsive polymeric nanoparticles were designed that could first release PEG, and then degrade into smaller particles via disulfide cleavage, with a reduction in size from 145 to 40 nm. This decrease in particle size is particularly useful for deeper penetration into a tumor and yielded a 4-fold enhancement in penetration within an A549 lung carcinoma compared to a non-responsive control.[61] More recently a pH-induced charge-switchable surface (negative to positive) was used to improve the penetration of biofilms, as they also exhibit a lower pH in some regions.[62]

2.3. Cellular Delivery of Nanoparticles

Most drug-delivery systems need to be internalized within an intracellular location to achieve effective therapeutic activity. The desired sub-cellular location is different depending on the nature of the therapeutic cargo. Thus, nanoparticles must both effectively internalize into a target cell and traffic throughout different cellular compartments in order to reach the site of optimal therapeutic activity.

2.3.1. Association and Internalization. Effective internalization is the first stage of the intracellular delivery pathway. Typically, nanoparticles enter the cell via endocytosis. This process involves the nanoparticle becoming enclosed in a membrane and engulfed into an intracellular vesicle that then matures through the endo/lysosomal pathway. There are five main mechanisms whereby nanoparticles can be taken up into cells: 1) clathrin-mediated endocytosis (CME); 2) fast endophilin-mediated endocytosis carrier (FEME); 3) clathrin independent (CLIC)/glycosylphosphatidylinositol-anchored protein enriched early endocytic compartment (GEEC) endocytosis; 4) micropinocytosis; or 5) phagocytosis.[7] A sixth mechanism of caveolin-mediated endocytosis has been commonly reported in the literature, but there is emerging evidence suggesting it is not a major pathway for nanoparticle delivery. For targeted systems, internalization in non-phagocytic cells is normally associated with CME, FEME, or CLIC/GEEC, but for particles with non-specific interactions with the cellular membrane, delivery occurs predominately through micropinocytosis, and is thought to be associated with membrane turnover.[7] Nanoparticle size, shape, and surface charge, as well as the presence of targeting ligands and protein coronas, have been shown to influence association with cells and thus impact internalization. Positively charged nanoparticles have been commonly used to drive higher association and internalization efficiency due to their stronger interactions with the negatively charged phospholipid layer of the cell membrane. However, this positive charge can lead to disruption of the cellular membrane and thus result in greater toxicity as well as non-specific uptake in non-target cells.[63] Shape has also been shown to impact the association of nanoparticles to cells. In a seminal study in this area, Kolhar et al. showed that rod-like polystyrene nanoparticles demonstrated significantly enhanced attachment to cells both as non-modified particles and with an antibody surface coating, as compared to a spherical control.[49] Importantly, this was also observed under flow conditions. Cellular association was also observed to increase when the aspect ratio of PEG coated worm-like micelles was increased, indicating that shape was playing a role in these nanoparticle−cell interactions. Interestingly, modifying the rigidity of the system had a minimal effect on association.[26] The superior association of particles with a higher aspect ratio is thought to be due to the greater probability of association to cells due to a maximized surface area.

Imbuing nanoparticles with specific targeting capability is another strategy that can be used to improve their cellular association and internalization efficiency, while at the same time minimizing off-target effects. The design of targeted nanoparticles involves functionalizing the surface of the nanoparticle with ligands that are designed to target specific receptors exclusive to or upregulated on the cells of interest. There are four main categories of targeting moieties that have been widely studied for polymeric nanoparticles: 1) small molecules; 2) peptides; 3) aptamers; and 4) antibodies and their associated derivatives. The density of targeting moieties needs to be carefully considered when designing targeted nanoparticles, as there is a balance between minimizing non-specific effects while enhancing the benefit of multiple targeting moieties acting in a coordinated approach (defined as multi-valent interactions). This delicate balance differs depending on the particle composition and target cell type. Recent work observed enhanced uptake of worm-like polypeptide micelles compared to their spherical counterparts, suggesting the benefits of multi-valency on cell interactions.[64]

Conjugating small molecules to polymeric nanoparticles is a simple and low-cost option to increase accumulation of nanoparticles within target cells. Folic acid (vitamin B9) is a commonly used moiety for targeting cancer cells due to the upregulation of the folate receptor alpha (FRα) on many

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Chem. Rev. 2024, 124, 5505−5616

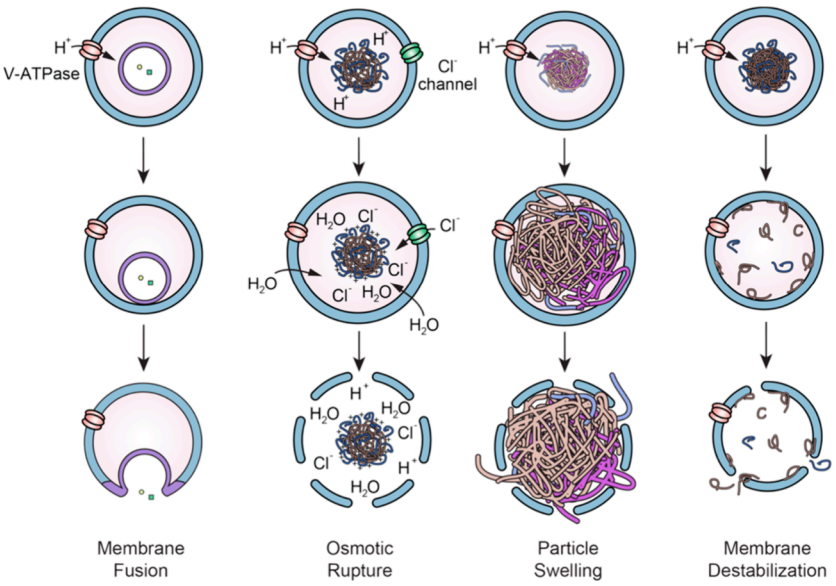

Figure 6. Schematic illustrations of proposed endosomal escape mechanisms including: membrane fusion—nanoparticle materials, usually lipids or amphiphilic materials, fuse with the endosomal membrane, releasing the cargo to the cytosol; osmotic rupture due to the proton sponge effect—polymeric materials that are capable of buffering the acidity of the endosome increases the influx of chloride counterion ions and lyses the endosome due to higher osmotic pressure; particle swelling—nanoparticle swelling ruptures the endosomal membrane due to increased mechanical strain; and finally membrane destabilization—free polymers resulting from the disassembly of pH-responsive nanoparticles can interact with endosomal membrane, prompting membrane destabilization and cargo release to the cytosol. Reproduced with permission from ref. 73. Copyright 2019, American Chemical Society.

cancers.[65] In one interesting study folic acid was conjugated onto an amphiphilic star polymer that self-assembled into a micelle of approximately 15 nm in size. The folic acid conjugated systems showed significantly higher association and uptake than the non-targeted controls, as well as greater killing performance when loaded with a chemotherapeutic doxorubicin (DOX) cargo.[66] Monosaccharides are another class of small molecules that have been investigated for targeting applications, such as galactose, due to potential targeting of the asialoglycoprotein (ASGP) receptors in the liver. Recent work demonstrating galactoseamine-modified small interfering RNA (siRNA) was approved for use in treatment by the FDA.[67]

Another approach to design nanoparticles with targeting capability is via the conjugation of peptides. Peptides have similar advantages to the use of small molecules as they are low-cost and simple to synthesize but are associated with many more potential targets compared to small molecules. The use of cell targeting peptides has been explored extensively in the literature over the last couple of decades. Such materials can be derived from natural receptor ligands or identified from synthetic library screens. One of the most well studied examples is arginylglycylaspartic acid (RGD) that is derived from a sequence in fibronectin that binds cell membrane integrins. This moiety has garnered interest due to the role of $\alpha_v\beta_3$ integrin in tumor angiogenesis.[68] Importantly, studies have shown that the structure of the RGD motif is critical for successful targeting and internalization.[69] More recently, researchers have started to investigate peptides such as V7, which changes structure under lower pH and thus facilitates targeted internalization, for example, in a pancreatic tumor environment.[70]

More sophisticated biological structures are also becoming increasingly important as targeting motifs. Like peptides, DNA and RNA chains can fold into complex 3D structures and can mediate intracellular functions and bind to specific targets. Synthetic oligonucleotides (15−100 bases long) that can fold into complex tertiary structures, known as aptamers, can bind to specific biological targets with high affinity.[71] These nucleotides are normally designed through the evolution of ligands using exponential amplification (SELEX).[7] For example, Fang et al. designed an aptamer targeting the cancer membrane protein PTK7 that was coupled to glutathione (GSH)-responsive micelles for the delivery of cytarabine, a chemotherapeutic drug, to treat leukemia.[72] The targeted nanoparticles demonstrated increased cellular uptake and antitumor efficacy compared to the free drug, without any apparent toxicity to healthy organs.

Antibodies are another useful tool to target specific cells, as they are highly stable and demonstrate high targeting specificity. However, the usefulness of antibodies is somewhat limited by their large size, making the conjugation of antibodies to nanoparticles a synthetic challenge. Therefore, research has focused on developing smaller derivatives that maintain the high specificity of their larger counterparts. These new technologies include single-chain variable fragments (ScFv) and single-domain antibodies (sdAb), also referred to as nanobodies.[7] The use of these specific technologies for nanoparticle targeting is less advanced than the use of small molecules or peptides but is expected to gain momentum in the coming years.

2.3.2. Endosomal Escape. Generally, polymeric nanoparticles are internalized into cells via endocytosis, meaning they become entrapped in endosomal/lysosomal compartments. These intracellular compartments are not the site of action for the vast majority of their encapsulated therapeutics. Thus, there is a need for nanoparticles and/or their cargo to escape these compartments, a process termed endosomal escape. As endosomes mature and ultimately fuse with lysosomes, their pH decreases. The final pH of the endo/lysosome ranges from 4.5 to 5.5 depending on the cell type.[50]

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Chem. Rev. 2024, 124, 5505−5616

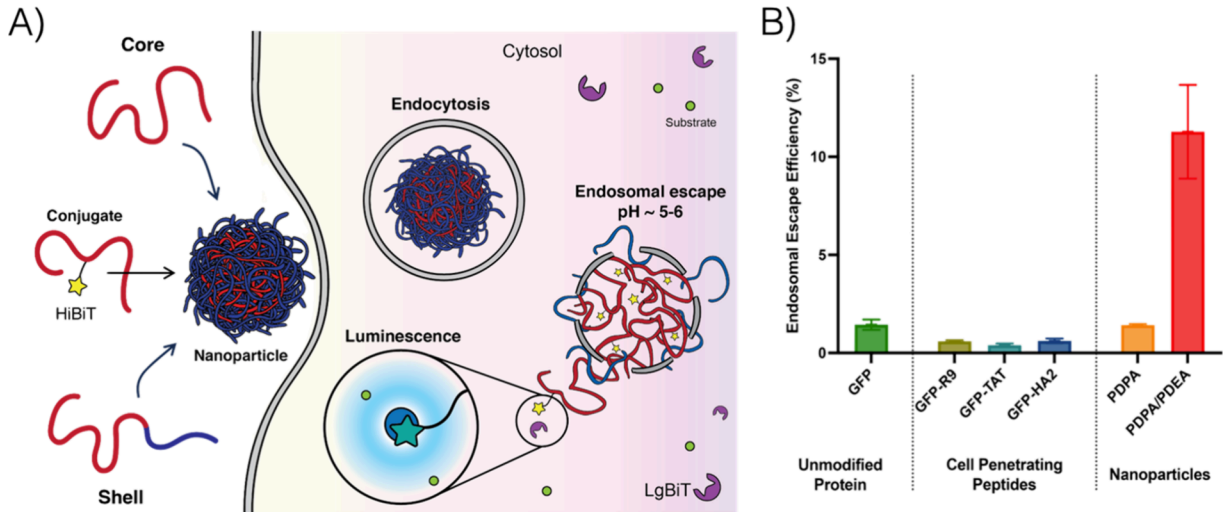

Figure 7. (A) The endosomal escape of pH-responsive polymeric nanoparticles was quantified with the SLEEQ assay. (B) Comparison of endosomal escape efficiencies in different systems obtained by SLEEQ assay. Reproduced with permission from ref. 7, 81. Copyright 2021, American Chemical Society (A) and Copyright 2017, Wiley-VCH (B).

Acidification occurs due to the proton pumps and channels that are associated with the endosomal membrane. There are also enzymes present within endo/lysosomal compartments that assist with processing foreign materials. For example, cathepsins, a class of proteases, are predominately located in these endosomal compartments. It has been shown that cathepsins are also involved in the initiation and development of cancer, and are highly upregulated in tumor and tumor associated cells.[50]

Nanoparticles internalized into cells must typically escape the endosomal/lysosomal pathway in order to deliver cargo to an active region within the cell. This is particularly critical for sensitive therapeutic cargo such as peptides, proteins, and nucleic acids, which are susceptible to degradation in the low pH environment of the endo/lysosome. Entrapment in endosomes remains a significant barrier to efficient cellular delivery, as how to achieve efficient release from these compartments while minimizing toxicity is poorly understood. Recent work has shown that even effective drug-delivery vehicles demonstrate minimal endosomal escape.[7,74] For example, a lipid nanoparticle study showed that ~2% of encapsulated siRNA escaped the endosome.[75] One of the reasons for this limited efficiency is the fact that the mechanisms underpinning the endosomal escape of nanoparticles are unclear.[73,76] Four mechanisms have been proposed for endosome escape of nanoparticles: 1) endosomal membrane fusion; 2) endosomal membrane destabilization; 3) pH-responsive swelling; and 4) the proton sponge effect (Figure 6).[74] Membrane fusion involves nanoparticle materials, usually lipids, fusing with the endosomal membrane, resulting in an inversion of the lipid particle, thus releasing the cargo into the cytosol.[77] The second mechanism is more common for polymeric nanoparticles, and it involves the disassembly of the nanoparticle based on a decrease in pH, which in turn destabilizes the endosomal membrane through interactions with the free polymer. Studies have shown that membrane destabilization could be optimized by tailoring the fraction of lipophilic moieties,[78] and by tuning the disassembly pH of the nanoparticles.[79] Recently, we quantified the endosomal escape efficiency of pH-responsive nanoparticles via a split luciferase endosomal escape quantification (SLEEQ) assay. This assay was far more sensitive and accurate than either traditional small-molecule fluorescence-based endosomal assays, or more recently developed assays such as the split green fluorescence protein assay, fluorescence correlation spectroscopy, and Nanoclick.[80,81] A number of nanoparticles were investigated based on pH-responsive poly(2-diethylamino)ethyl methacrylate (PDEAEMA) and poly(2-diisopropylamino)ethyl methacrylate (PDPAEMA), with a complementary peptide (HiBiT) conjugated to the nanoparticle via a disulfide linkage. Following endosomal escape, HiBiT combined with its complementary protein Large BiT(LgBiT), expressed in the cytosol, to produce bright luminescence, thus allowing a quantitative measurement of endosomal escape (Figure 7A). In this work, we demonstrated that the endosomal escape efficiencies varied with the disassembly pH of the nanoparticles. Figure 7B shows that a particular nanoparticle design comprising PDPAEMA and PDEAEMA has far superior endosomal escape efficiency (~10%) compared to either another polymeric nanoparticle design (PDPAEMA alone), other drug-delivery strategies (cell penetrating peptides), and naked cargo without a drug-delivery vehicle (GFP). This underscores the power of polymeric nanoparticles as endosomal escape vectors, as well as how particle properties and chemical functionality affects escape efficiency.

The final two endosomal escape mechanisms are the subject of growing debate in recent years.[82] The proton sponge effect relies on the addition of a cationic component that buffers the endogenous pH decrease in the endosomal compartment. This buffering causes the cell to pump protons into the endosome until the increase in osmotic pressure causes the endosome to rupture. This mechanism is similar to the third mechanism, where nanoparticles that swell in response to pH first buckle and then rupture the endosome as they expand. There are, however, a number of studies that cast doubt on the completeness of these mechanisms. For example, in a recent study we developed a series of pH-swelling nanoparticles with different ratios of PDEAEMA and PDPAEMA. These particles displayed up to 200% swelling, a strong buffering capacity, and high cellular association. No evidence of endosomal escape was found.[83] Another interesting study, which utilized a protein pH biosensor, revealed that there was no variation in the pH of

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Chem. Rev. 2024, 124, 5505−5616

endosomes when incubated with polyethylene imine (PEI) relative to an untreated endosome. This suggests that PEI has no effect on endosomal pH. The proton sponge effect, however, dictates that PEI should buffer the endosome, thus leading to an increase in pH relative to an untreated endosome.[84]

There is also evidence suggesting that polymeric nanoparticles can migrate through cellular barriers without internalization through endocytosis. Such a nanoparticle represents a highly attractive drug-delivery vehicle, given its ability to bypass endosomal escape, a limiting factor in efficient intracellular drug delivery. In recent work, nanoparticles based on an electrostatic complexation of a cationic guanidinium functionalized poly(oxanorbornene) imide polymer (PONI-Guan) was shown to complex with negatively charged protein cargo to form nanoparticles that could deliver cargo directly into the cytosol.[85,86] Initial work employed e-tagged proteins to make the naive protein negatively charged, and more recently a straight-forward approach to direct cytosolic delivery was demonstrated based on the modification of native lysines with citraconic anhydride (CA).[87] A library of nanoparticles comprising six different proteins was designed with a range of sizes and isoelectric points. Cytosolic delivery was confirmed by the visualization of EGFP in the cytosol and nucleus after 40 s, suggesting a membrane fusion type process for cell internalization. This conclusion was supported by the limited impact of a range of cellular inhibitors on internalization, as well as a decrease in internalization when cells were pre-treated with a cholesterol sequestration agent. One challenge with this approach is limiting the delivery of cargo to target cells alone, as these interactions are non-specific; however, designing a releasable surface represents a plausible solution. This PONI-Guan polymer was also used more recently to design complex nanoparticles based on PONI-Guan and nucleic acid cargos, siRNA, and pDNA.[88,89] Importantly, colocalization with endosomal/lysosomal compartments was not observed in these systems. However, it cannot be ruled out that some of the nanoparticles localized within these compartments, but endosomal escape was too rapid to visualize effectively. Regardless, these systems provide an interesting direction for further work. Other groups have also used guanidium functionalized polymers to show effective cytosolic delivery of biological cargo.

2.3.3. Delivery to Sub-cellular Locations. There are a number of biological therapeutics that require delivery to specific sub-cellular locations to achieve therapeutic efficacy. For example, while RNA target sites are typically in the cytosol, DNA needs to be delivered intact to the nucleus. Once DNA is delivered into the nucleus, it is transcribed into mRNA for protein expression. An advantage of delivering DNA instead of RNA is that a single DNA template produces multiple copies of mRNA, leading to higher gene expression. However, it remains very challenging to deliver cargo to the nucleus. The ability to traffic cargo from the cytosol to the nucleus is initially determined by the size of the cargo being delivered. Transport through the double phospholipid bilayer is mediated by the nuclear pore complex, which allows passive diffusion of materials 45 kDa or approximately 9 nm and below.[21] Delivery of cargo that is above this size relies on an active transport mechanism. Entry is governed by the nuclear pore complex, a group of proteins that tightly control nuclear access. Thus, a number of studies have demonstrated that transport through this system can be achieved using nuclear localization sequences (NLSs), which comprise a short peptide sequence 8−40 amino acids long. Most NLSs appear to achieve delivery to the nucleus via recognition by cytoplasmic importins that facilitate passing through the nuclear pore complex.[90] In recent work, a polymersome was conjugated to a NLS sequence, and the localization of this polymersome was compared to a non-targeted control.[90] It was observed that significantly more of the NLS conjugated carrier was located in the nucleus interior (45%), compared to the unmodified system (minimal in nucleus, 77% observed in the cytosol). Rotello and co-workers also used a series of NLS sequences to deliver eGFP.[91]

The mitochondria is another common site for both nucleic acid and protein delivery. Many biochemical processes are governed by the mitochondria, which play an important role in human disease. Mitochondria possess their own genome and limited protein synthesis machinery. There are a number of different biological conditions present in the mitochondria that can be used to target release in this region. They include a higher pH and oxidizing conditions due to the reactive oxygen species (ROS) generated as a result of the energy production that occurs there.[50] Previous work has shown materials can be localized in the mitochondria by modifying the surface with mitochondrional targeting moieties, they typically involve the combination of lipophilic properties to cross membranes as well as positive charge to facilitate binding to the negatively charged mitochondrial membrane[92,93] However, it is likely that such functionality will lead to non-specific interactions with other regions of the cell and thus have reduced specificity. Thus, the development of more targeted sub-cellular localization will be an important area of research in the future.

3. POLYMERS

Before reviewing the properties and applications of polymeric nanoparticles, it is necessary to touch on their constituents—polymers. What distinguishes polymers from the building blocks associated with other drug-delivery vectors, such as lipids and metals, is their versatility. As well as specific size and shape control, this versatility is most apparent in the incredibly diverse range of potential chemical functionality that can be readily incorporated into their structure. This functionality, among other polymer properties, is what imbues nanoparticles with their tunability and stimuli-responsiveness, as well as their ability to load therapeutic cargo, thus impacting delivery performance. The literature generally categorizes these constituent polymers into natural polymers, which are derived from natural products, and synthetic polymers, which are produced from monomers. Generally, natural polymers are non-toxic and biodegradable, but lack tunability, batch-to-batch consistency, and diverse functionality associated with synthetic polymers.[94,95] Furthermore, as polymer synthesis methods develop over time, the potential for even more sophisticated nanoparticle designs continues to grow. Recently, the development of reversible deactivation radical polymerization (RDRP) techniques such as atomic transfer radical polymerization (ATRP), nitroxide-mediated polymerization (NMP), and reversible addition-fragmentation chain transfer polymerization (RAFT) have imparted an unprecedented degree of control over the design of synthetic polymers.[96] The key to this control lies in a fast and reversible activation/deactivation of propagating chains, which yields polymers with a narrow polydispersity and a highly controllable molecular weight (MW). Furthermore, these techniques allow for the controlled synthesis of exceedingly complex polymer archi-

https://doi.org/10.1021/acs.chemrev.3c00705
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tectures, including di-block and tri-block copolymers, brush, graft, comb and star polymers, bioinspired materials containing biological components either synthetically or naturally derived, as well as polymers conjugated to a wide variety of functional groups.[97] Highly controlled polymers are also useful in the design of monodisperse and size-controlled nanoparticle samples; however, these particle characteristics are also strongly influenced by their formulation techniques, which are discussed in Section 4. Such advances in polymer synthesis have opened the way to increasingly diverse and functional nanoparticle design.

Below, we have classified the various polymers employed in nanoparticle formation according to type, beginning with predominantly non-responsive polymers including, but not limited to poly(amino acids), polyesters, vinyl polymers, and PEG derivatives, followed by stimuli-responsive polymers, which constitute more sophisticated nanoparticle designs. It is important to note that the number of different polymer designs used in the preparation of polymeric nanoparticles is vast and continues to grow as RDRP techniques gain prominence. An in-depth description of every single relevant polymer is beyond the scope of this review; however, we have chosen to highlight certain polymers within each family that are widely explored or have distinct properties that are important for successful drug delivery. These polymers are described below, along with a depiction of their structure and a summary of their strengths and weaknesses in regard to nanoparticle functionality. For a more detailed discussion of relevant polymers, we refer the reader to the following reviews.[6,98−102]

3.1. Poly(amino acids) and Proteins

Poly(amino acids) (PAAs) are a class of polymers composed of repeating units of amino acids, and are among the most important polymers employed in the design of polymeric nanoparticles. Their significance is underscored by the fact that PAAs permeate a significant fraction of the clinically relevant polymeric nanoparticle designs at present. PAAs are versatile, tunable, biocompatible, biodegradable, functionally diverse, and the subjects of facile, well-studied and economically viable synthetic procedures including solid-phase synthesis and ring-opening polymerization (ROP).[103,104] Such attractive properties are derived from their constituents, amino acids, which are organic molecules containing both amino and carboxylic functional groups with a side chain moiety unique to each amino acid. There are hundreds of naturally derived amino acids, with 20 comprising the proteins found in the human body. It is from this select group of 20 that PAAs are formed. Among the myriad of different PAAs, poly(glutamic acid) (PGlu), poly(L-lysine) (PLL), and poly(aspartic acid) (PAsp) are some of the most prevalent in the design of polymeric nanoparticles for drug delivery (Figure 8).[105] Such nanoparticles can also be derived from many other PAAs, including, but by no means limited to, poly(histidine), poly(alanine), poly(serine), poly(valine), poly(leucine), poly(arginine) (PArg), which carries the guanidine moiety, and poly(cysteine), whose thiol group makes it a common choice for redox-responsive applications. Polymers that combine many different amino acids, rather than blocks of one or two repeating amino acids, are known as polypeptides. As well as the immense functional versatility already on offer from the diverse set of amino acids that comprise PAAs, additional functionality can be easily grafted to these polymers through

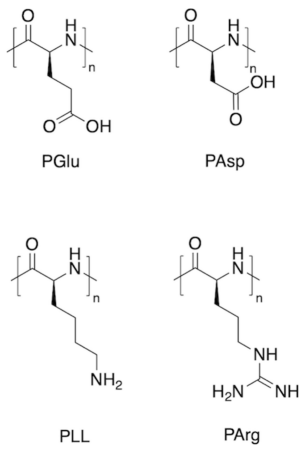

Figure 8. A selection of preeminent poly(amino acids) used in drug delivery; poly(L-glutamic acid) (PGlu), poly(L-aspartic acid) (PAsp), poly(L-lysine) (PLL), and poly(L-arginine) (PArg).

esterification and amidation reactions, further enhancing their drug-delivery potential.[106,107]

The hydrophobic characteristics of PAAs can be finely tuned through controlling the amino acid monomer composition and their relative ratios.[108] Specifically, the hydrophobicity of PAAs can be adjusted through the combination of different ratios of leucine, a relatively hydrophobic amino acid, and lysine and glutamic acid, two relatively hydrophilic amino acids.[109] PAAs also contain cationic or anionic side groups, allowing them to load oppositely charged therapeutic cargoes through electrostatic interactions, and self-assemble into nanoparticles. For instance, PAAs with cationic amino acids, such as PLL and PArg, have been widely applied in nucleic acid delivery.[108] In addition, PAAs built from anionic amino acids, including PGlu and PAsp have been used in delivery of cationic therapeutic cargo, such as cationic peptides,[110] amine containing drugs such as DOX,[111] and platinum(II)-based anti-cancer drugs like cisplatin.[112]

PAAs contain highly versatile functional groups such as hydroxyl, carboxyl, amino, and thiol groups that can be readily modified for appropriate loading and release of therapeutic cargo.[112,113] Thus, PAAs can be easily endowed with stimuli-responsive characteristics to achieve controlled drug release, either by introducing naturally occurring amino acid residues with innate stimuli-responsive characteristics, or by introducing responsive linkages to their side chains.[114] For example, PEG-*b*-PAsp was functionalized with a pH-responsive hydrazone bond to conjugate epirubicin, which then self-assembled to form micellar nanoparticles at physiological pH. This pH-responsive micellar design, known as NC-6300, facilitates the pH-triggered release of the drug in the low pH of the tumor microenvironment, and is presently undergoing clinical trials for cancer therapy. Moreover, PAAs can load drugs through electrostatic and hydrophobic interactions, owing to pH-responsive ionizable groups such as carboxyl groups, imidazole groups, primary amines, and tertiary amines that are derived from amino acids such as glutamic acid, aspartic acid, histidine, and lysine. It has been reported that charge conversion of these ionizable groups at a low pH can result in nanoparticle disassembly, resulting in controlled drug release at targeted therapeutic sites.[111] In addition, redox-responsive PAAs have also been designed by incorporating disulfide bonds as a linkage to conjugate drugs to their peptide backbones, or as

https://doi.org/10.1021/acs.chemrev.3c00705
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nanoparticle core cross-linkers, facilitating redox-responsive drug release.[114,115] Cysteine is the most common amino acid for introducing disulfide bonds, due to its reactive thiol group.[116] Thioether-containing PAAs, such as poly(L-methionine), have been employed to design ROS-responsive nanoparticles.[117,118] Thus, the advancement of PAAs synthesis has led to more sophisticated nanoparticle designs for controlled drug-delivery applications.[114,115,119]

In addition, the chirality of PAAs is another factor that can affect the physicochemical properties and biological activity of self-assembled nanoparticles.[120] However, for most polymeric nanoparticle studies, the impact of chirality is not carefully considered, with the majority of previous investigations focusing on PAAs with L-amino acids.[121,122] In a recent work, Ding et al. studied the chirality effect on the anti-tumor efficacy of DOX-loaded nanoparticles with a P(D,L-leucine) core compared to those with a P(L-leucine) core but did not show a strong correlation between the chirality and therapeutic efficacy of PAA-based nanoparticles.[123] It should be noted that three-dimensional folding (α-helix, β-folding) significantly influences the properties of PAA-based nanoparticles, similar to the folding of proteins. Mochida et al. reported that the α-helix structure of PGlu prolonged particle stability compared to nanoparticles made from PEG-*b*-PGlu with a random conformation, thus improving their plasma half-life and tumor-targeting efficiency.[124]

Whereas PAAs are polymers composed of one or two different amino acids, natural macromolecules formed from many different amino acids can self-assemble into a three-dimensional structure known as proteins, and have also generated interest in the design of polymeric nanoparticles for drug delivery. Silk fibroin, collagen, and albumin are a few important protein-based polymers used in drug delivery. As a protein-based biomaterial derived from silkworms, silk fibroin has garnered increasing attention for its exceptional biocompatibility, biodegradability, and versatile mechanical properties. Its amino acids are organized into a repeating sequence of glycine-alanine-glycine-alanine-glycine-serine (Gly-Ala-Gly-Ala-Gly-Ser), and their self-assembly yields a crystalline anti-parallel β-sheet configuration facilitated by hydrogen bonding interactions.[125] These sequences subsequently form nanoparticles, whereas the hydrophobic core is surrounded by a hydrophilic shell. The active side chains of silk fibroin allow for additional modification, such as serine, threonine, and tyrosine grafting, thereby enhancing the drug-delivery capability or conferring additional advantageous properties.[94] Furthermore, the anionic nature of silk fibroin offers the ability to load positively charged cargo via electrostatic attraction.[126]

Collagen, an essential protein abundantly present in the extracellular matrix of various tissues, has also been widely studied in relation to drug delivery and wound healing. Like silk fibroin, collagen possesses outstanding biocompatibility and biodegradability. These advantages, coupled with the unique ability to interact with receptors on the surface of cells, have made collagen an attractive candidate for incorporation into drug-delivery vehicles.[127] In the preceding decade, substantial information has been discovered regarding the intrinsic characteristics and targeted interactions of collagen with its molecular counterparts. An array of review articles has summarized the recent progress in harnessing collagen-based materials as drug-delivery systems.[128,129]

Albumin is another versatile protein-based polymer, with advantageous drug-delivery properties. Albumin can be extracted from a variety of sources including human serum (human serum albumin), egg white (ovalbumin), bovine serum (bovine serum albumin), and also from soyabeans, milk and grains. Its inherent advantages, such as non-toxicity, non-immunogenicity, biocompatibility, biodegradability, and water-solubility, have made albumin an ideal candidate in nanoparticle formulations for drug-delivery applications.[130,131] Its unique chemical structure, conformation, and water solubility can help improve the delivery of hydrophobic drugs, thus enhancing their pharmacokinetic properties. In addition, albumin nanoparticles also possess active targeting potential by interacting with specific receptors present at disease sites without the need for further modification with external ligands.[132,133] Abraxane (albumin bound paclitaxel) is an important FDA approved albumin-based nanoparticle that is used in the treatment of breast, pancreatic, and non-small-cell lung cancers.[134] Additionally, there are a number of recent clinical and preclinical studies exploring the use of albumin nanoparticles in drug delivery, which have been reviewed elsewhere.[132,133]

3.2. Polysaccharides

Polysaccharides are polymeric materials composed of carbohydrate molecules bound together through glycosidic linkages (Figure 9). Polysaccharides are derived from renewable

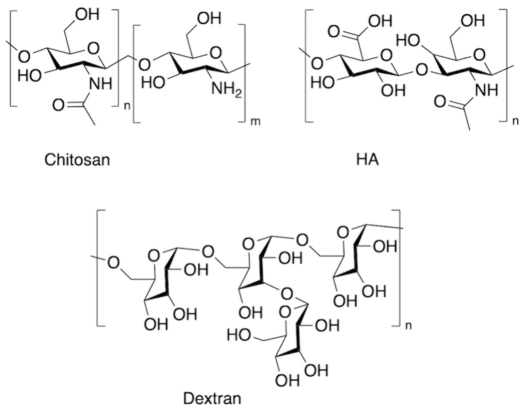

Figure 9. General chemical structures of polysaccharides used in drug delivery: chitosan, hyaluronic acid (HA), and dextran.

sources, such as plants, algae, and microorganisms, and blend remarkable biocompatibility and biodegradability with an array of functional groups that can be modulated for targeted drug delivery. Furthermore, polysaccharides are highly tunable. Their molecular weight, architecture (branched or linear), physicochemical properties, and electrostatic charge all impact drug-delivery performance.[135] Polysaccharides also exhibit an intrinsic capacity for receptor recognition, particularly targeting receptors that are overexpressed on the surfaces of pathological tissues. The distinct binding interactions between these polysaccharides and specific receptors offer an additional route in the design of "smart" nanoparticles for drug delivery.[136] Presently, the polysaccharides that have garnered the most interest as the basis for polymeric nanoparticles are chitosan,[137] hyaluronic acid (HA),[138] and dextran,[139] all of which are biodegradable through enzymatic degradation.[94] Cyclodextrins are also a specific type of cyclic sugar molecule that is often incorporated as a building block in nanoparticles

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

due to its ability to load hydrophobic cargo in its interior or to facilitate self-assembly. For example, Li et al. loaded two hydrophobic drugs, DOX and celastrol, into a pH-responsive, amine-functionalized cyclodextrin nanoparticle.[140] The presence of amine-functionalized cyclodextrin promoted self-assembly based on electrostatic and supramolecular interactions, yielding nanoparticles with oral delivery capability. Furthermore, the functionalized cyclodextrin was pH responsive, allowing the particles to remain stable in the harsh acidic conditions of the stomach, while disassembling to release their encapsulated hydrophobic drugs in the more basic conditions of the intestine.

3.3. Glycopolymers

Glycopolymers are polymers that have carbohydrate (saccharide) moieties as pendant groups and have received significant attention as building blocks for drug delivery (Figure 10).[102]

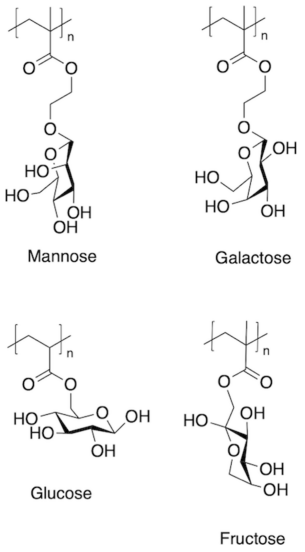

Figure 10. General chemical structures of common glycopolymers used in drug delivery: mannose, galactose, glucose, and fructose functionalized methacrylates: poly(2-(β-D-mannopyranosyloxy)ethyl methacrylate), poly(2-(β-D-galactopyranosyloxy)ethyl methacrylate), poly(6-O-acryloyl-β-D-glucoside, and poly(1-O-acryloyl-β-D-fructopyranose), respectively.

Glycopolymers have variable hydrophilicity depending on the nature of their saccharide pendants, which yields more complex behavior than PEG when used as a nanoparticle shell component. The strong intermolecular hydrogen bonds formed between glycopolymer chains can lead to cross-linking, aggregation, and the formation of hydrogels, even when the polymers appear to be soluble in aqueous solutions.[141,142] Glycopolymers are attractive due to their capacity to bind to lectins, which is a useful feature for targeted drug delivery.[143] However, given that glycopolymers are structurally similar to other natural polymers, such bioactivity can prompt unwanted interactions and a strong immune response, which can significantly reduce circulation time in the blood.[102,144] Functionalizing glycopolymers with certain saccharide moieties, such as mannose, fructose, and glucose, promotes specific targeted drug delivery.[102] Mannose-functionalized glycopolymers are able to target cells with mannose receptors, including macrophages, dendritic cells, and endothelial cells.[144] Galactose-based glycopolymers target asialoglycoprotein receptors (ASGPR) and galectin-3.[145,146] Glucose-based glycopolymers are employed as PEG alternatives[147] and are suggested to target the glucose transporter 1 (GLUT-1).[148] Fructose glycopolymers can target the GLUT-5 transporter and can also improve cellular uptake of drugs.[149,150] Additionally, glycopolymers have also been used to target viruses and bacteria through nanostructure-based[151] anti-viral coatings and anti-adhesion treatment, respectively.[152]

3.4. Polyesters

Polyesters are polymers composed of repeating ester moieties, and are some of the most attractive and widely adopted components for designing polymeric nanoparticles for drug delivery due to their versatility, biodegradability, and biocompatibility. Among the myriad of different polyesters, four in particular are pre-eminent: polylactide or poly(lactic acid) (PLA), poly(glycolide) or poly(glycolic acid) (PGA), their copolymer poly(lactide-*co*-glycolide) (PLGA), and poly(ε-caprolactone) (PCL) (Figure 11). Specifically, these

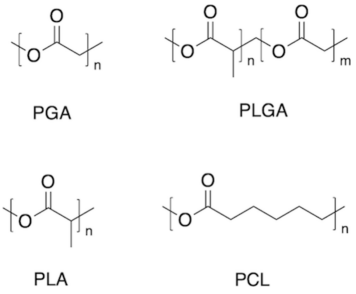

Figure 11. Common examples of polyesters used in drug delivery: poly(glycolic acid) (PGA), poly(lactide-*co*-glycolide) (PLGA), poly(lactic acid) (PLA), and poly(ε-caprolactone) (PCL).

polyesters are typically utilized as core components in micelles, a kind of nanoparticle whereby the core and shell components are based on one amphiphilic block copolymer. Micelles based on polyester cores normally employ PEG as a shell, and already represent a number of FDA-approved products.[153−155] Compared to PGA, PLA is slightly more hydrophobic and resistant to hydrolytic degradation. Hence, their combination, PLGA, is highly tunable in terms of its hydrophobicity and degradation profile.[153] PCL is highly hydrophobic and resistant to endogenous degradation, and therefore is often applied to manufacture devices for long-term release.[156] The degradation rate of PCL can be increased significantly through functionalization with oxalate linkages on the backbone.[157] PLGA and PCL polymers are hard to modify, and functionalization generally requires advanced organic synthesis techniques on small scales, which is not cost-effective.[158] On the other hand, polyester synthesis via polycondensation allows for the addition of a wide variety of functional moieties.[159,160] Similar to PAAs, the importance of polyesters such as PLGA and PCL as polymeric nanoparticle constituents is evident by the fact that polyesters comprise a significant fraction of the nanoparticle designs currently undergoing clinical trials, as well as those with the most clinical potential.

Poly(amino esters) (PAEs) are polyesters with amine or amide moieties on their backbones. These amines provide sites for functionalization[161], while the backbone amines themselves offer the potential for pH-responsiveness.[162] Almutairi and coworkers reported a synthesized random polymer containing two pH-responsive functional groups: amino ester and ketal.[163]

https://doi.org/10.1021/acs.chemrev.3c00705
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The tertiary amine backbone underwent a hydrophobic-to-hydrophilic switch in response to a decrease in pH, facilitating acid-catalyzed hydrolysis of ketal groups. These polymeric materials showed excellent stability in neutral conditions and rapid degradation in acidic conditions. In contrast, PAEs bearing secondary amines can be quickly degraded in neutral or basic conditions via intramolecular nucleophilic attack. In acidic conditions, the polymer structure is maintained, making such polymers attractive for release of nucleic acids within cytosolic conditions.[164]

Another important derivative of polyesters are aliphatic polycarbonates (APCs). APCs have a lower degradation rate in aqueous media, less crystallinity, and are easier to modify compared to polyesters.[165,166] APCs with controlled molecular weight and dispersity can be produced by ROP, with the addition of alkene pendants a preferred method for grafting functional groups via the thiol−ene click reaction. For example, Wang et al. reported a polycarbonate nanoparticle that was ultra-sensitive to pH due to the amine pendants introduced via thiol−ene reactions, with the protonation of the amines inducing nanoparticle disassembly.[167]

3.5. Phosphate-Based Polymers

Polyphosphoesters (PPEs) are a class of polymers that are versatile and biodegradable and hence provide a useful platform for the design of polymeric nanoparticles for drug delivery (Figure 12).[100,168,169] The versatility of PPEs is due to

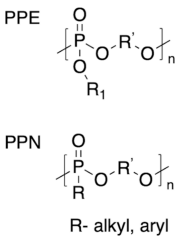

Figure 12. General chemical structures of phosphate-based polymers: polyphosphoesters (PPEs) and poly(phosphonates) (PPNs).

the fact that they can be designed as either hydrophilic or hydrophobic, depending on the functional groups they bear. This allows them to act as both the hydrophobic core or the hydrophilic shell of micelles and other core−shell nanoparticle designs.[170,171] PPEs generally have faster degradation profiles than PLGA or PCL under physiological conditions.[168]

Poly(phosphonates) (PPNs) are similar to PPEs in that they utilize the O−P linkages, and have very strong backbone biodegradability (Figure 12). With short alkyl side chains attached to phosphorous atom, these PPNs are water soluble with low cytotoxicity. Even high concentrations (1 mg/mL) of PPNs show no cytotoxicity in HeLa cells.[172] The length of these alkyl chains can be used to adjust the hydrophilicity of the resultant polymers.[173,174] Simon et al. designed Polystyrene-*b*-PPN nanoparticles, and were able to tune the hydrophilicity of the PPN shell by adjusting the length and ratio of the PPN alkyl chains.[173]

3.6. Vinyl Polymers

Vinyl polymers are a class of synthetic polymers with a carbon-based polymer backbone, derived from substituted vinyl monomers.[175] Among the plethora of vinyl-based polymers, acrylates, methacrylates, acrylamides, and methacrylamides have gained particular interest in drug delivery (Figure 13).[6] A

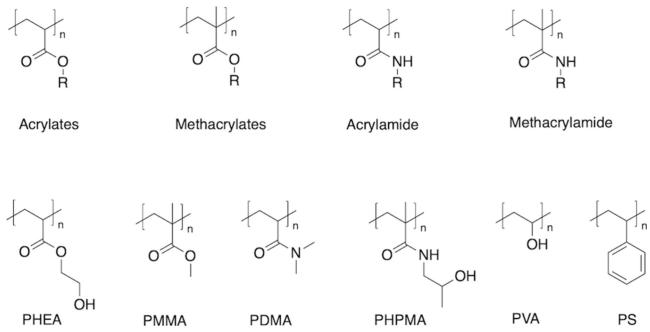

Figure 13. General classes of vinyl polymers used in drug delivery; acrylates, methacrylates, acrylamides and methacrylamides with common examples: poly(hydroxyethyl acrylate) (PHEA), poly(methyl methacrylate) (PMMA), poly(*N*,*N*-dimethylacrylamide) (PDMA), poly(*N*-(2-hydroxypropyl) methacrylamide (PHPMA), poly(vinyl alcohol) (PVA), and polystyrene (PS).

few commonly used vinyl polymers include poly(*N*-(2-hydroxypropyl) methacrylamide) (PHPMA), polystyrene (PS), poly(methyl methacrylate) (PMMA), poly(vinyl alcohol) (PVA), poly(butyl methacrylate) (PBMA), poly(2-hydroxyethyl methacrylate) (PHEMA), poly(hydroxyethyl acrylate) (PHEA), and poly(*N*,*N*-dimethylacrylamide) (PDMA).[175,176] Despite the non-biodegradable backbone, vinyl polymers stand out as versatile synthetic polymers in therapeutic delivery owing to their biocompatibility, non-toxicity, low-immunogenicity, and high stability. For example, PS nanoparticles are typically used as model systems to study how particle properties impact various aspects of drug-delivery performance. Dawson and co-workers used PS nanoparticles to understand the effect of nanoparticle size and surface charge on protein corona composition. They found that even with similar material types, variability in particle size and surface charge can impact the nature of the particle's corona composition, ultimately affecting biological interaction.[177] In a recent study, the same group utilized PS nanoparticles to investigate the arrangement of functional protein motifs on the outer surface of the nanoparticle's corona, providing valuable insight into how nanoparticle corona proteins engage with specific cell receptors.[178]

RDRP has enabled the synthesis of well-defined vinyl polymers with highly controlled molecular weights and lower dispersity. For instance, ATRP and RAFT polymerization techniques are commonly used in the polymerization of a wide variety of vinyl monomers with various functional groups, and facilitate the synthesis of more advanced and sophisticated vinyl polymers with tunable molecular weights, chemical compositions (e.g., different types of copolymers), and architectures (e.g., linear, branched polymers such as graft, star, and hyperbranched).

The existence of numerous reactive functional groups, such as hydroxyl, carboxyl, amine, and amide groups, along the vinyl polymer structure enables the creation of copolymers with diverse physicochemical characteristics. For instance, PHPMA-based copolymers are highly water soluble and biocompatible, which leads to the design of efficient drug-delivery vehicles, especially in cancer therapy.[179,180] In addition, the presence of distinct functional groups at the chain ends or otherwise as pendant groups on the vinyl polymer backbone allows for the attachment of therapeutics or targeting ligands, making them highly versatile in the field of drug delivery. Similarly, vinyl polymers have found extensive application in the design of

https://doi.org/10.1021/acs.chemrev.3c00705
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stimuli-responsive nanoparticles, owing to their ease of modification with a variety of environmentally responsive functional groups, such as those responsive to variations in pH, redox, temperature, or enzymes, and this is discussed in Section 3.9.[175] In addition, hydrophilic polymers derived from vinyl monomers, such as poly(oligo(ethylene glycol) methyl ether methacrylate) (POEGMA), poly(vinylpyrrolidone) (PVP), and poly(2-hydroxypropyl methacrylamide) (PHPMA), have been employed as PEG alternatives to enhance the stealth properties of polymeric nanoparticles to improve their *in vivo* stability and blood circulation time while reducing non-specific uptake by the immune system.[181,182] These vinyl polymers, which can be used as alternatives to PEG, will be discussed in detail in Section 3.8. Thus, vinyl polymers are highly customizable materials, making them versatile in controlled and targeted drug delivery.

RDRP techniques produce non-degradable polymers which can be a challange for delivery applciations. Therefore, recently techniques hve been developed to introduce degadability into the system. Radical ring-opening polymerization (rROP) of cyclic ketene acetals (CKAs) is the most common method to incorporate degradable ester linkages into the vinyl polymer backbones.[183,184] Common CKA monomers, which have been employed in nanoparticle synthesis and drug-delivery applications, are summarized in Figure 14. By using RDRP techniques such as RAFT polymerization, good control over MW and polydispersity can be achieved; however, copolymerization with CKA's can, to a certain extent, increase the dispersity of the resulting polymers. Polymerization-induced self-assembly (PISA)—a nanoparticle formulation technique discussed in Section 4—has been more recently employed to

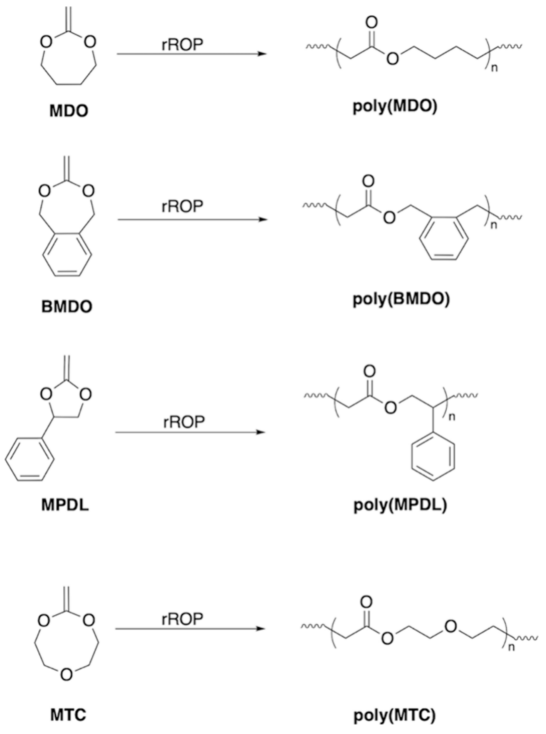

Figure 14. Common examples of cyclic ketene acetals (CKAs) and their general polymeric ester products after radical ring-opening polymerization: 2-methylene-1,3-dioxepane (MDO), 5,6-benzo-2-methylene-1,3-dioxepane (BMDO), 2-methylene-4-phenyl-1,3-dioxolane (MPDL), and 2-methylene-1,3,6-trioxocane (MTC).

polymerize CKAs in combination with other polymerization techniques such as ROP to form a new method termed "ROPISA".[185] It is important to note that the final molar incorporation of CKAs is often limited, and gradient copolymers are usually obtained. In a practical polymer synthesis, a large excess of the CKA co-monomer is required. In addition, the rate of degradation is largely affected by the nature of the comonomers—methacrylates vs vinyl ethers, hydrophobic vs hydrophilic monomers—and, of course, the content of CKA units.[186−188] Recent work has shown some progress in higher levels of incorporation using alpha-lipoic acid.[189] Nevertheless, the ability to easily impart polymer chain degradability offered by CKAs has made them an attractive subject of research into more efficient drug-delivery designs.[184]

3.7. Polyethyleneimine

Polyethyleneimine (PEI) is a highly versatile synthetic cationic polymer that is widely studied for drug-delivery applications, particularly in regard to gene delivery.[190] PEI can be broadly categorized into two distinct forms: linear PEI and branched PEI (Figure 15). Linear PEI is typically synthesized by

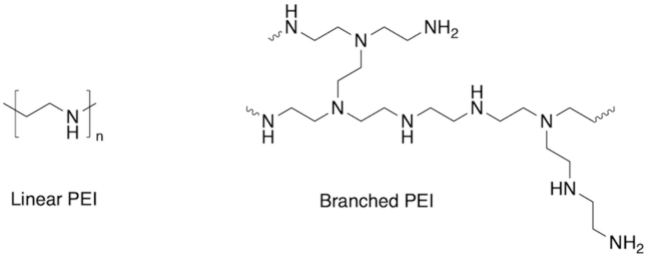

Figure 15. General chemical structures of poly(ethyleneimine) (PEI): linear PEI and branched PEI.

initiating the cationic ROP of 2-oxazoline to form POx, followed by transformation of POx into linear PEI through hydrolysis, which is catalyzed under either acidic or basic conditions. However, branched PEI can be directly synthesized through cationic ROP of aziridine monomers.[181,190] The general chemical structure of PEI is composed of repeating units of ethylenimine with a high density of amino groups in the polymeric backbone. Branched PEI contains primary, secondary, and tertiary amino groups in an approximate ratio of 1:2:1, while linear PEI only contains primary and secondary amino groups. Since approximately 20% of its amino groups are protonated under physiological conditions, PEI can complex with negatively charged macromolecules, such as nucleic acids and proteins, resulting in compact nanoparticles, and hyperbranched/dendritic scaffolds or polyplexes with an enhanced intracellular delivery capability.[6,191−194] It has been reported that both architecture and molecular weight strongly impact the intracellular delivery efficiency and cytotoxicity of PEI-based nanoparticles.[195,196] PEI is also frequently modified with other functionality, aiming to overcome the limitations associated with unmodified PEI, such as higher cytotoxicity (associated with molecular weight, and architecture), aggregation under high ionic strength conditions, and opsonization. For example, polymers such as PEG, chitosan, and dextran have been widely employed in PEI modification to enhance biocompatibility and blood circulation time, resulting in improved transfection efficiency.[190,194]

PEI is commonly used as a transfection agent for nucleic acid delivery. A significant number of studies have proposed

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

that the higher transfection efficiency of PEI-based nanoparticles is governed by their ability to facilitate endosomal escape through the proton sponge effect, whose mechanism remains a hotly debated topic.[190,197] For instance, using a pH dependent fluorescent lifetime imaging microscopy technique, Johnston and co-workers demonstrated that PEI did not impact the pH of endosomes as would be expected by the proton-sponge effect.[84] Owing to the presence of highly functionalized amino groups, PEI has found applications beyond gene delivery, including the delivery of anti-cancer drugs such as DOX, PTX, and epirubicin.[198] Moreover, PEI-based nanoparticles have also been utilized in encapsulating various agents for imaging and theranostic applications.[199] Thus, PEI is a versatile synthetic polymer that has found extensive use in a wide range of drug-delivery applications, and has been comprehensively reviewed in a number of recent publications.[193,198,199]

3.8. Poly(ethylene glycol) and Alternatives

Poly(ethylene glycol) (PEG), also named poly(ethylene oxide) (PEO), is a class of synthetic polymer whose primary advantage is strong water solubility. PEG is also very stable and highly biocompatible. It is generally regarded as safe by the U.S. Food and Drug Administration (FDA). For these reasons, PEG is sometimes referred to as a "gold standard" for nanomedicines, and is a vital component for polymeric nanoparticles.[200−203] In fact, a significant fraction of all polymeric nanoparticles utilize PEG as a hydrophilic shell component. This is because the addition of PEG (PEGylation) enhances nanoparticle performance by improving stability, minimizing toxicity, prolonging retention during blood circulation by avoiding the immune system, and heightening the EPR effect.[201,204,205] Such "stealth" effects are often explained by the presence of a strong hydration shell at the water−PEG interface due to hydrogen bonding. This hydration shell acts as a steric barrier to reduce nonspecific protein adhesion, which is the primary mechanism by which the immune system recognizes foreign material.[206,207] It has become clear that the density of PEGylation, the molecular weight of the PEG chains as well as PEG architecture (brush or linear) can significantly affect protein adsorption.[208−210]

Well-defined linear PEG polymers, such as methoxy-poly(ethylene glycol) (mPEG), are profoundly influential in products already on the market. However, branched PEG analogues, such as POEGMA and similar branched polymers prepared by ring-opening metathesis (ROMP) polymerization, have been found to reduce recognition by the immune system compared to linear PEG in regard to protein−polymer conjugates[211−213], antifouling surfaces,[214] and nanoparticles functionalized with PEG-lipid surfactants[215]. This suggests that engineering nanoparticles with more complex PEG architectures may be a strategy to combat anti-PEG immune reactions.[215,216]

A variety of other hydrophilic synthetic polymers have been investigated for a variety of drug delivery applications, including poly(glycerol) (PG),[217,218] POx,[219,220] PHPMA,[221] and other poly(methacrylamides) such as poly(*N*,*N*-dimethyl acrylamide) (PDMA), poly(*N*-acryloyl morpholine) (PNAM),[222−224] and poly(acrylamide) (PAAm)[225] (Figure 16A). Much of the research into these hydrophilic polymers has been motivated by an attempt to find alternatives to PEG, in order to offset accelerated blood clearance (ABC). When probing the circulation and ABC effect of these polymers,

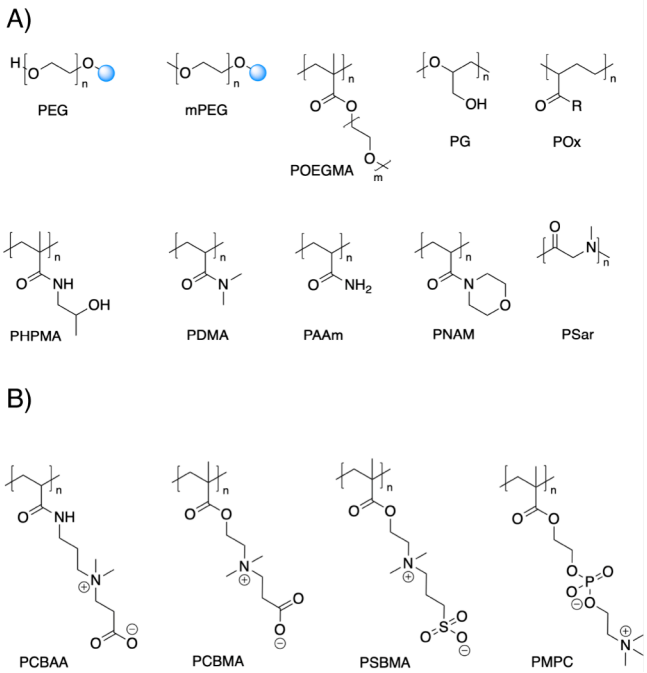

Figure 16. General chemical structures of polymer building blocks that are used as hydrophilic components for nanoparticle delivery systems. (A) PEG and hydrophilic PEG alternative polymers: mPEG, POEGMA, PG, POx, PHPMA, PDMA, PAAm, PNAM, and polysarcosine (PSar). (B) Zwitterionic polymers: poly(carboxybetaine acrylamide) (PCBAA), poly(carboxybetaine methacrylate) (PCBMA), poly(sulfobetaine methacrylate) (PSBMA), and poly(methacryloyloxyethyl phosphorylcholine) (PMPC).

certain PEG alternatives, PHPMA, PDMA, PNAM, and PVP, were shown to display a lower circulation half-life than PEG, with a significantly higher resistance to ABC.

Polysarcosine (PSar) is a hydrophilic, biodegradable polymer that is a promising candidate to replace PEG as a shell component in prospective polymeric nanoparticle designs (Figure 16A). PSar is a polypeptoid—a kind of pseudo-peptide that is a polymer composed of N-substituted amino acids. Studies suggest that PSar is also more biocompatible and less immunogenic than PEG.[226−228] Mao and Ling et al. found that gold nanoparticles functionalized with PSar had a longer circulation time compared to a PEGylated control, with both displaying similar levels of low toxicity.[229] Saji et al. reported that PSar had an enhanced tumor targeting performance compared to PEG, via the synthesis of a conjugate consisting of PSar and a photoacoustic agent.[230]

Another major class of synthetic hydrophilic polymers often used as the shell of a polymeric nanoparticle are zwitterionic polymers.[231−235] These polymers, or polyzwitterions, have zwitterionic functional groups, meaning that they contain both a negatively and positively charged moiety. These polymers have displayed many of the benefits bestowed on nanoparticles by PEG, but seemingly lack the rapid clearance in the blood associated with PEG, and hence are a promising class of PEG alternatives. In fact, polyzwitterions resemble the behavior of PEG in almost every aspect, with high hydrophilicity, strong antifouling performance, and low immunogenicity.[236−239] Carboxybetaine, sulfobetaine, and phosphobetaine, which consist of both positively and negatively charged moieties resulting in an overall neutral charge, are some of the most common choices when synthesizing zwitterionic polymers. For

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

example, zwitterionic polymers, such as poly(carboxybetaine acrylamide) (PCBAA), poly(carboxybetaine methacrylate) (PCBMA), poly(sulfobetaine methacrylate) (PSBMA), and poly(methacryloyloxyethyl phosphorylcholine) (PMPC), are commonly used in drug-delivery applications (Figure 16B).[101,240]

3.9. Stimuli-responsive Polymers

The design of effective polymeric nanoparticles for drug delivery relies on maximizing therapeutic delivery while minimizing off-target effects. Polymeric nanoparticles that respond to biologically relevant stimuli are one of the most promising designs to achieve highly efficient drug delivery. These kinds of nanoparticles rely on stimuli-responsive polymers or cross-linkers as the basis for their elevated performance. The stimuli-responsive capability of these polymers induces physical and/or chemical structural changes within the polymer backbone, allowing spatial and temporal control over the release of therapeutic payloads, thereby improving the site-specific drug release (Figure 17). Stimuli-responsive polymers rely on a vast array of clever functionality to yield remarkable changes in their behavior based on slightly altered environmental conditions either external, or inherent within the body. In the last 20 years, the advent of controlled polymerization methods has allowed for the synthesis of more functionally sophisticated polymers. To yield nanoparticles with stimuli-responsive properties, stimuli-responsive moieties can be incorporated within the backbone, grafted to the polymer side chains, attached to the end-caps, or, in the case of advanced nanoparticle designs, a combination of all three.

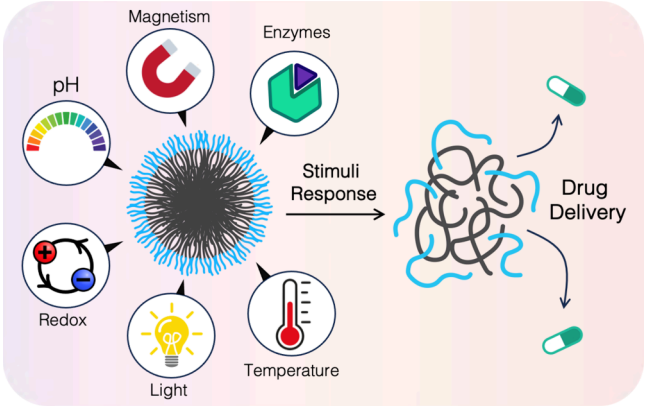

Figure 17. Nanoparticles comprising highly functionalized polymers can respond to a myriad of stimuli to enhance drug-delivery performance. These stimuli include, but are not limited to, temperature, light, redox and enzymatic environment, pH, and exposure to a magnetic field.

3.9.1. pH. pH is one of the most important endogenous stimuli, and thus a significant number of polymeric nanoparticle designs have sought to achieve improved drug-delivery performance by utilizing it. These designs generally respond to changes in pH by transforming their size, shape, or morphology in order to achieve clearance of a particular biological barrier, or to deliver drugs at a specific site.[241] Strategies to introduce pH responsiveness usually involve employing polymers that can alter their hydrophilicity/hydrophobicity or cleave a particular linkage.

Many pH-responsive polymers alter their solubility through the protonation/deprotonation of acidic or basic moieties at a given pH. As a result, these polymers are generally referred to as charge shifting polymers. The polymers with weakly basic groups contain amino groups, such as tertiary amines like morpholine, pyrrolidine, imidazole, piperazine, and pyridine moieties. Another example is the PAE bearing tertiary amine backbone. These polymers can be protonated and become positively charged when the pH is below their respective pK_a. This results in the polymers transforming from hydrophobic to hydrophilic, leading either to the disassembly of nanoparticles when the charge shifting element forms the hydrophobic component of a self-assembled system, or to the swelling of the nanoparticles when a charge-shifting system is cross-linked.[241,242] Examples of well-known tertiary amine-containing monomers used in the preparation of pH-responsive polymers include (2-dimethylamino)ethyl methacrylate (DMAEMA), (2-diethylamino)ethyl methacrylate (DEAEMA), and (2-diisopropylamino)ethyl methacrylate (DPAEMA) (Figure 18A). Using these charge shifting polymers, the pH transition point can be precisely tuned either by using a polymer with a single tertiary amine,[243,244] a combination of polymers with different tertiary amines,[79,245,246] or the same tertiary-amine containing polymer blended with other non-ionizable moieties at varying ratios.[247]

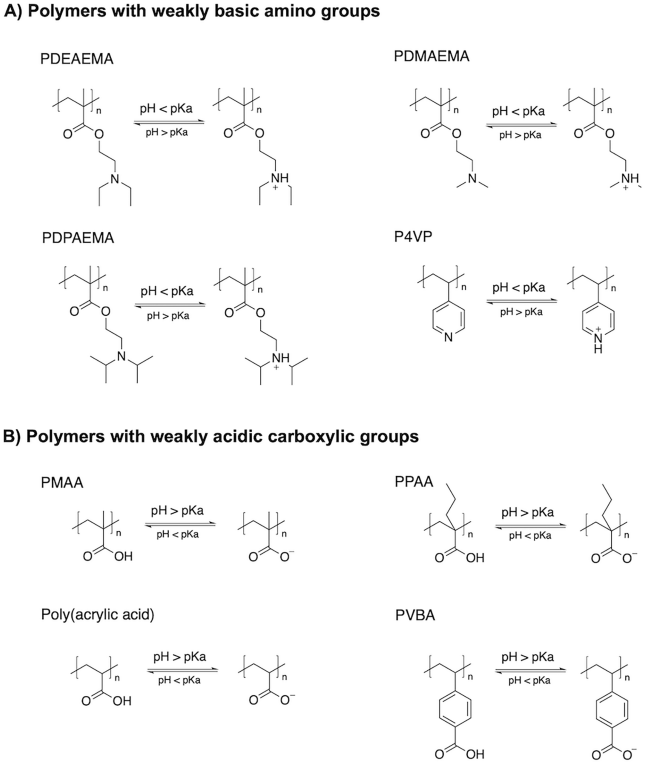

Figure 18. A selection of pH-responsive polymers and their charge transitions; (A) polymers with weakly basic amino groups: PDEAEMA, PDMAEMA, PDPAEMA, and P4VP. (B) Polymers with weakly acidic carboxylic groups: PMAA, PPAA, poly(acrylic acid), and PVBA.

In contrast, polymers that contain weakly acidic groups such as carboxylic acid or sulfonic acid can be ionized when the pH is above their respective pK_a (Figure 18B). The most commonly used polymers with carboxylic functional groups are poly(methacrylic acid) (PMAA), poly(acrylic acid), poly(propylacrylic acid) (PPAA), poly(butyl acrylic acid)

https://doi.org/10.1021/acs.chemrev.3c00705
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(PBAA), poly(4-vinyl benzoic acid) (PVBA), and PGA. Boronic acid, phosphonic acid, and sulfonamide-functional groups containing polymers are another class of anionic polymers that have been applied in designing responsive polymeric nanocarriers for drug-delivery applications.[241,242]

Another strategy to design pH-responsive materials involves the incorporation of pH cleavable linkers either as cross-linkers within a polymer or nanoparticle structure, as a component of the backbone, or as part of pendant groups linking cargo to the polymer backbone. pH-responsive linkages normally work by rapid hydrolysis in an aqueous biological environment.[241] Such linkages include: 1) ester derivatives such as acetals,[248] N/O-aminals,[249,250] *ortho*-esters,[251] borates,[252] and *β*-thiopropionates;[253] 2) C=N double bond derivatives such as hydrazones,[254] oximes,[255] and imines;[256] 3) maleic amide derivatives[257] including *cis*-aconityls[258] and 2-propionic-3-methylmaleic anhydride (CDM); and 4) trityl-based protecting groups or linkers (Figure 19).[259,260] When choosing a pH

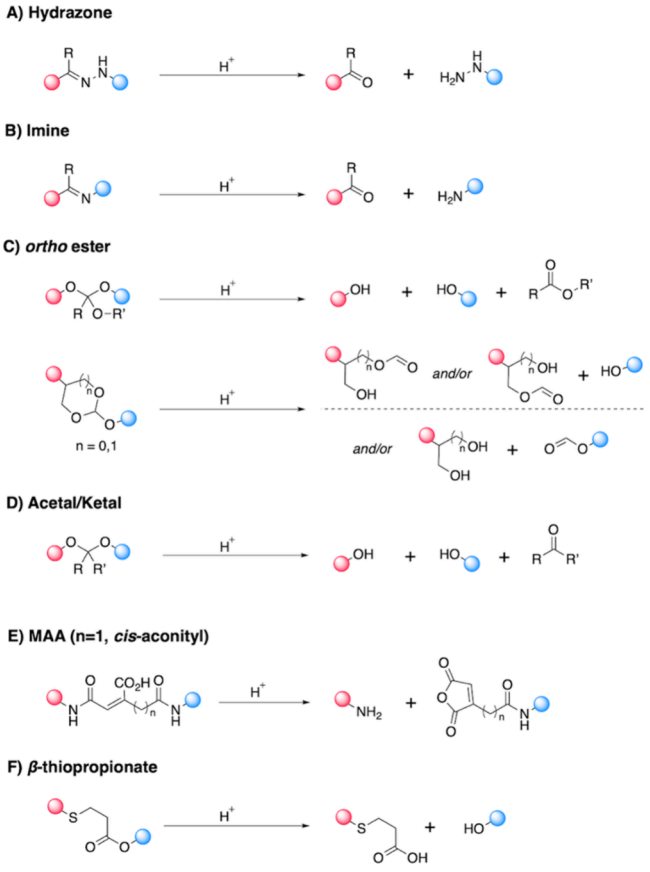

Figure 19. General examples of pH-responsive linkages and their corresponding hydrolyzed products. Adapted with permission from ref. 241. Copyright 2019, Wiley-VCH.

cleavable linker, it is important to consider the stability in physiological conditions (pH 7.4) as many linkers will have partial cleavage even at this pH. The rate of cleavage can often be tuned by modifying the substituents on the linkers.[261] Stability needs to be investigated not only *in vitro* but also *in vivo* as biological molecules can impact the stability of responsive linkages.[261] The hydrazone linkage is one of the most commonly used linkers in drug delivery. It has been applied to a range of backbones to attach drugs such as DOX. Thurecht and co-workers used this linkage to conjugate DOX to hyperbranched nanoparticles, showing an 80% release at pH 5.0 compared to less than 10% at pH 7.4.[241,262] Such linkages have also been used to design releasable PEG coatings.

Maleic acid derivatives including *cis*-aconityls and 2-propionic-3-methylmaleic anhydride (CDM) are also important pH cleavage linkages. 2,3-Dimethylmaleic amide has been extensively used to induce charge reversal in materials by fragmentation to positively charged amines from negatively charged carboxylate.[257,263] Interestingly, work has centered around this member of the maleic acid family, possibly as the hydrolysis rate was shown to be faster than those for other variants.[264] Acid-responsive linkages can also be used as protecting groups to release functional groups at lower pH values, thus changing the solubility or function. Frechet and co-workers demonstrated the use of acetal-modified dextran particles to release a range of cargos via the hydrolysis of the acetal groups that results in the polymer's transition from hydrophobic to hydrophilic, thus inducing particle disassembly and cargo release. The disassembly rate could be tuned by the use of cyclic vs acyclic acetals.[265,266] Many other functionalities can be used as pendants to induce a change in particle properties to cause disassembly or drug release. Tetrahydropyran esters are more prone to hydrolysis than ordinary acetals and can be used as carboxylate protecting groups that release carboxylic acid at a lower pH, a higher temperature, or exposure to ultrasonication.[267,268] Vinyl ethers are also sensitive and degradable under acidic conditions.[269−271] pH-responsive linkages can also be incorporated into the backbone of polymers to tune the properties of nanoparticles such as toxicity or drug release. In one study *ortho*-esters were incorporated into low-molecular weight PEI and demonstrated lower toxicity in a number of cell lines, yet demonstrated higher transfection efficiency.[272]

Boronic acids bind to vicinal diols and form a reversible boronate complex that is more stable at higher pH values while less stable at lower pH values, thus allowing pH-triggered association/dissociation of nanoparticle components. For example, Kang and Liu et al. designed "immunomodulating nanoparticles" with encapsulated bovine serum albumin (BSA) modified with boronic acid functionality and IgG. This core was coated with zwitterionic shell polymers which were linked with dynamic pH-responsive boronate bonds between boronic acid and the glucose pendants.[273] In the tumor environment, the shell dissociated and the boronic acid surface containing the IgG was free to bind to the surface of tumor cells via the stronger boronate recognition of the sialic acid overexpressed on the surface of tumor cells. This led to a modification of the tumor surface with the IgG, thus providing immune-activating signals at the tumor site.

3.9.2. Redox. Similar to pH, redox environment is a stimulus that has been widely studied in the design of stimuli-responsive nanoparticles for drug delivery. Specifically, endogenous redox environments vary across different drug target sites, often involving either the overproduction of ROS, which results in an oxidizing environment, or the presence of excess glutathione (GSH), which results in a reducing environment. Polymers that utilize this variation in redox environment normally bring about nanoparticle morphological changes or bond cleavage, yielding either clearance of a particular biological barrier or targeted drug delivery.

The concentration of GSH varies in the range of 2−100 μM in the blood, and 1−10 mM in the cytosol.[274] Disulfide functionality is reducible through cellular thiols like GSH and

https://doi.org/10.1021/acs.chemrev.3c00705
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cysteine, and is widely employed as a linker for drug−polymer conjugation and even as the backbone of degradable polymers (Figure 20).[274,275] When combined with self-immolative chemistry, the disulfide linkage allows traceless release with GSH.[275] It should be noted that if the disulfide bond links two macromolecules, it is susceptible to ultrasonic (US) forces to allow US-triggered release.[276] Trisulfides or polysulfides that a have higher number of continuous sulfur atoms are also responsive to GSH reduction and release hydrogen sulfide (H_2S) that also regulates cancer cell growth. As a result, polysulfide bonds can not only be utilized as a GSH-responsive linkage, but also themselves can act as a drug moiety to release small-molecule anti-cancer drug H_2S.[277−279] These disulfide containing polymers will be discussed in detail in Section 3.9.6.

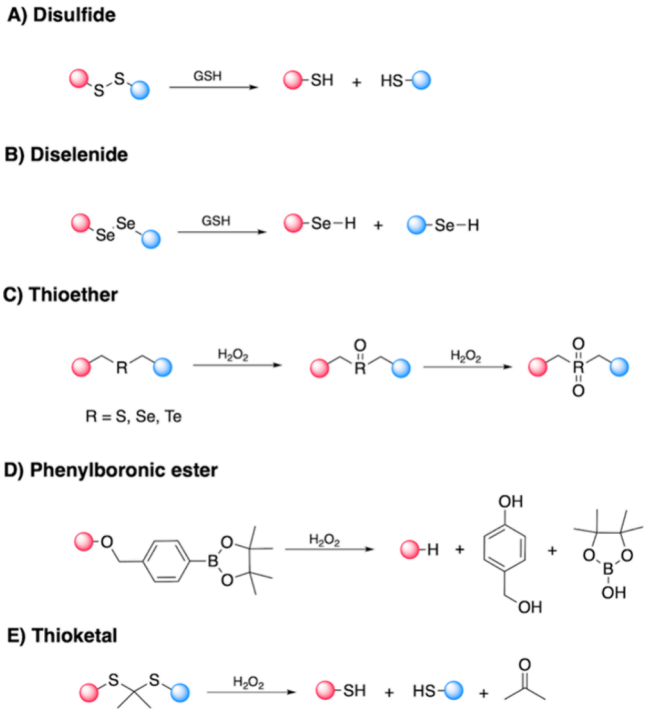

Figure 20. Common examples of redox-responsive linkers and their degradable products.

Polythioethers are polymers that contain sulfide/thioether bonds within either their backbone or as pendant groups. These bonds can be oxidized through exposure to endogenous oxidants such as hydrogen peroxide (H_2O_2). Oxidation results in the hydrophobic sulfide bonds transitioning into hydrophilic sulfoxides, resulting in the whole polymer's solubility shifting.[280,281] The sulfide bonds can be incorporated into the backbone, for example in poly(propylene sulfide),[282] or as pendant groups on various platforms such as polyacrylamides,[283] polyphosphoesters,[284] and certain peptides (cysteine and methionine).[285] These polythioethers can act as reactive oxygen species (ROS) scavengers,[282,286−288] and as moieties to enhance therapeutic delivery by responsively altering nanoparticle solubility and morphology.[283,285,289] Similarly, selenoethers have similar oxidative potential, as they form water soluble selenoxides when exposed to H_2O_2. This process, unlike sulfide-based polymers, is reversible under physiological conditions. For instance, selenoxide can be reduced back to selenoether under mild reducing conditions or in the presence of endogenous reducing agents such as vitamin C.[290,291] Tellurium has lower electronegativity than selenium, making it even more sensitive to oxidants than selenide. The oxidative properties of tellurium^{II}-containing polymers are less well studied, but still a promising method to design redox-responsive nanoparticles, particularly for cancer therapy (Figure 20).[292−294]

In addition to a redox-induced solubility transition, a variety of functional groups can be cleaved either by cellular H_2O_2 or other biological ROS.[295] Boronates, specifically the phenylboronic acid pinacol ester moiety, are well known for their ROS-responsiveness, while at the same time being responsive to changes in pH. These boronate moieties can be oxidized by cellular ROS such as H_2O_2 to form borate esters. As an electron receptor, boronate also forms complexes with amine-containing moieties, and hence can be employed to form ROS-responsive drug−polymer conjugates, facilitating targeted and highly efficient drug release.[296,297] Thioketal-based polymers are also responsive to ROS and can be integrated with self-immolative chemistry to allow the release of the drug without any remnants of the parent conjugate—a process known as traceless release (Figure 20).[298,299]

3.9.3. Enzymes. Certain polymers can be engineered to make use of intracellular enzymatic environments to achieve precise and controlled drug release via moieties that can cleave or degrade in the presence of certain enzymes (Figure 21).

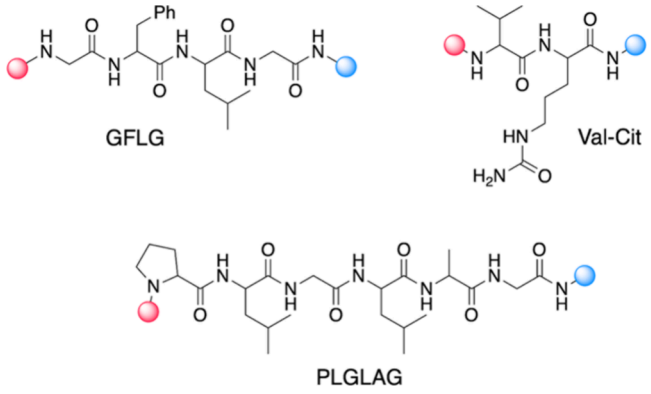

Figure 21. Common examples of enzyme-responsive linkages used in the design of enzyme-responsive polymers for drug delivery.

Enzymatic responsiveness is also a useful strategy to reduce toxicity by minimizing off-target effects.[300−302] Enzymes can be used to cleave linkers, release therapeutic cargo, or to unmask functional groups, yielding a change in polymer properties such as solubility or electrostatic charge. Membrane γ-glutamyl transpeptidase (GGT) and aminopeptidase N (APN) are two enzymes that are overexpressed in tumors, and hence can be utilized to design enzyme-responsive polymeric nanoparticles with targeted drug-delivery performance. Specifically, GGT and APN catalyze the hydrolysis of glutamine containing polymers.[303,304] Another family of enzymes that are overexpressed in tumors are cathepsins, toward which the tetra-peptide GFLG (Gly-Phe-Leu-Gly) is responsive. Polymers that utilize this tetra-peptide have been used to form polymeric nanoparticles that are responsive to cathepsin B.[305] Matrix metalloproteinases (MMPs) are another enzyme family associated with the growth and progression of cancer, which is overexpressed in the tumor microenvironment. Polymers built from polypeptides such as PLGLAG and GPLGIAGQ are

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responsive to MMPs, and hence can be used as building blocks to design MMP-responsive polymeric nanoparticles.[306,307]

3.9.4. Temperature. Polymers that respond to temperature changes are some of the most well studied stimuli-responsive polymers in the field of drug delivery, due to slight temperature variations that exist across endogenous environments. These polymers are known as thermoresponsive polymers. Thermoresponsive polymers can be classified into two main groups: negative temperature-sensitive systems, where polymers exhibit a hydrated state through hydrogen bonds formed when temperatures fall below their lower critical state temperature (LCST); and positive temperature-sensitive polymers, which experience hydration above their upper critical state temperature (UCST) and dehydration below this temperature.[308,309,219] Integrating these polymers into the composition of nanoparticles renders them responsive to temperature fluctuations, leading to remarkable changes in their structure, and ultimately facilitating the controlled release of their therapeutic cargo.

Poly(*N*-isopropyl acrylamide) (PNIPAm) is the most prominent temperature-responsive polymer. Its ability to undergo reversible transitions in response to slight changes in temperature has garnered it substantial attention as a building block for temperature-responsive nanoparticles.[310] This polymer exhibits a LCST behavior. Above 32 °C, water molecules are pushed out of the polymeric network, inducing a contraction due to the dehydration of the isopropyl groups. PNIPAm also displays another important characteristic, whereby its LCST can be modulated through the introduction of surfactants, salts, or by copolymerization with a variety of hydrophilic/hydrophobic moieties. Incorporating hydrophilic segments into the polymer chain can elevate the LCST, while copolymerization with hydrophobic monomers can lower the LCST.[311]

Non-ionic ABA tri-block copolymers such as PEG-*b*-PPO-*b*-PEG and PEG-*b*-PLGA-*b*-PEG, known as poloxamers, are two other widely studied thermoresponsive polymers that are often used to form temperature sensitive cross-linked hydrophilic polymer nanoparticles, known as hydrogels. Upon variations in temperature, these polymers cause the hydrogel to undergo a sol-to-gel or gel-to-sol transition, yielding stimuli-responsive drug release.[312]

3.9.5. Light. Polymers that respond to light irradiation have long been the subject of extensive research, due to the fact that light is a localized and controllable stimulus that rarely requires additional reagents, thus limiting undesirable by-products. Irradiation can result in either reversible or irreversible changes to polymeric properties, which can include the cleavage of conjugated therapeutic cargo or a hydrophobic−hydrophilic transition of polymer segments. Polymeric nanoparticles composed of these polymers can undergo a light-responsive morphological change to enhance the efficiency of drug delivery. Photoresponsive polymers are composed of functional groups that can include *ortho*-nitrobenzyl esters, pyrenylmethyl esters, coumarinyl esters, and *p*-methoxyphenacyl esters (Figure 22).[313]

Most light-responsive polymers require UV irradiation to trigger certain changes in polymer properties. Utilizing polymers that employ this higher energy irradiation presents safety challenges for the biomedical industry, as UV light can damage healthy cells depending on how it is applied, as well as having limited penetration through tissue.[314] This low penetration depth (~10 mm) is mainly due to the strong

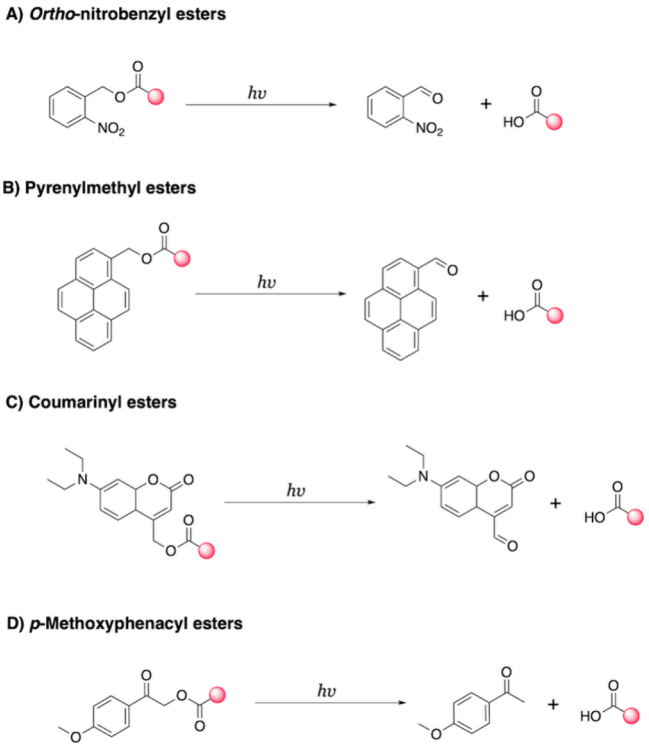

Figure 22. Common examples of light-responsive functional groups used in the design of photo-responsive polymers.

UV−vis scattering properties of soft tissue.[315] Thus, recent research has focused on developing polymers that are responsive to near-infrared (NIR) light, as the longer wavelengths do not cause tissue damage and have higher tissue penetration. In an important study, Yan et al. modified an *ortho*-nitrophenyl functionalized block copolymer with inorganic particles that were able to upconvert external IR light (980 nm) to UV light, yielding photocleavage and light-induced drug release in a micellular system.[316]

3.9.6. Self-Immolative Polymers. More recently, polymers with prompt and on-demand degradability have been explored as building blocks for polymeric nanoparticles. Self-immolative polymers (SIPs) are a class of synthetic macromolecules with a unique depolymerization mechanism in which one reaction, normally triggered by a specific stimulus, spontaneously causes the whole polymer chain to disassemble (immolate) through repeated bond cleavage.[317] The immolation of these polymers can be tailored to occur in response to a specific stimulus by cleavage of a responsive end-cap to start the self-immolation process. Previous work has demonstrated the potential of these materials to respond to pH, redox and light.[259,318−320] The self-immolation of polymer chains is stepwise, and analogous to the domino effect. Three classes of SIPs have been studied as drug-delivery vehicles, including quinone methide (QM)-based SIPs, poly(glyoxylates) including poly(ethyl glyoxylate) (PEtG) and poly(glyoxylamide) (PGAm), and poly(disulfide)-based SIPs (Figure 23).

Quinone methide (QM)-based self-immolative linkages are capable of triggering disassembly of polymer chains from head to tail (Figure 23A).[317,321] These polymers comprise repeating QM-based units either within their backbone or grafted to spacers, and can undergo a self-immolative cascade reaction, such as cyclization and CO_2 elimination.[322] The synthesis of these polymers is not straightforward, requiring a multi-step

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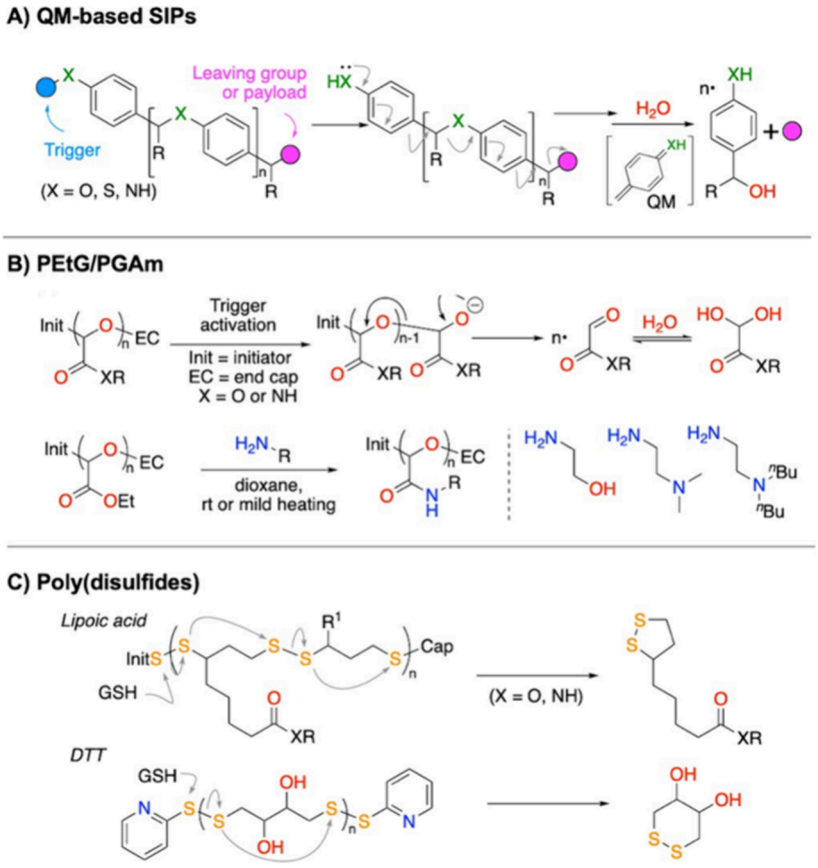

Figure 23. General examples of self-immolative polymers and their depolymerization mechanisms: (A) QM-based SIPs, with only 1,6-elimination, (B) PEtG/PGAMs, and (C) poly(disulfides).

preparation of the monomers. Furthermore, their water-solubility is relatively hard to tailor, and the QM byproducts can also be toxic.[323] Nevertheless, some studies have utilized QM based polymers to design drug-delivery vectors that self-immolate via redox, light, and UV stimuli.[324]

SIPs based on poly(glyoxylate) have been studied in depth by Elizabeth Gillies' group, who first reported this new class of SIP (Figure 23B). This group demonstrated poly(ethyl glyoxylate) (PEtG) could be functionalized with a variety of end-caps that were responsive to stimuli including pH, light, ROS, as well as GSH, and were able to undergo head-to-tail depolymerization.[319,325,326] These polymers can be used as building blocks to form nanoparticles that undergo stimuli-responsive self-immolation, promising to enhance the targeting potential and efficiency of drug delivery. Furthermore, the byproducts of the immolated PEtG polymers are non-toxic glyoxylate esters, which further degrade to alcohol and glyoxylic acid in endogenous conditions.[327−329] Polyglyoxylamides (PGAms) are self-immolative polymers whereby the pendant ethyl ester in PEtG is substituted with an amine moiety (Figure 23B). PGAms also undergo end-to-end depolymerization, but the added amine functionality can be used to tune the rate of depolymerization, as well as other important polymer properties such as solubility. PGAm can be combined with PEG to form self-assembled nanoparticles that can undergo tunable disassembly in acidic conditions, potentially through two mechanisms, i.e., depolymerization and solubilization of polymers. Interestingly, recent work showed these systems had limited endosomal escape compared to other charge-shifting nanoparticles suggesting depolymerization might impact effective membrane interactions.[330] The introduction of certain end-caps can also introduce stimuli-responsive self-immolation to PGAms; some of the stimuli include pH, temperature, and redox environment.[331,332] These nanoparticles showed potential for successful nucleic delivery, which is possibly enhanced by the ability to release cargo as a result of the polymer depolymerization.[333]

Poly(disulfides) are redox-responsive polymers that can undergo rapid and complete self-immolation in biological reducing environments such as the cytosol, which contains significant levels of GSH, an endogenous reducing agent. Poly(lipoic acid) (PLp) and its derivatives can depolymerize (self-immolate) via its backbone, where thiol-induced chain scission takes place (Figure 23C).[334] The polymers from other cyclic disulfides like asparagusic acid derivatives can self-immolate in a similar way.[335] The polymerization of 6-membered cyclic disulfide has not been reported; however, the corresponding polymer was achieved via a different approach, i.e., through solid-state oxidative polymerization of dithiothreitol (DTT).[336] The controlled polymerization method for lipoic acid esters is thiolate-initiated anionic ROP or thiol-initiated ROP of aggregated amphiphilic lipoic acid esters/amides in water at room temperature, reported by research from Moore and Lu co-workers, respectively.[337,338] The thiolate-free polymerization of lipoic acid derivatives can be triggered by various factors, including high temperature,[339−341] light,[342] acid,[343] and thiol initiators when the monomers are at a high concentration, either achieved by aggregation of amphiphilic monomers in water[338] or low-temperature-induced phase separation (also termed cryopolymerization).[344]

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Cell-penetrating poly(disulfides) are based on lipoic acid or related molecules with a 1,2-dithiolane structure (e.g., asparagus acid). They are of interest as they have low cytotoxicity and can undergo complete degradability after delivery.[335,345−347] These poly(disulfides) have found use as components of polymeric nanoparticles for drug delivery when coupled with other polymers, as well as oligonucleotides,[348] miRNA,[349] small-molecule drugs like DOX,[350] and proteins.[351]

4. NANOPARTICLE PREPARATION METHODS

Polymeric nanoparticles are colloidally stable nanometer structures formed through the self-assembly of their component polymers. This process can be achieved through a wide array of techniques, each suited to the variable chemistry of the polymers, and yielding specific and controllable nanoparticle properties. These properties include shape, size, concentration, functionality, stability, and drug-loading efficiency. The following section outlines the various nanoparticle preparation methods and how they impact specific nanoparticle parameters, before evaluating the general strengths and weaknesses of each technique, which we have summarized in Table 1. Sections 5 and 6 discuss more specific particle design challenges concerning spherical nanoparticles and non-spherical nanoparticles, respectively.

4.1. Self-Assembly

The spontaneous ordering of disparate polymer chains into a highly controlled suspension of particles is known as self-assembly, and is by far the most common process for creating polymeric nanoparticles. It is a complex balance between the internal energy (enthalpy) of the system, which involves covalent and supramolecular attractive and repulsive forces such as electrostatic interactions, hydrogen bonding, and van der Waals forces, and the entropy of the system.[352] At first, it appears that self-assembly is entropically disfavored, as the rotational, translational, and vibrational degrees of freedom of the polymer chains are massively reduced when confined in a nanoparticle.[353] However, using the self-assembly of amphiphilic polymers in an aqueous environment as an example, the water molecules at the interface between the hydrophobic polymer and the bulk solution are forced into a unique, well-ordered state. These water molecules have significantly fewer degrees of freedom than the water molecules that comprise the bulk, and represent a low-entropy system.[354] Thus, the minimization of these surface interactions, via the formation of nanoparticles, is an entropically favorable process. This is a simplification of what is known as the hydrophobic effect. The mechanisms that govern the entropy of nanoparticle self-assembly are highly complex, and understanding them remains an active area of research.[355] The hydrophobic effect is a dominating contribution to the spontaneous self-assembly of amphiphilic polymers into nanoparticles. In 1995, Eisenberg et al. utilized the concept of a packing parameter to predict how amphiphilic block copolymers with varying block lengths would self-assemble into different nanoparticle morphologies.[356] In simple terms, the packing parameter (p) can be defined by the following equation:

$$p = \frac{v}{al}$$

Where l and v are effectively the hydrophobic block length and volume, respectively, and a is the cross-sectional area of the hydrophilic block. Generally, if $p < 1/3$, spherical micelles are favored, if $1/3 \leq p \leq 1/2$, cylindrical particles are favored, and if $p > 1/2$, vesicles (polymersomes) are favored (Figure 24).[357] Increasingly diverse polymer architectures, as well as the incorporation of functional chemistry, have allowed for the development of more complex nanoparticle designs well beyond amphiphilic block copolymer self-assembly.[358] It is important to note that this packing parameter equation is a simplified model, and the reality of polymer self-assembly is complex. A polymer's concentration, MW, and chemical functionality all dictate the process of self-assembly, as does the temperature and conductivity of the environment. The nature of the solvent itself, as well as the presence of any other additives, also plays a large role in self-assembly.[359]

Table 1. A Summary of the Advantages and Disadvantages of Each Nanoparticle Preparation Technique

Technique	Advantages	Disadvantages
Nanoprecipitation	Simple	Reduced particle stability
	Scalable	Reduced drug loading efficiency
	Wide variety of particle architecture	Drug leakage
Dialysis	Simple	Time consuming
	Forms pH-responsive nanoparticles	High solvent volume
		Unfeasible scalability
Emulsion techniques	Robust	High solvent volume
	Scalable	Can include chlorinated solvents
	Well-studied	
	Reproducible	
Emulsion polymerization	Robust	Harsh reaction conditions
	Scalable	High polymer dispersity
	Reproducible	Employs hydrophobic monomers
	High solids content	Limited biological cargo loading
Ionic gelation	Simple	Requires purification
	Cost effective	Lack of size and dispersity control
	Encapsulates charged cargo (DNA)	
PISA	One pot and efficient	Requires careful choice of monomers and solvents
	High particle concentration/solids content	Expensive
	Exotic morphology	
Spray drying	Scalable	Mechanical machinery
	Robust and reproducible	Particles > 1000 nm
	Rapid particle production	Harsh reaction conditions
		Multistep
Templated assembly	Tunable	Complex and multistep
	Robust	Requires careful reactant choice
	Forms hybrid nanoparticles	Expensive
	Utilizes a diverse array of building blocks	

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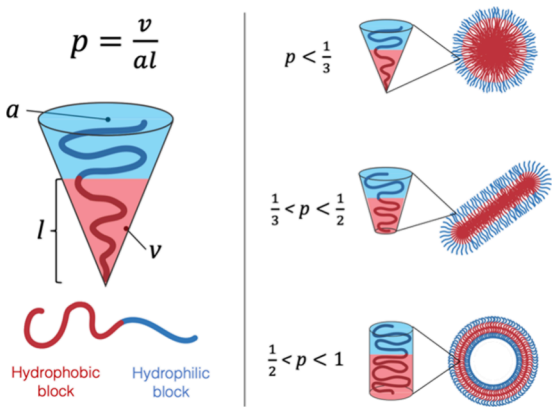

Figure 24. The packing parameter, p, is a concept that predicts the morphology of nanoparticles based on amphiphilic block copolymers. The various different morphologies of nanoparticles for different ranges of p are shown above, where p is proportional to the volume of the hydrophobic component, v, and inversely proportional to its length, l, and the cross-sectional area of the hydrophilic component, a.

4.2. Nanoprecipitation

Nanoprecipitation, also known as solvent displacement or desolvation, is a simple and commonly used method for preparing nanoparticles of different morphologies and functionalities. Nanoprecipitation relies on pre-made polymers self-assembling into nanoparticles. These polymers are dissolved in a miscible organic solvent and slowly added into an aqueous environment. Due to the fast displacement of the miscible organic solvent, the polymers self-assemble immediately via the hydrophobic effect, forming nanoparticles characterized by a well-defined size and narrow distribution (Figure 25).[360] Surfactants or amphiphilic copolymers can be

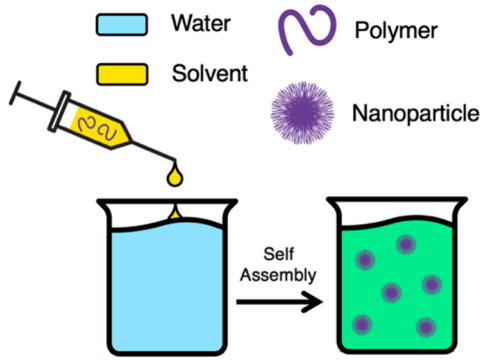

Figure 25. A schematic illustration of nanoprecipitation. Polymers are dissolved in a miscible solvent, which is then added to water. The polymers, which are insoluble in an aqueous environment, self-assemble into nanoparticles as the solvent dissolves into the water.

included in either the organic or aqueous phase to stabilize the nanoparticles. Subsequent purification techniques such as dialysis are required to completely remove miscible organic solvent and free polymer building blocks, from the resulting nanoparticle dispersion. Nanoprecipitation is one of the most widely used particle synthesis techniques, particularly in the pharmaceutical industry, due to its speed, its simplicity, and its capacity to form a wide variety of architectures including core–shell nanoparticles and polymersomes.[361] Challenges still remain, however, regarding particle stability and loading drugs into nanoparticles at high efficiencies without potential cargo leakage. The size, shape, surface charge, and dispersity of particles created via nanoprecipitation are highly dependent on a number of factors, including the nature of the organic solvent, the amount of organic solvent relative to the aqueous phase, the ionic strength and temperature of the environment, the nature and properties of the polymers, the relative concentration of the polymers, the presence of any other additives such as surfactants or drugs, and even the way in which the two phases are mixed.[362] Flash nanoprecipitation makes use of vortex mixing or high velocity opposing jets to generate turbulent flow in a confined volume, yielding diffusion rates faster than the growth rate of particles and locally supersaturated areas of insoluble material. This results in the sudden precipitation and formation of particles, hence the use of the word "flash". Flash nanoprecipitation generally results in both superior reproducibility, and a greater degree of control over particle size and distribution. This method also enhances the loading efficiency of hydrophobic drugs, due to local supersaturation.[361] A more recently developed variant of nanoprecipitation involves mixing via molecular diffusion in a laminar flow environment. This technique is known as microfluidic nanoprecipitation, and allows for precise tailoring of nanoparticle properties such as size and shape through controlling the flow rate. Microfluidic nanoprecipitation also occurs at a small volume, which is advantageous for loading more expensive drugs.[363]

4.3. Dialysis

Dialysis is a simple and effective method to prepare polymer nanoparticles that, like nanoprecipitation, relies on solvent displacement. Unlike nanoprecipitation, however, where the solvent is displaced immediately, dialysis removes solvent gradually. In general, the polymers are dissolved in an organic solvent and added to a dialysis membrane with pore sizes appropriate to the MW of the polymer. The membrane is then added to an aqueous solution such that only the organic solvent is slowly removed from the membrane via diffusion. This gradual transition to an aqueous environment causes the polymers to self-assemble into nanoparticles.[364] Dialysis is a robust technique and can also be used to form pH-responsive nanoparticles by exploiting a slow change, not in the solvent environment, but the pH environment, for example, slowly increasing the pH of the environment from acidic to basic conditions (e.g., moving from low to high pH).[81,365]

4.4. Emulsion-Based Self-Assembly

An emulsion is a blend of two or more immiscible liquids, where one liquid is present in the mixture as tiny droplets dispersed continuously throughout the other. The term "emulsion" encompasses a wide variety of similar techniques that, taken together, represent the most common, well-studied, and widely applicable method for forming nanoparticles. In general, nanoparticles are formed via an oil-in-water (o/w) emulsion. The polymer is dissolved in an organic solvent that constitutes the oil phase, and is then added to an aqueous phase that can contain a stabilizer. Shear force is applied via vigorous stirring, homogenization, or sonication to form an emulsion of organic droplets dispersed in the aqueous phase. As the organic solvent evaporates, the dissolved polymers in the oil phase self-assemble to avoid the water molecules in the aqueous phase (Figure 26).[366] This process is known as solvent evaporation. Sometimes a partially miscible organic solvent is used as the organic phase, rather than one that is immiscible. Subsequent dilution of the aqueous phase induces

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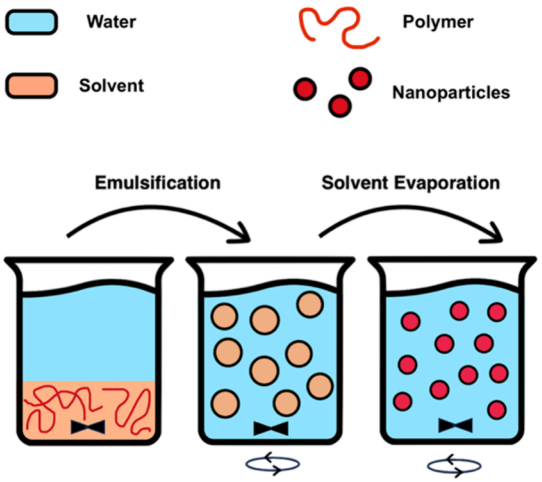

Figure 26. A schematic illustration of the solvent evaporation technique. Polymers are dissolved in a miscible solvent that is then emulsified in water. As the solvent evaporates, the polymers self-assemble into nanoparticles.

the solvent to disperse from the droplets, leaving behind only an aqueous nanoparticle dispersion. This technique is known as solvent diffusion, and requires higher volumes of water.[367] Certain miscible solvents such as acetone or ethanol can form an emulsion in water when the aqueous phase (either a liquid or a gel) contains a salting out agent and surfactant, which serves to stabilize the emulsion. Once the aqueous phase is sufficiently diluted, the effect of the salting out agent is minimized, allowing the dispersion of the solvent and formation of nanoparticles. This technique is referred to as the salting-out method.[368] Emulsion techniques are most widely used for the formation of micelles.

4.5. Emulsion Polymerization

Unlike emulsion-based self-assembly, which requires pre-formed polymers, emulsion polymerization involves the preparation of nanoparticles based on the polymerization of monomers. In an o/w emulsion, a hydrophobic monomer forms emulsified oil droplets, while stabilizers form micelles in the aqueous phase. The monomer transports through the aqueous phase to the micelles and, in the presence of an initiator, polymerizes within the micelles to form a nanoparticle (Figure 27).[367] Drug-delivery nanoparticles can be prepared by conventional emulsion polymerization, as well as more exotic forms of the technique. Pickering emulsions, for example, yield nanoparticles with generally superior stability and low toxicity by using inorganic particles as stabilizers.[369] Interfacial polymerization is used to create drug-containing nanocapsules through the polymerization of monomers only on the interface between the monomer droplets and the aqueous phase.[366] Emulsion polymerization is a highly industrially applicable technique, as it is able to be scaled up easily due to the fact that it is a very well understood technique, and the underlying infrastructure already exists. Furthermore, emulsion polymerization yields highly consistent nanoparticle properties in comparison to other techniques, particularly in regard to batch-to-batch reproducibility, as well as highly controlled particle size and dispersity. Emulsion polymerization, however, generally does not yield highly sophisticated polymeric nanoparticle designs. The necessary reaction conditions limit, to a large extent, both the incorporation of sensitive therapeutic cargo such as nucleic acids, as well as highly functional chemical moieties and monomers.

4.6. Ion Gelation/Sol–Gel Method

Ionic gelation, also known as ionotropic gelation, is a simple and cost-effective method to synthesize nanoparticles via electrostatic cross-linking.[370] Ionic gelation involves the combination of a polyelectrolyte with either a suitable counter ion or counterionic macromolecule in an aqueous medium. The electrostatic attraction between the two polyions results in a highly cross-linked polyelectrolyte complex (nanoparticle) and the formation of a nanoparticle gel. The nanoparticles are

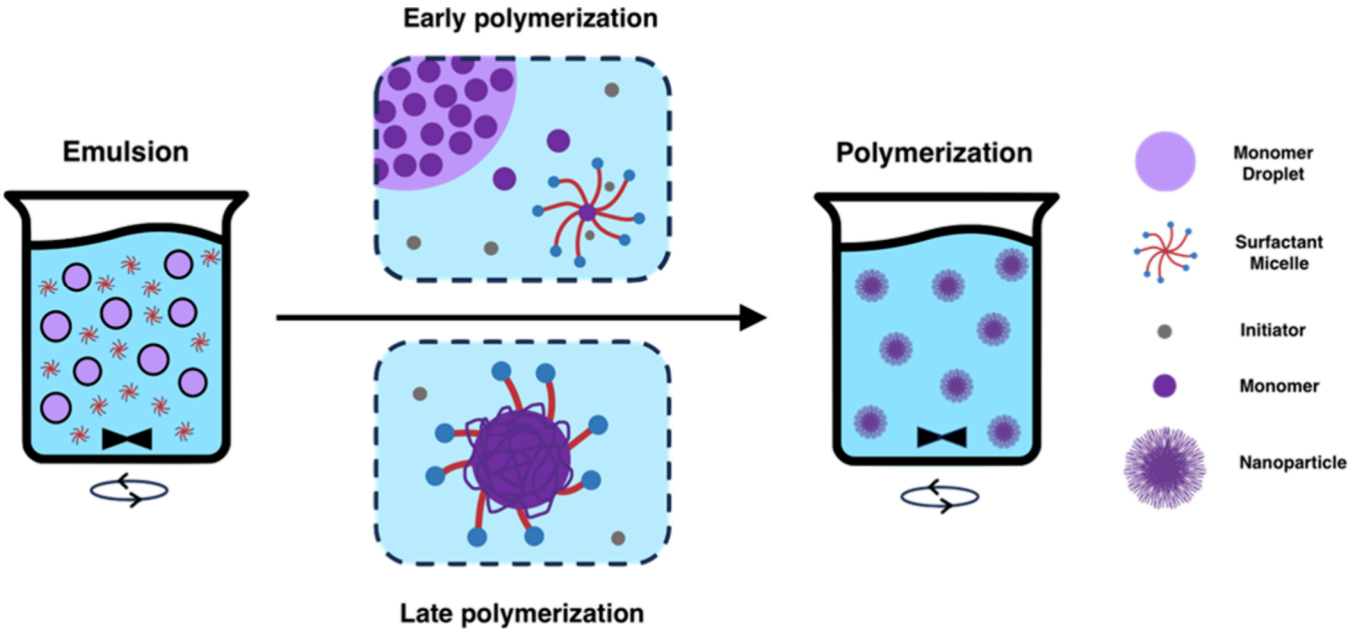

Figure 27. A schematic illustration of emulsion polymerization. The monomer is added in the form of a droplet to a solution containing surfactant micelles. As monomers migrate from the droplets to the micelles, polymerization occurs in the micelles, forming larger polymeric nanoparticles.

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then purified and isolated by centrifugation. Ionic gelation is a common technique to form nanoparticles based on biodegradable polymers. Chitosan, for example, exists as polycations in an acidic aqueous environment, and will form spherical nanoparticles when mixed with a solution of anionic phosphate polymers.[371] Alginate, on the other hand, is an anionic polymer due to its negatively charged carboxylate groups. Ionic gelation is commonly used to form chitosan-alginate nanoparticles due to the electrostatic attraction between the cationic chitosan and anionic alginate.[372] Such a nanoparticle assembled from electrostatic interactions is known as a polyion complex. Dextran, glycerol, and poly(lysine) are other polymers commonly employed to form polyion complexes with chitosan via ionic gelation.[373] Chitosan alone can be used to form polyion nanoparticles via ionic gelation. Zue et al., for example, employed ionic gelation to assemble an anionic chitosan polymer functionalized with carboxymethyl groups, and a thiolated cationic chitosan polymer to form a nanoparticle.[374] This polyion nanoparticle was used to load DOX, and underwent morphological changes when exposed to a decrease in pH and a reducing environment. Polyion complexes are also a common strategy to load biological cargo such as nucleic acids through the electrostatic interaction between their negatively charged backbone with positively charged polymers.

4.7. Polymerization-Induced Self-Assembly

Polymerization-induced self-assembly (PISA) combines both the synthesis of polymers and their subsequent self-assembly into a simplified one-pot strategy. This streamlined strategy yields significant cost and scalability advantages over other two-step techniques, and allows for high polymer concentrations of up to 50 wt %.[375] PISA is a form of dispersion polymerization, where solvophilic monomer and a solvophilic precursor/stabilizer are mixed in a continuous phase of either water or organic solvent. The polymerization of monomer over time leads to the formation of a solvophobic block that induces phase separation, and the self-assembly of nanoparticles (Figure 28). As the degree of polymerization increases, the solvophobic block occupies a larger volume relative to the solvophilic block, resulting in a higher packing parameter, p. This in turn leads to the formation of spherical nanoparticles, followed by rods and other exotic morphologies such as toroids and worms, and ultimately vesicles/polymersomes.[376] PISA employs various controlled polymerization techniques, but most often utilizes RAFT, due to its mild reaction conditions and wide set of applicable monomers.[377] In this context, a soluble macro-RAFT agent acts as the precursor from which the solvophobic block grows. Though often termed a dispersion polymerization, PISA does allow for the polymerization of insoluble/immiscible monomers, usually through an emulsion polymerization-based strategy.[378] PISA of immiscible monomers can also occur due to chemical modification of the monomers before polymerization. Highly hydrophobic styrene, for example, was polymerized into a polystyrene-PEG block copolymer in an aqueous environment through a PISA strategy that utilized styrene-cyclodextrin host−guest complexes.[379]

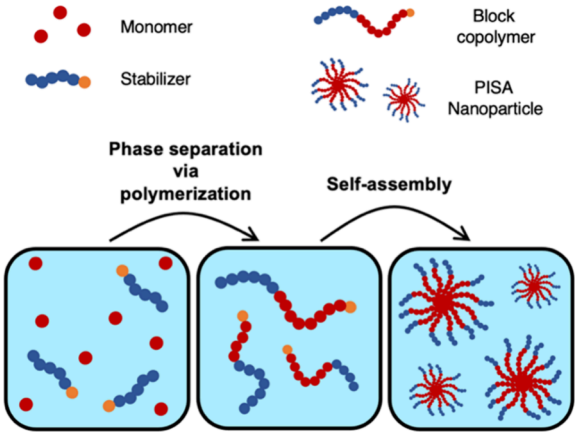

Figure 28. A schematic illustration of polymerization-induced self-assembly (PISA). Two processes, polymerization and self-assembly, are combined into one step. As the monomers polymerize, they self-assemble at the same time, forming a suspension of nanoparticles.

4.8. Spray Drying

Unlike other nanoparticle formation methods, which rely on physicochemical changes to induce nanoparticle formation, spray drying is a mechanical process that converts a fluid into a fine powder through atomization. The fluid in question is generally either an emulsion or a suspension of nanoparticles in a liquid (most often water). This liquid is first atomized into tiny droplets (spray). The droplets are then passed through a hot gas (most often air) to evaporate the liquid and form dry particles, which are then separated from the gas and collected (Figure 29).[380] Spray drying is an industrial technique commonly used in the cosmetics, food and pharmaceutical industry, and produces particles on the micrometer scale. Nano-spray drying, a relatively recent technique, allows for the synthesis of sub-micron nanoparticles, which are most often favored for drug-delivery applications. Such small nanoparticles (less than 200 nm) are achieved via enhancements to the atomization process, which yields smaller nanometer droplets, and an electrostatic particle collector.[381] Generally, protein nanoparticles and nanoparticles based on polymers such as alginate, cyclodextrin, and chitosan are prepared via nano-spray drying. Spray drying and nano-spray drying are almost always used in the preparation of nanoparticles for oral delivery and respiratory delivery via inhalation.

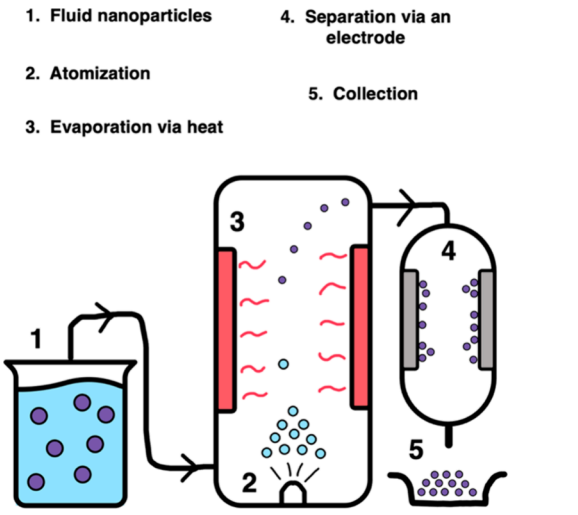

Figure 29. A schematic illustration of spray drying. A fluid containing nanoparticles is atomized into droplets. When these droplets are passed through heat, the rapid evaporation of the solvent forms nanoparticles, which are then separated and collected.

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There are a number of advantages associated with spray drying as a nanoparticle formulation technique, including its scalability, its speed, its batch-to-batch reproducibility, and its narrow particle dispersity.[382] Furthermore, spray drying is a continuous process that generally avoids the freeze drying and cooling steps associated with other pharmaceutical preparation methods.[383] As previously alluded to, however, spray drying is most commonly used for the synthesis of microparticles, not nanoparticles. Spray drying also involves atomization and elevated temperatures, which constitute harsh conditions for certain thermally sensitive material. Moreover, on smaller laboratory scales, particle yield actually decreases, as a greater fraction of particles relative to the total feed volume is lost during the drying stage.[384] Finally, spray drying is generally not suited to the synthesis of functionally sophisticated polymeric nanoparticle designs that involve either active drug loading or stimuli-responsive behavior.

4.9. Templated Assembly

Another important method to design polymeric nanoparticles is the use of templated assembly. This technique involves the use of a template as the base, which can then be coated with polymeric components (Figure 30). The principal advantage of templated assembly is that the size and shape of the template can be readily tuned, and thus so can the properties of the nanoparticle. Templates that are commonly employed include inorganic nanoparticles such as silica or gold. Recently, however, more diverse models such as cells have been used as templates in the design of polymeric nanoparticles.[385] A well-known templated assembly method is layer-by-layer (LbL) assembly. This method relies on the sequential addition of components based on complementary interactions such as electrostatic attraction, hydrogen bonding or highly efficient covalent reactions. One advantage of LbL assembly is that, depending on the choice of template, polymeric capsules can be prepared based on the use of degradable templates such as pH-responsive calcium carbonate capsules, to name one example.[386] In addition, the characteristics of a multi-layer structure mean that the properties of the polymer coating, including its charge, hydrophilicity and functionality, can be easily tuned. Recently, a LbL capsule was designed incorporating fibrinogen that could bind to platelets. These hybridized platelets remained dormant in the blood until a vascular injury, where they bound to the fibrin network causing contraction and subsequent rupture of the polymer capsule, releasing the pro-clotting drug biotherapeutic factor VIII. Templated assembly can also be achieved through the use of specific molds with specific shapes and sizes. This feature is attractive as it is one of the only straight-forward strategies to design non-spherical particles in a reproducible manner. It can also facilitate straight-forward fundamental studies on the impact of nanoparticle properties by designing libraries of materials with a single property tuned, e.g., size or shape. Particle replication in non-wetting templates (PRINT) is a well-studied preparation technique in this regard[387] and is discussed in more detail in Section 6.1.3.

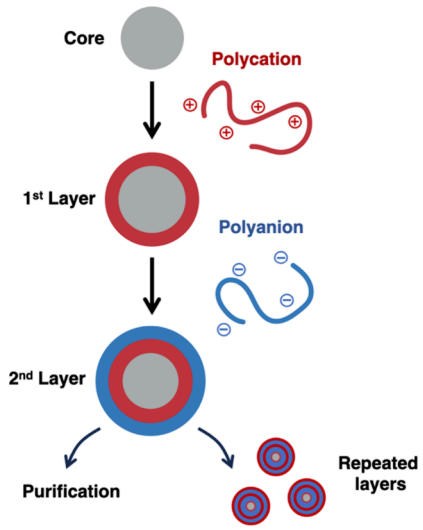

Figure 30. A schematic illustration of layer-by-layer assembly, a form of templated assembly. A core is gradually coated with separate polymeric layers to form a nanoparticle. Other building blocks can also be included such as inorganic nanoaprticles or drugs. In this example, oppositely charged polyelectrolytes form a layered nanoparticle through electrostatic attraction.

Recent work has demonstrated techniques to simplify the coating process using a one-step assembly strategy. One approach to synthesize polymer coatings in one-step involves the polymerization of polydopamine (PDA). PDA coatings have the advantage of being reactive to a range of functional groups such as amines and thiols, thus allowing post modification for drug loading or PEGylation.[388] Another important one-step assembly approach was reported by Caruso and co-workers in 2013: it involved the formation of polymer coatings by the use of tannic acid, a ubiquitous natural phenol and Fe^{3+}.[389] Later work showed these films could be tuned by using different metals[390] or polyphenols and could be engineered to have stimuli-responsive properties.[391]

4.10. Drug Loading and Release

The encapsulation of drugs within nanoparticles is generally a far more advantageous drug-delivery strategy than methods that involve passive accumulation of a free drug. This is not only because nanoparticles can protect drugs from degradation due to the variety of harsh endogenous environments within the body, but also because nanoparticles, via sophisticated functionality, have the potential to achieve targeted drug release and hence yield higher drug performance while minimizing potentially toxic off-target effects. Thus, when designing a polymeric nanoparticle that aims to maximize its drug-delivery efficiency, it is important to examine the strategies used to encapsulate drugs. There are generally two strategies associated with nanoparticle drug loading: passive loading, which can involve the hydrophobic effect or electrostatic attraction, and active loading, which is based on covalent conjugation (Figure 31).

4.10.1. Passive Loading. Passive loading involves entrapping drugs via physical interactions within the nanoparticle. These physical interactions include the hydrophobic effect, which is the tendency of hydrophobic substances to aggregate in an aqueous environment, and is discussed in Section 4.1, or electrostatic interaction, whereby oppositely charged drugs and nanoparticle components attract. The efficiency with which drugs are loaded and subsequently released from polymeric nanoparticles is determined by a variety of factors: the inherent properties of the drug, the characteristics of the polymeric matrix, the method by which the drug is incorporated into the nanoparticles, and the physical attributes of resulting nanoparticles. These all play

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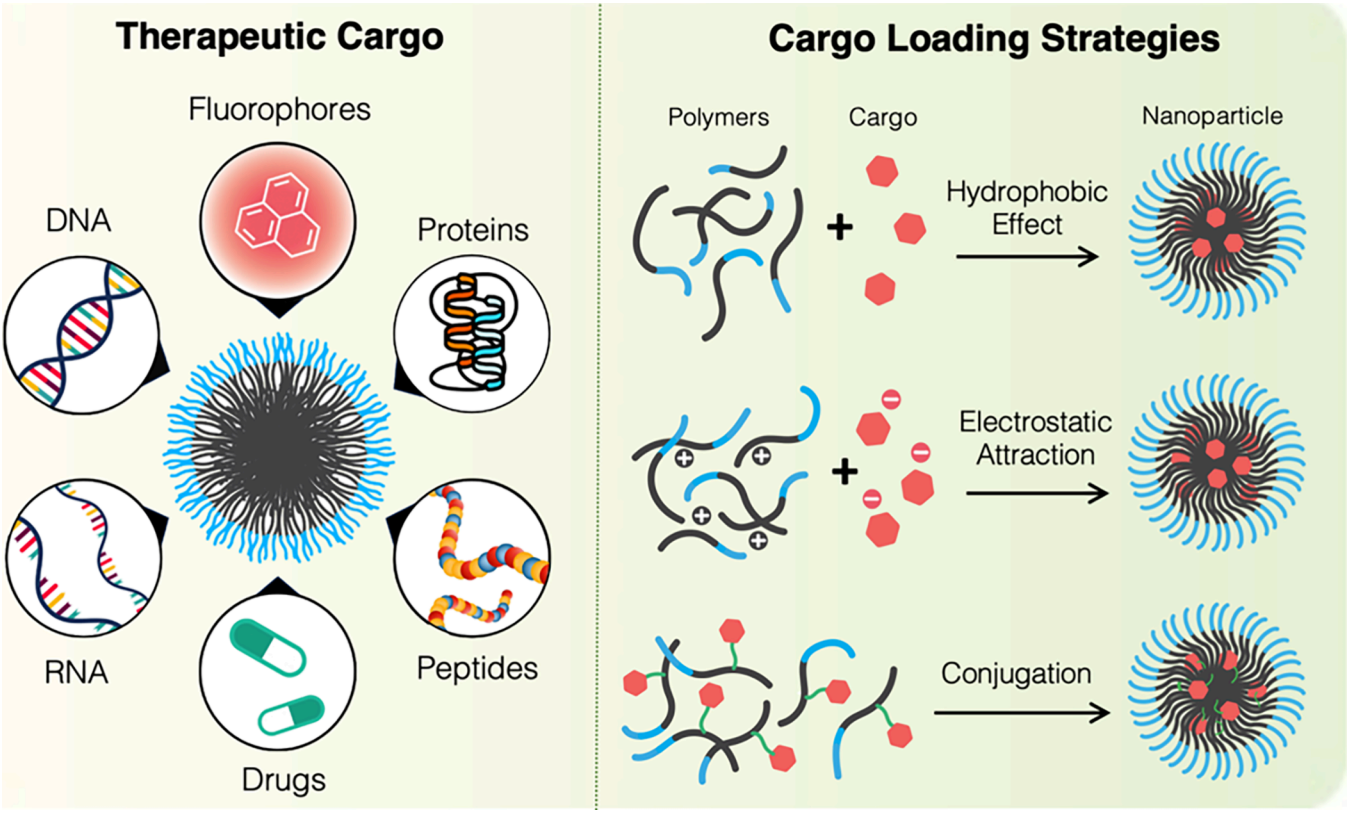

Figure 31. Nanoparticles can encapsulate a range of diverse therapeutic cargo, from small-molecule drugs to large biomacromolecules such as proteins and nucleic acids. These therapeutics can be loaded through physical interactions such as the hydrophobic effect, electrostatic interactions, as well as covalent conjugation.

critical roles in dictating the overall loading capacity and release kinetics. Presently, small-molecule drugs are often loaded into the core of nanoparticles through hydrophobic interactions, resulting in an enhanced solubility and targeting capability, as well as reduced biotoxicity. Consequently, the compatibility between polymers and drugs is crucial for the stability and drug-delivery performance of the resulting nanoparticles. Liu et al. selected Ellipticine as a model drug and used a series of amphiphilic polymers with varying degrees of compatibility with this drug to study their loading efficiency and release profiles. Their results indicated that a drug's encapsulation efficiency into nanoparticles correlated with higher levels of interaction between the polymer and the drug; however, the release of the drug from the particle was slower.[392]

As well as interaction strength, the density/porosity of the nanoparticle also impacts drug release behavior. Sant et al. prepared a series of nanoparticles with varying Propafenone content using the emulsion-solvent evaporation method. The pore size distribution of these nanoparticles was measured using nitrogen adsorption porosimetry. *In vitro* release revealed that nanoparticles with denser structures and smaller pores exhibited slower drug release rates.[393] Additionally, for biodegradable polymer matrixes, the drug release process is influenced by the degradation rate of the polymer and the specific surface area of the nanoparticles. If the degradation rate of the nanoparticle is slow, drug release primarily occurs through concentration gradient diffusion as well as osmotic pressure.[394] Conversely, if the degradation rate is fast, the drug may exhibit a burst release pattern. Furthermore, a larger specific surface area can also enhance the diffusion rate of small molecules into the environment.[395]

The rate of drug release in passively loaded systems is often correlated with a drug's half-life (the amount of time the concentration of a drug is reduced by half in the body), and this rate is highly variable. For passively loaded systems, half-lives can range from a few hours to days, depending on the size, steric hinderance and chemical nature of the drug, its interaction with the polymeric nanoparticle, and the wider environment.[396] The hydrophobic effect is the most common method to encapsulate drugs, and its efficiency is determined by the compatibility between a nanoparticle's hydrophobic core and the hydrophobicity of the encapsulated drug. Some of the predominant techniques involved in loading hydrophobic drugs into nanoparticles include emulsion (particularly solvent evaporation), nanoprecipitation, and dialysis.[397] As a well-established drug loading strategy, several comprehensive review articles have systematically summarized the relevant studies and discussed the progress of these techniques.[398−400]

Electrostatic interactions arise from the attraction between opposite charges, and are generally a slightly more controllable and efficient means to achieve drug loading. For macromolecular, charged biopharmaceuticals, such as peptides, proteins, and nucleic acids, it is nearly impossible to effectively load them into nanoparticles solely through hydrophobic interactions. Instead, a more prudent delivery method involves neutralizing surface charges through electrostatic interactions. The strength of these interactions is generally higher than the hydrophobic effect, yielding minimal leakage and higher loading efficiency. In contrast to the hydrophobic effect, ionic interactions can encapsulate charged therapeutics such as

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Chem. Rev. 2024, 124, 5505−5616

proteins, peptides, and nucleic acids at very high efficiencies in polymeric nanoparticles. Polyion complexes (PICs), which are formed either through the interaction between two oppositely charged polyelectrolytes or through a single copolymer and an oppositely charged therapeutic, have received significant attention due to their ability to load charged therapeutics at high efficiencies.[120,401] Under ideal conditions, cargo and ionic block copolymers at equimolar charged amounts should lead to the formation of well-defined PICs. However, in practice, because the spatial distribution of surface charges on biopharmaceuticals may not perfectly align with that of the polymers, varying ratios are required to balance the overall charge in different studies.[402] Another significant bottleneck in the practical application of PICs is their stability under high ionic concentrations. Given that the ionic strength of biological particles typically remains around 150 mM, enhancing the stability of PICs is essential. This can be achieved by incorporating hydrophobic groups,[403] adding homopolymers carrying a charge similar to the payload,[404] or even through internal cross-linking within the PICs.[405] It is important to mention that the ionic attraction established between the copolymer and the associated charged cargo is subject to a range of influencing factors, including pH environment, the length of the charged segment within the copolymer, and the ionic strength of the solution.[406] Passively loading drugs either through the hydrophobic effect or ionic interactions is a process that can occur at the beginning of nanoparticle formation, known as pre-loading, during nanoparticle formation, known as co-loading, or after the nanoparticle has already been formed, referred to as post-loading.

Passive loading is facile, one-pot, and cost-effective, and hence is by far the most common drug loading strategy for polymeric nanoparticles either in late-stage clinical trials or on the market currently. The downsides of passive loading are related to drug loading efficiency, which can be reduced in passive systems mainly via drug leakage and weaker hydrophobic or electrostatic effects. Typically, the drug loading efficiency of passive system is only a few weight percent.[396] There are a number of strategies to enhance drug loading efficiency, which can include small alterations to the loading process. In nanoprecipitation, for example, drug loading efficiency is highly dependent on the mixing time, and the introduction of surfactant coupled with highly tailored mixing can yield drug loading efficiencies >49%.[407] The creation of drug dimers, whereby two drugs are attached via a linkage, is another highly successful strategy to increase drug loading efficiency. The dimerization of drugs significantly enhances their aggregation properties while reducing size-dependent leakage, and is particularly useful when loading hydrophobic drugs into polymeric micelles. Conjugating two drugs together with a stimuli-responsive linkage is a method that can enhance drug loading efficiency, as well as therapeutic efficacy, to an even greater extent.

4.10.2. Active Loading and Controlled Release. Active loading involves the connection of a drug to the nanoparticle through a covalent linkage. This can be achieved by the design of a drug−polymer conjugate, the inclusion of a drug functional linker, a drug template, or by postmodification using functionality present within the system.[396,408] This kind of drug loading is sometimes referred to as co-loading, and most often this occurs through a cleavable covalent bond between a fragment of polymer and the drug, which can range from a small organic compound to large biomacromolecules such as proteins and nucleic acids. The principal advantage of active loading, as opposed to passive loading, is high drug loading efficiency. This efficiency is due to the strength of the covalent attachment between the drug and the polymer, which minimizes drug leakage, poor solubility, and undesirable aggregation. Moreover, the number of possible chemical moieties that can make up a drug−polymer conjugate is vast, and many of these moieties perform a functional role in drug delivery, such as stimuli-responsiveness, which further enhances therapeutic efficacy. For highly sensitive macromolecular therapeutics such as peptides, proteins, and nucleic acids, covalent conjugation to a polymeric nanoparticle is often the delivery mode of choice, due both to high loading efficiency as well as the enhanced cargo protection. It is important to note that the conjugated systems that provide drug loading efficiencies of essentially 100% are not universal, and require careful knowledge and selection of both the drug and polymer. Unlike passive loading, active loading is generally more complex, often requiring a multi-step synthetic process and drug modification. These modified drug−polymer conjugates almost always have a reduced therapeutic efficacy compared to the free drug.[409] Conjugating a drug to a polymeric nanoparticle via a cleavable linkage is a well-studied solution to this problem; however, the reversibility inherent in such a system can result in drug leakage or off-target release.[396] Prodrugs are another plausible solution to the loss of drug potency when conjugated to a polymer. A prodrug is an inert material that, when undergoing a metabolic or endogenous enzymatic reaction, releases the pharmacologically active ingredient as a biproduct.

The choice of an appropriate linker between therapeutic cargo and polymer is important to the overall performance of the delivery system, and depends on the nature of both the drug and polymer, as well as intended delivery site and biological barriers that need to be navigated. The number of different linkers is significant, and Figure 32 provides a selection of some of the most widely used chemistries. Ester and amide linkages are commonly employed to form drug−polymer conjugates, particularly for amino acid-based therapeutics, and are cleavable through hydrolysis. Imine, hydrazone, and ketal/acetal moieties provide pH-induced cleavage and drug delivery, while disulfide bonds and coumarin esters respond to redox and light stimuli, respectively. Michael addition and various "click" reactions are also used to quickly and efficiently synthesize conjugates with robust linkages. For drug delivery, it is useful to mask the biological activity of cargo before reaching the targeted sites, and then release the cargo without chemical attachments that could impede therapeutic activity. Self-immolative linkages (SILs) or spacers that degrade spontaneously in response to specific stimuli have been employed in a variety of biological applications to provide this functionality.[410,411] While various cleavable spacers have been comprehensively reviewed in Section 3, this section will pivot its attention toward SILs.

Two types of SILs are generally employed in drug-delivery systems. QM-based SILs require a benzyl alcohol or similar structure with a protected electron-rich functional group like −OH, $-NH_2$, and −SH at the *para*- and/or *ortho*- positions. The elimination of *para* and *ortho* substituents can happen at the same time, leading to amplified release.[321,412,413] Figure 33A depicts the elimination mechanism using the ROS-responsive phenylboronate as an example. The cyclization-based SILs make use of the driving force of intramolecular

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Chem. Rev. 2024, 124, 5505−5616

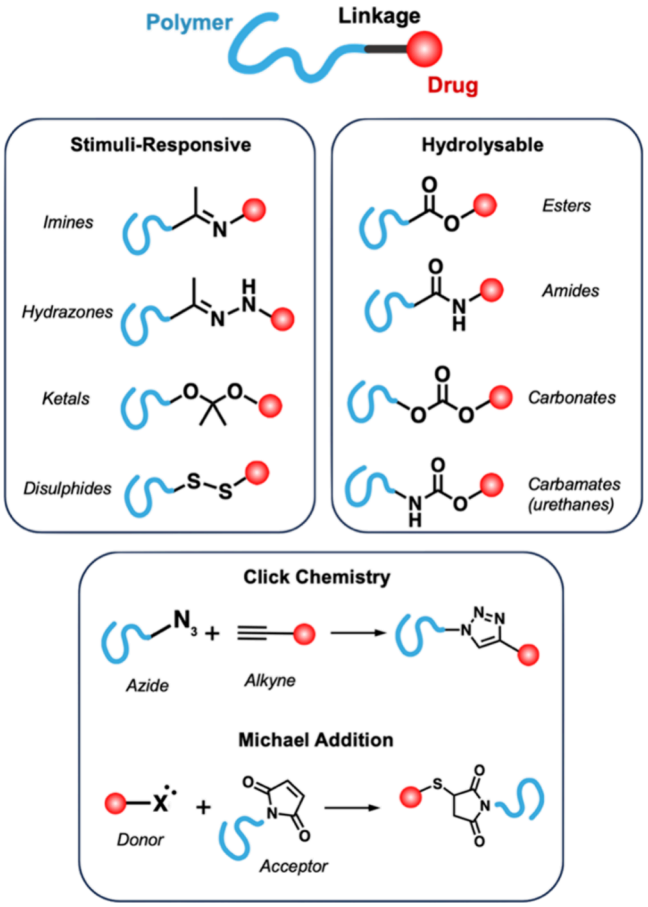

Figure 32. Drug−polymer conjugates can be created via an enormous amount of distinct chemical linkages. A selection of the principal linkages are depicted, including stimuli-responsive and hydrolyzable moieties as well as common conjugate forming reactions.

nucleophilic cyclization. The cyclization kinetic is a combination of Baldwin's rules (ring size, 5-membered rings are preferred), the Thorpe−Ingold effect (substitutions), and reactive rotameric effects (*gem*-substations).[410,414,415] Figure 33B depicts the release mechanism of a GSH-responsive SIL with a disulfide bond.[275] Even minor structural and chemical variations can markedly influence the rate of cargo release. For instance, Sengee et al. investigated the impact of different linker types on cargo release, specifically comparing mercaptoalkanol (MCA)-type linkers and aminoalkanethiol (AAT)-type linkers.[416] They observed that MCA-type linkers were capable of releasing up to 90% of the encapsulated drug within 2 h. However, due to the enhanced stability of AAT-type linkers, the drug release within the same timeframe was significantly lower, falling below 10%. The rate of fragmentation of the SILs also directly affects the potency of the drug-delivery system. To illustrate this, Caruso and co-workers compared two disulfide-based SILs and found that the QM-based one displayed overwhelmingly more toxicity to cancer cells compared to the cyclization-based one.[417]

Many drugs have multiple functional groups that can be used to incorporate into polymeric building blocks. Studies have shown that the drugs can be integrated as the backbone of polymers, which act as both the drug-delivery vehicles and prodrugs (Figure 34). The advantage of this strategy is that such polymers have high drug loading capacity and generate minimal waste after delivery. Complete degradation is required for efficient delivery and maximal activity so that self-immolative chemistries for traceless release and fast degradation are ideal for these systems.[298,418−420] Cheng and co-workers reported a study on a drug polymer, coined as chain-shattering polymeric therapeutics (CSPTs), integrating amino or dihydroxy CSPT derivatives (9-aminocamptothecin and SN-38) as the backbone with alternating stimuli-responsive SILs (Figure 34A). The former, under UV light exposure for ten minutes, achieved a 59% release of 10-hydroxycamptothecin, whereas the latter, in a 20mM DTT environment, released the vast majority of SN-38 within 48 h.[418,419] Oupický and co-workers reported a study for cancer therapy based on the combination of polyamine and miRNA.[420] The polymer was made of N^1,N^{11}-bis(ethyl)norspermine (BenSpm) linked by disulfide-based SIL, acting as both miRNA carrier before degradation and polyamine prodrug that released the anti-cancer agent BenSpm in the presence of GSH with complete degradability within 24 h (Figure 34B). Shi and Farokhzad et al. used the thioketal SIL to link mitoxantrone (MTO) into a polymer that was responsive to ROS (Figure 34C).[298] Yang et al. incorporated an antimicrobial cinnamaldehyde agent into a pH-responsive polymer linked by acid-labile acetal and pH-responsive aminoethylpiperazine moieties (Figure 34D). At a neutral pH of 7.4, only a limited release was observed. However, in a more acidic environment with a pH of 5.5, there was a significant release of the cinnamaldehyde agent, with approximately 40% being released after 60 h.[421]

5. SPHERICAL NANOPARTICLES

"Polymeric nanoparticle" is a broad term that roughly describes a particle between 1 and 1000 nm composed mainly of polymers. Under this umbrella term there are a number of different kinds of polymeric nanoparticles with varying architectures, properties, advantages, drawbacks, and applications. Polymeric nanoparticles that take the shape of a sphere are the most widespread and well-studied design. The following section introduces, categorizes, and describes the different kinds of spherical nanoparticles, with a focus on structure, characteristics, and sophisticated (state-of-the-art) designs (Figure 35).

5.1. Micelles

Micelles have shown great potential as drug-delivery vehicles due to their simplicity, ability to protect and solubilize hydrophobic drugs in their core, and capacity to respond to physiological stimuli through the addition of functional chemistry. Micelles are solid spherical nanoparticles formed through the self-assembly of a single amphiphilic polymer in an aqueous environment. The polymer is normally an AB diblock copolymer, where A and B represent hydrophilic and hydrophobic blocks, respectively.[422] However, tri-block co-polymers such as poloxamers (PEG-*b*-PPG-*b*-PEG), as well as graft copolymers can also be used to form micelles.[423] The hydrophobic block of the polymer comprises the core of the micelle, while the hydrophilic block serves as a stabilizer, making up the shell of the micelle (Figure 36). Given that they are composed of a single amphiphilic polymer, micelles are typically small, ranging from 5 to 100 nm in size, with most falling between 20 and 60 nm.[112] Micelles are most frequently used to solubilize small hydrophobic drugs, as their size, to a certain extent, limits the encapsulation of large macromolecules.[112] This small size, however, yields a superior tissue penetrating ability compared to larger nanoparticle designs,

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Chem. Rev. 2024, 124, 5505−5616

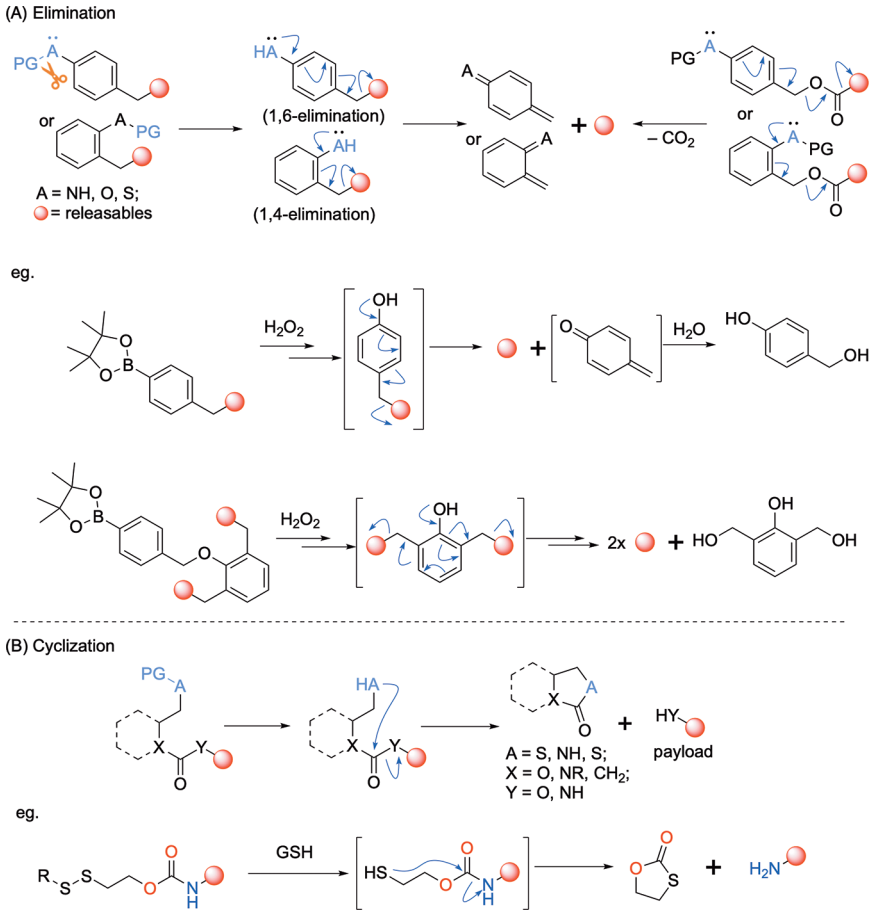

Figure 33. Two types of SILs and their fragmentation mechanism: (A) elimination and (B) cyclization.

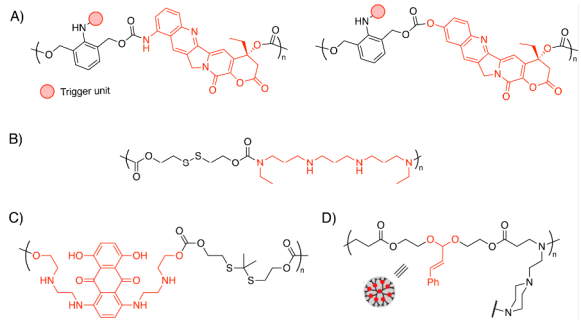

Figure 34. Drug integration as the polymer backbone (therapeutic moieties are highlighted in red). Panels A–D represent specific studies using these degradable backbones that are referenced in the text.

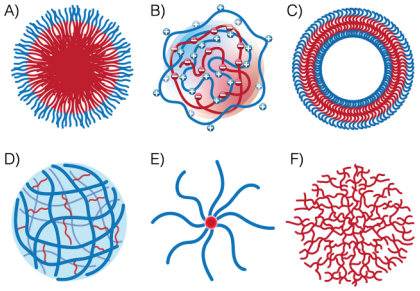

Figure 35. A myriad of different spherical nanoparticle designs. The hydrophobic sections are shown in red, and the hydrophilic sections are shown in blue. (A) Core–shell nanoparticle, (B) polyion complex, (C) polymersome, (D) nanogel, (E) star polymer, and (F) hyperbranched polymer.

and is crucial to exploiting the EPR effect, whereby micelles passively accumulate at tumor sites.[422] Furthermore, of all the polymeric nanoparticle designs based on self-assembly, micelles are the simplest, and hence most feasible for large-scale manufacturing.[424] Micelles are most commonly synthesized via emulsion techniques including solvent evaporation, but can also be formed through nanoprecipitation and dialysis.

The self-assembly of amphiphilic polymers into micelles is spontaneous and entropically favored, mainly due to the hydrophobic effect.[112] This self-assembly occurs above what is known as the critical micelle concentration (CMC). The CMC is the concentration at which the water–air interface of the solution is completely saturated with an amphiphilic polymer, which forces the remaining polymer into the bulk aqueous solution, forming micelles.[424] The CMC is the primary determinant of micelle stability and *in vivo* circulation time, as a high CMC implies disassembly when diluted in biological fluid.[425] The CMC of polymeric micelles is often a thousand times lower than traditional lipid-based micelles and surfactant systems. This superior CMC is often attributed to a longer hydrophilic polymer block, as opposed to a lipid/surfactant's short hydrophilic head.[424] A viable strategy for further decreasing the CMC is increasing the length of the hydrophobic block to enhance hydrophobic interactions. This strategy, however, is a balancing act, as increasing the hydrophobic block increases the size of the particle, which may

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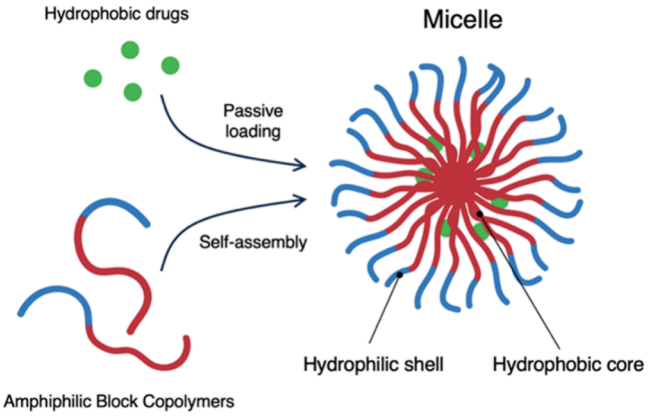

Figure 36. A schematic illustration depicting the self-assembly of micelles.

affect its delivery efficacy, and will eventually result in morphological changes.[426] Cross-linking is the most popular and effective technique to decrease a micelle's CMC while leaving certain important parameters such as size, shape, and concentration unaffected.[427] Covalent cross-linking between the polymers within either the core or the shell of a micelle is most often employed to increase stability, given the relative strength of the covalent bond. However non-covalent cross-linking based on supramolecular interactions are also widely used in the design of cross-linked micelles. Of these interactions, hydrogen bonding and electrostatic interactions via the incorporation of polyelectrolytes, are significant. It is important to note that cross-linking does affect many important micelle properties, and hence is a parameter that must be carefully considered. For example, Stenzel and co-workers, showed that micelle cross-linking strongly impacts both drug release efficiency and cellular uptake efficiency.[428]

PEG is frequently used as a micelle's hydrophilic block due to its versatility, efficient bioavailability, strong antifouling properties, and favorable FDA safety regulation.[426] The molecular weight of the PEG shell is normally quite low, <20 kDa, and plays a vital role in stability, toxicity, and stealth properties of the resultant micelle.[429] Other hydrophilic blocks include zwitterionic polymers[430], poly(oxazolines),[431] and biodegradable polymers including dextran and chitosan, which have hydrophilicity and stealth properties similar to PEG, but lack any risk of accelerated blood clearance associated with PEG exposure.[432] The two most widespread and well-studied hydrophobic blocks are poly(amino acids), including derivatives of glutamic acid, aspartic acid and lysine, and polyesters, including derivatives of polylactides, poly(glycolic acid), and ε-caprolactone.[422] These hydrophobic cores are favored due to their low toxicity and biodegradability, their synthetic accessibility via ring-opening polymerization, and their ability to load small hydrophobic drugs.

Micelle drug loading most often occurs through passive solubilization, whereby a small hydrophobic drug is held within the hydrophobic core of the micelle, surrounded by the hydrophilic shell. Encapsulated drugs can impact the size of the micelle, and generally stabilize the hydrophobic core and lower CMC.[426] Though initially attributed to the hydrophobic effect, drug loading in micelles is in reality a complex system that can involve hydrogen bonding, steric cross-linking, $\pi-\pi$ stacking, and van der Waals forces.[426] Theoretical and computational models have been employed to predict this complex interaction between drug and micelle, including Hansen's solubility parameter, Flory–Huggins theory, and Quantitative structure-property relationships (QSPRs).[426] Hydrotropes, compounds that enhance the solubility of hydrophobic compounds by factors >100, have also been employed to increase the drug loading efficiency of micelles without significantly altering their structure.[433] Passive loading of drugs into micelles is a powerful technique given it is applicable to a wide variety of hydrophobic drugs regardless of their exact chemical structure or functionality. However, such systems typically have some non-specific release due to leakage from the polymer structure. PEG-*b*-PAA[434] and PEG-*b*-polyester[435] micelles have shown significant potential as anti-

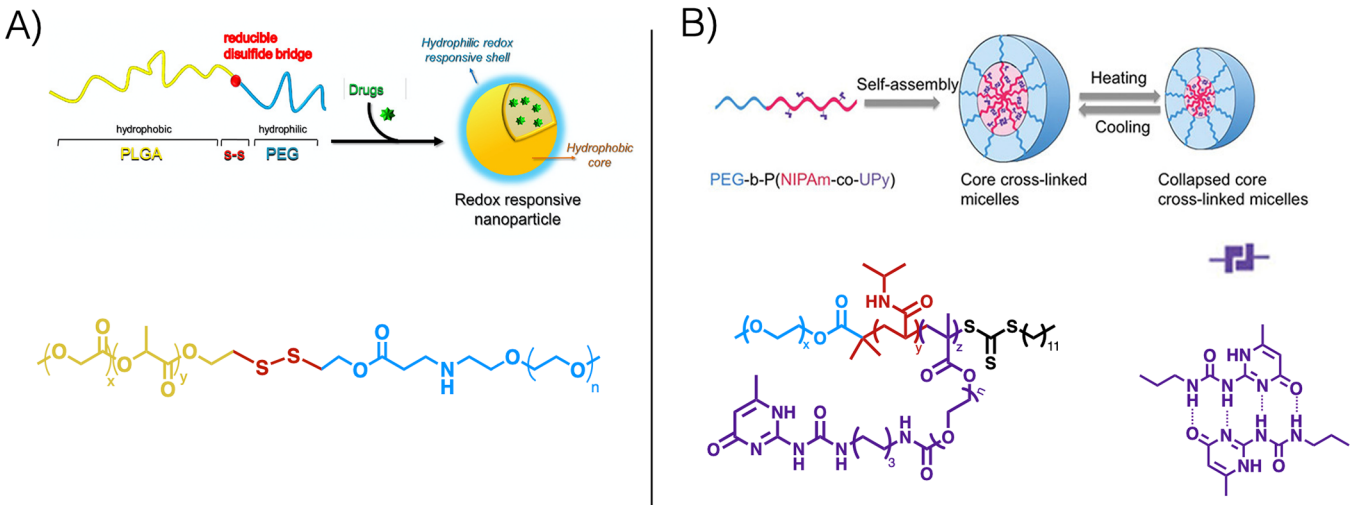

Figure 37. (A) A redox-responsive micelle based on the self-assembly of a PEG-*b*-PLGA amphiphilic block copolymer. This micelle was functionalized with the disulfide bond, which is reducible under endogenous conditions, allowing for superior therapeutic cargo delivery, as well as enhanced cellular uptake in a lung cancer model. (B) A temperature-responsive PEG-*b*-PNIPAm micelle cross-linked via supramolecular hydrogen bonding. This micelle was able to undergo reversible temperature-induced swelling and shrinking, not only due to the presence of PNIPAm, but also due to the quadruple hydrogen bonding cross-linking imbued by the UPy unit. Adapted with permission from ref. 442, 443. Copyright 2018, Elsevier (A) and Copyright 2017, Royal Society of Chemistry (B).

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cancer therapeutics due to their ability to load large amounts of small drugs such as DOX and paclitaxel and deliver them to tumor cells via the EPR effect.

More active loading methods, whereby the drug is conjugated to the micelle, offer the ability to encapsulate hydrophilic and macromolecular therapeutics and enhance the loading efficiency of hydrophobic drugs. For example, Ashford and co-workers were able to load the extremely insoluble anticancer hormone fulvestrant via conjugation with lysine telodendrimers that comprised the micelle core.[436] Such conjugation can also be used to enhance the targeting efficiency of micelles as shown by Stenzel and co-workers, who conjugated estrone, a targeting hormone for breast cancer, to the shell of PEG-*b*-Poly(*tert*-butyl methacrylate) micelles.[437] Drug dimers, whereby two drugs are conjugated, have been observed to significantly enhance the loading capability of poorly soluble therapeutics.[438] Wooley and co-workers designed a disulfide linked dimeric PTX prodrug that formed part of polycarbonate micelles.[439] These micelles had a high surface charge for enhanced tumor penetration, and redox responsiveness for stimuli-induced drug release.

Polymers that respond to stimuli such as temperature, pH, light, redox environment, and enzyme activity have also allowed for the design of micelles with superior targeting and drug releasing efficiency. Ramirez et al. designed a pH-responsive micelle based on a PDPAEMA core that, at pH < 6.1, protonates and becomes charged, resulting in the disassembly of the micelle.[440] This design was used to deliver a pain killing agonist to endosomes, whose environment is acidic. Ji et al. designed a complex thermo/redox dual-responsive micelle based on a single amphiphilic polymer comprising a targeting folate ligand conjugated to a PEG shell block that was connected to a temperature-responsive PEI-*b*-poly(acrylamide-*co*-acrylonitrile) core block via a redox active disulfide linkage.[441] The resultant micelle encapsulated a near-IR photosensitizer, and upon IR irradiation (λ = 800 nm) was able to release DOX in a controlled fashion. The disulfide bond, which is cleavable under reducing conditions, is a common motif of redox-responsive drug-delivery vectors, and was employed by Cameron Alexander's group to design a redox cleavable PEG-*b*-PLGA micelle with anti-lung cancer performance (Figure 37A).[442]

Degradable cross-linking is another method to imbue micelles with stimuli-responsiveness, increased stability, and biodegradability. For example, Qu et al. designed a 50 nm micelle whose core was cross-linked via carboxylic acid and disulfide functionality, resulting in pH and redox-responsive behavior, respectively.[444] The pH and reducing environment of the endosome resulted in micelle disassembly and the rapid release of DOX. Ganguly et al. also designed a cross-linked micelle based on pH-responsive chemistry, but utilized iron-catechol supramolecular coordination bonds that were acid labile, as opposed to acid cleavable linkers.[445] This design also employed a tri-block copolymer composed of polydopamine, PNIPAm, and a zwitterionic polymer component to form micelles that underwent morphological changes at pH levels relevant to the endosome. Temperature-responsive cross-linked micelles were designed by Chen et al., who utilized the thermoresponsive behavior of PNIPAm (Figure 37B).[443] This design employed supramolecular cross-linking in the form of 2-ureido-4-[1H]pyrimidinone (UPy), which forms strong self-complementary quadruple hydrogen bonds and is a common motif in self-healing materials.[446] Crucially, this strong hydrogen bonding enhanced micelle stability, even at a low cross-linker concentration, and allowed the nanoparticles to undergo temperature-induced swelling/shrinking.

Generally, the polymeric blocks that micelles are derived from, such as poly(esters) and vinyl polymers, degrade very slowly due to hydrolysis, and hence are poorly biodegradable. Thus, synthesising micelles with biodegradable functional groups has the potential to minimize toxicity and off-target effects. For example, phospho-esters have been studied as moieties for micelle cores, due to the degradability of the O−P bond under mild conditions. For example, Wooley and co-workers utilized a PPE core with a variety of different shells to create biodegradable micelles that were 6 times less toxic than a commercial transfection agent.[170] Researchers have also utilized thiol-ester and cyclic ketene acetal moieties to drastically increase the rate of hydrolytic degradation for traditionally non-degradable micelle components, such as vinyl copolymers.[186−188,447,448] Self-immolative polymers have also been employed to design micelles, which, under certain stimuli, can depolymerize completely.[319,325,326] Such a design represents the combination of stimuli-responsive drug release and reduced toxicity through complete biodegradability.

Research has also focused on employing nucleic acids to form part of the amphiphilic block copolymers that create the micelle structure. Such a design promises to reduce toxicity, enhance both DNA uptake and biodegradability, and impart dual functionality, as DNA can act as both the component and therapeutic cargo of a micelle.[449,450] Furthermore, various studies have suggested that DNA−polymer conjugate micelles both enhance cellular uptake of DNA,[451,452] and minimize enzymatic (nuclease) degradation, possibly due to denser DNA packing as part of a micellular shell.[453] Initial work by Park and co-workers focused on DNA-*b*-PLGA micelles, and subsequently a range of core components have been analyzed.[451,454] In 2015, Chad Mirkin's group designed DNA−polymer conjugates whereby the DNA was in a brush-like architecture, as opposed to a linear form. These conjugates assembled into micelles, and were observed to have superior *in vitro* uptake compared to linear DNA.[455] Inspired by this DNA−polymer conjugate design, Tan et al. replaced the polymer with the chemotherapeutic PTX, creating a DNA−drug amphiphile, which self-assembled into micelles.[452] The DNA and drug were connected by a redox-cleavable disulfide moiety, yielding a nanoparticle that had high targeting efficiency, resistance to DNA/drug degradation, and stimuli-responsive drug release.

5.1.1. Core−Shell Nanoparticles. The fact that micelles are composed of a single polymer component, often an amphiphilic block copolymer, allows for simple designs and scalable synthesis, but limits, to a certain extent, their complexity and functional power. Nanoparticles that comprise a distinct core polymer and a distinct shell polymer generally yield a larger, more stable and generally more sophisticated design (Figure 38).[397] These kinds of nanoparticles, which we have termed a "core−shell" nanoparticle, are often referred to as "micelles", "micellular", and "micelle-like" in the literature. Such nanoparticles are typically formed through nano-precipitation, or gradual environmental changes that induce self-assembly, such as dialysis. They are in a sense similar to micelles; however, they are generally larger, between 100 and 200 nm, able to incorporate a wider range of complex chemical functionality as well as larger therapeutic macromolecules, and are more stable to dilutions, with very low CMCs.[456] Core−

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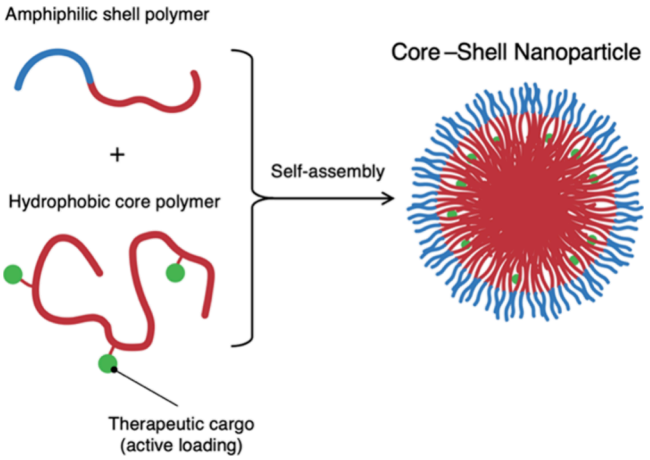

Figure 38. A schematic illustration depicting the self-assembly of distinct core−shell polymeric nanoparticles.

shell nanoparticles are almost always designed with a sophisticated targeting and stimuli-responsive behavior, and thus often display powerful drug-delivery efficiency compared to other strategies.

pH-responsive nanoparticles, for example, are a well-studied drug-delivery vehicle composed of charge shifting polymers such as PDMAEMA, PDEAEMA, and PDPAEMA. These particles undergo pH-induced chemical, structural, and morphological changes that enhance their targeting and delivery capabilities.[457] For example, pH-responsive nanoparticles whose core is based on a blend of PDEAEMA and PDPAEMA groups have shown the capacity to encapsulate hydrophilic peptides via conjugation and escape endosomes with efficiencies as high as 10%, a noticeable improvement over both lipid nanoparticles and other endosomal escape vectors such as cell penetrating peptides.[81] Kermaniyan et al. utilized such pH-responsive polymers to design a nanoparticle that can undergo swelling at pH levels relevant to endosomal escape (Figure 39A).[458] Crucially, this nanoparticle could be synthesized via emulsion polymerization, a technique that lends itself to low-cost, highly efficient, and easily scalable nanoparticle production, and hence more applicable for widespread commercial application. Seeking to design a biodegradable, efficient, stimuli-responsive drug-delivery vector, Gillies and co-workers explored the potential of nanoparticles formed from self-immolative polymers. Their design employed the self-immolative PGAm moiety as a core component, which, when combined with a pH-responsive PEG-based shell polymer, yielded a nanoparticle that was able to release cargo via UV, redox, or pH triggered immolation.[331,459] Core−shell nanoparticles offer the ability to enhance drug-delivery efficiency by conjugating a wide variety of biological macromolecules as therapeutic agents or targeting motifs. Guo et al. illustrated the degree to which these nanoparticles can be functionalized, by designing a redox- and

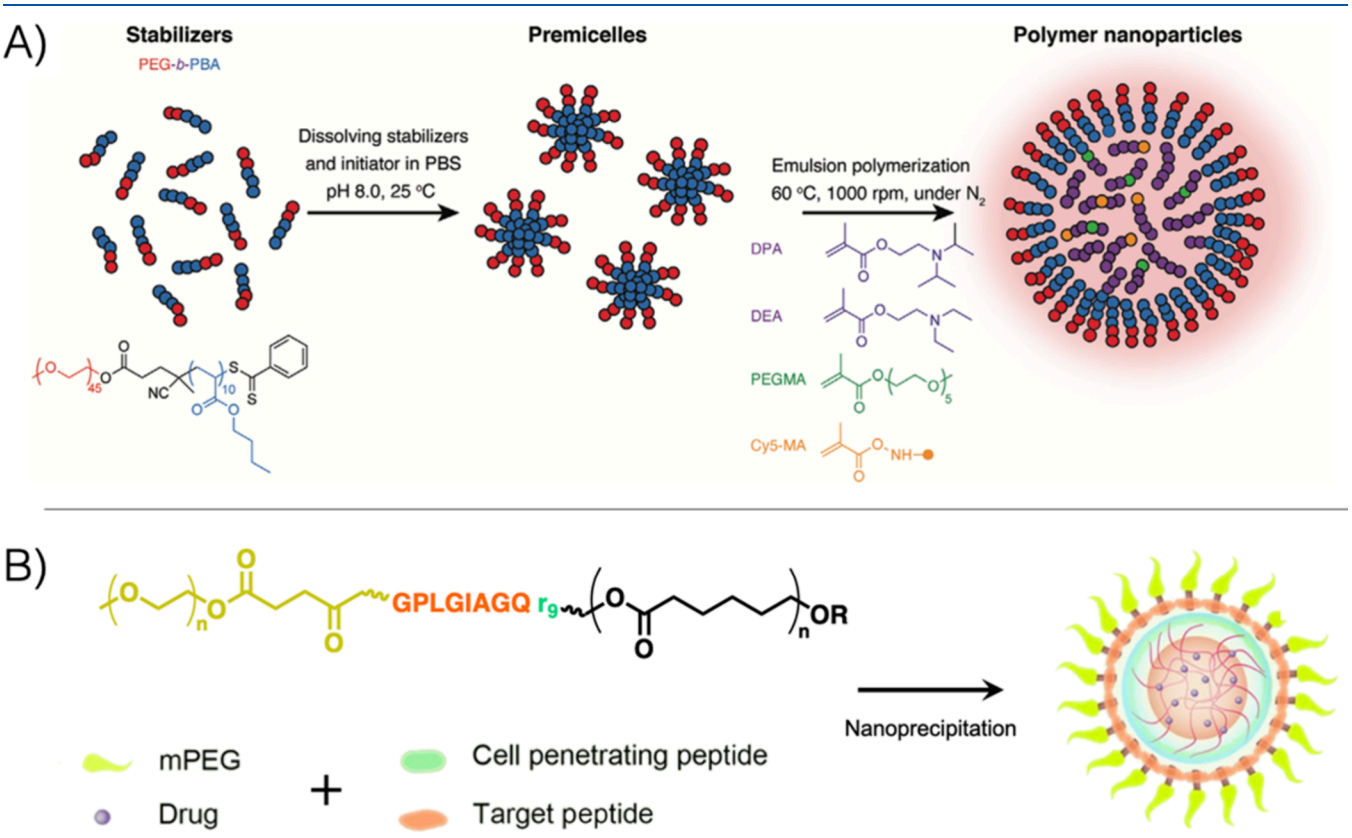

Figure 39. Two sophisticated core−shell polymeric nanoparticle designs. (A) Emulsion polymerization, a more clinically relevant preparation procedure, was employed to synthesize pH-responsive nanoparticles. These nanoparticles were based on the charge shifting polymers PDPAEMA and PDEAEMA, and underwent swelling in response to acidic conditions that mirrored the endosomal environment. (B) A curcumin-loaded nanoparticle based on a PEG shell and a PCL core. This nanoparticle incorporated both a cell penetrating peptide and a tumor targeting peptide, and showed strong tumor penetration and anti-tumor efficacy. Adapted with permission from ref. 83, 460. Copyright 2022, Wiley-VCH (A) and Copyright 2020, Springer Nature (B).

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enzyme-responsive nanoparticles formed from the self-assembly of a star-based ϵ-caprolactone-tricarballylic acid core loaded with curcumin, and a PEG shell conjugated to both a cell penetrating peptide and a tumor targeting peptide (Figure 39B).[460] These nanoparticles showed a superior tumor penetrating efficiency and resulted in 80% *in vivo* tumor growth inhibition. Deloney et al. investigated a dual temperature and GSH-responsive hollow core−shell nanoparticle for dynamic peptide loading.[461] The hollow nanoparticles were derived from PNIPAm and were cross-linked by a disulfide-containing cystamine cross-linker that was redox-responsive. Below the LCST of PNIPAm, the nanoparticle expanded in size to allow the loading of a cationic peptide. However, while at body temperature, the nanoparticle retracted, thus protecting the peptide. A loaded immunosuppressant peptide was shown to suppress IL-6 production via redox-responsive release. Gong et al. designed a nanoparticle that underwent a morphological change from a sphere into a sheet.[248] This shape change was induced by a decrease in pH, and was posited to enhance endosomal escape and drug-delivery performance.

5.2. Polyion Complex

Polyion complexes (PICs) are nanoparticles formed via the self-assembly of oppositely charged polymers due to electrostatic interactions (Figure 40). These polymers include

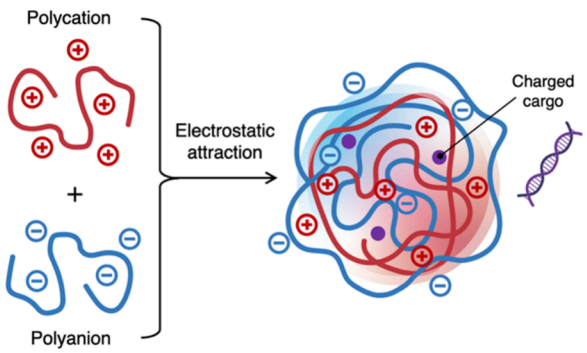

Figure 40. A schematic illustration depicting the self-assembly of polyion complexes.

ionomers, which are polymers that contain both charged and neutral units, or polyelectrolytes, which can carry repeating units of positive charges (polycations), negative charges (polyanions), or a combination of both, known as zwitterionic polymers. Many macromolecular therapeutics are themselves polyelectrolytes, which makes them especially suited to encapsulation within and complexation to PICs.[462] Nucleic acids such as DNA and RNA are anionic due to phosphate groups in their nucleotide backbones, and proteins are often charged depending on their size, chemistry and the pH environment. PICs have also shown the capacity to encapsulate and release a wide variety of neutral hydrophobic drugs, albeit with greater difficulty.[463]

The formation and colloidal stability of PICs is dictated by electrostatic interactions, specifically opposite charge attraction; however, van der Waals forces, hydrogen bonding, and the hydrophobic effect also contribute somewhat to PIC stability.[464] As well as solvent molecules, there are also many more counterions associated with the interface of the charged polymers, and their liberation into solution during polymer precipitation provides a significant entropic driving force for PIC formation.[465] Given the additional electrostatic bonding, PICs generally lack the need for chemical cross-linking; however, they are dynamic systems that exist in equilibrium with free ions in solution and thus are sensitive to the electronic composition of the environment. Dilution, pH, salt content, and the addition of charges species can break this equilibrium, leading to a loss of PIC stability.[462] Of course, under certain circumstances, this loss of stability due to the environment, if controllable, can be beneficial for targeted drug delivery. PIC stability is strongly correlated with charge density, which can be maximized by increasing the molecular weights of the respective polyelectrolytes, adding a greater number of charge moieties per polymer chain, or by using more exotic dendritic/branched/star polymer architectures.[462] These polymer architectures have shown a greater RNA encapsulation efficiency than their respective linear counterparts, likely due to greater density of charged monomer units.

PICs can take on various morphologies dictated by the relative ratio, stoichiometry, and density of charged sections, as well as the chemical and ionic nature of the environment. A 1:1 mixture of oppositely charged polyelectrolytes will generally attract and precipitate into structures, but too uneven a ratio of charged sections will result in the excess polyelectrolyte totally enveloping its counter polyelectrolyte, thus maintaining solubility.[465] PIC micelles involve the addition of two block copolymers, each containing either a polycation or polyanion connected to a neutral hydrophilic block. The self-assembly of the two polyions forms an electrostatic insoluble core stabilized by a hydrophilic shell. One example of this is the combination of polybases and polyacids to form the core of PIC micelles. Pham et al. designed PIC micelles that were formed from the combination of PEGylated block copolymers containing cationic PS-*b*-PDMAEMA and anionic PS-*b*-poly(styrene sulfonate).[466] These PIC micelles were stable to significant changes in the salt concentration of the environment due to the additional $\pi-\pi$ stacking interactions of the styrene groups.

Often, PIC micelles will involve the complexation of a PEG-polycation with an anionic therapeutics such as DNA or RNA. These kinds of PICs are called polyplexes.[467] PEG is by far the most common shell segment for PIC micelles, and cationic core segments such as PEI, PLL, and various PAAs have been extensively studied in tandem with anionic DNA/RNA. In 2021, Kataoka and co-workers developed a cationic polyplex micelle with a PEG shell and a modified PAsp core (Figure 41).[468] This PIC was able to encapsulate two separate sets of RNA (mRNA and single guide RNA (sgRNA)) via electrostatic interactions, and induced genome editing in mouse neurons via CRISPR/Cas9 technology. Amongst the various PIC core segments, PEI is the most well studied and widely utilized cation, due to its strong complexation with anionic nucleic acids, and its pH-responsive endosomal escape capabilities.[469] Gao et al. designed a 120 nm PIC composed of PEG-*b*-PLA-*b*-poly(histidine) conjugated to pH-responsive PEI via a redox cleavable disulfide bond.[470] This polyion nanoparticle showed a successful multi-drug-delivery capability, as it was able to both encapsulate DOX within its poly(histidine) core and complex siRNA via electrostatic attraction with PEI. Seeking to design PIC micelles that reduce the cytotoxic effects of cationic PEI, Jundi et al. designed a PIC that incorporated double hydrophilic polymers; that is, a polymer that contains two separate water-soluble blocks.[471] These polymers were functionalized with carboxylic acid groups and the non-toxic cationic polymer poly(lysine). The resultant nanoparticle formed highly efficient complexes with

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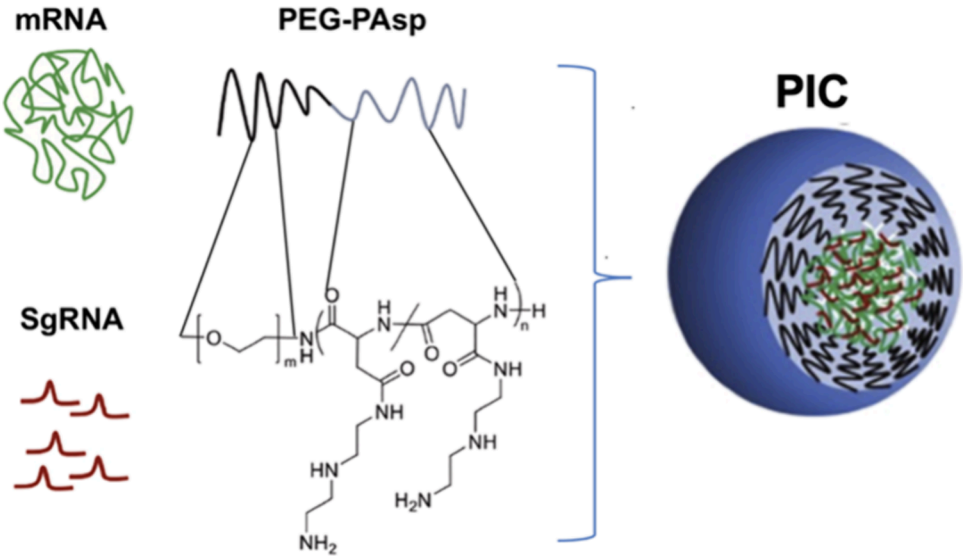

Figure 41. A PIC was designed that was able to edit various cell genomes through the delivery of two sets of RNA, *Cas9* mRNA, and single guide RNA (sgRNA). The ∼65 nm PIC was formed via the assembly of a cationic block copolymer composed of PEG and modified PAsp, and anionic RNA. This design successfully loaded, protected, and delivered RNA to neurons when injected into mice, yielding cerebral gene editing. SgRNA is a single strand of RNA that forms complexes with ceratin enzymes to target and often cleave sections of DNA. Adapted with permission from ref. 468. Copyright 2021, Elsevier.

hydrophobic drugs and showed high siRNA loading efficiency >75%.[472] Another method to reduce toxicity is to utilize biodegradable functionality. Sirianni et al. designed a PIC that was based on self-immolative PGAm rather than PEI, and was able to undergo endogenous pH-responsive depolymerization.[332] This biodegradable PIC encapsulated plasmid DNA and provided similar gene expression levels to PEI functionalized PICs, but was notably less toxic. Oupický et al. reported a PIC consisting of anionic RNA and a cationic anti-cancer prodrug, which was functionalized with disulfide moieties.[420] The resultant redox-responsiveness of the PIC allowed for strong *in vitro* and *in vivo* anti-tumor performance, due to the posited enhancement of endosomal escape and drug release.

5.3. Polymersomes

Polymersomes are spherical vesicles that comprise an aqueous core surrounded by a bilayer membrane of amphiphilic polymers (Figure 42). First proposed as a drug-delivery vehicle in the mid 1990s, polymersomes were specifically designed to mimic the lipid bilayer structure of liposomes, a highly successful delivery system.[473] Unlike liposomes, however, the tunability of the polymeric membrane confers polymersomes with size and shape control, membrane thickness, stability, mechanical strength, and a wide variety of stimuli-responsive functionality.[474,475] Polymersomes are formed via the self-assembly of amphiphilic polymers into vesicles. The common polymer architectures are AB, ABA, or occasionally ABC di-/tri-block copolymers, where A and C represent hydrophilic blocks and B represents the hydrophobic block.[476] The polymers self-assemble such that the hydrophilic blocks face inward to the aqueous core and outward to the aqueous phase, while the hydrophobic block comprises the membrane surrounding the hydrophilic core. In terms of the packing parameter model, polymersomes are formed when $p > 1/2$, which in practice normally equates to increasing the fraction of the hydrophobic block B, relative to A and C.[477] Cross-linking between the polymers that comprise the membrane is a useful method to increase the stability of polymersomes for transport through robust physiological conditions.[478] This cross-linking is often achieved through the incorporation of stimuli-responsive linkers, yielding a polymersome that can undergo a morphological change across specific endogenous environments, which is important for more efficient drug delivery. Polymersomes contain an amphiphilic membrane, which allows them to act as a delivery vector for both hydrophilic drugs such as enzymes, peptides/proteins, and DNA/RNA, as well as poorly soluble hydrophobic drugs, which can be encapsulated in the polymersome's hydrophobic shell. Film rehydration is the most common technique for synthesizing polymersomes, as it is a facile technique that is relatively inexpensive and solvent free.[477] Emulsion techniques, nanoprecipitation, and gradual dialysis are also used to form polymersomes, while PISA has received more recent attention as polymersomes can be formed *in situ* by tuning only the degree of polymerization.[479]

PEG is generally favored as the hydrophilic block, given its high hydrophilicity, synthetic accessibility, and its *in vivo* "stealth properties" that allow the polymersome to avoid opsonization. Other hydrophilic blocks such as POx and

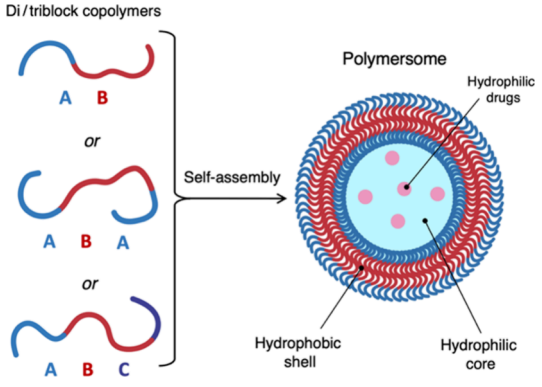

Figure 42. A schematic illustration depicting the self-assembly of polymersomes.

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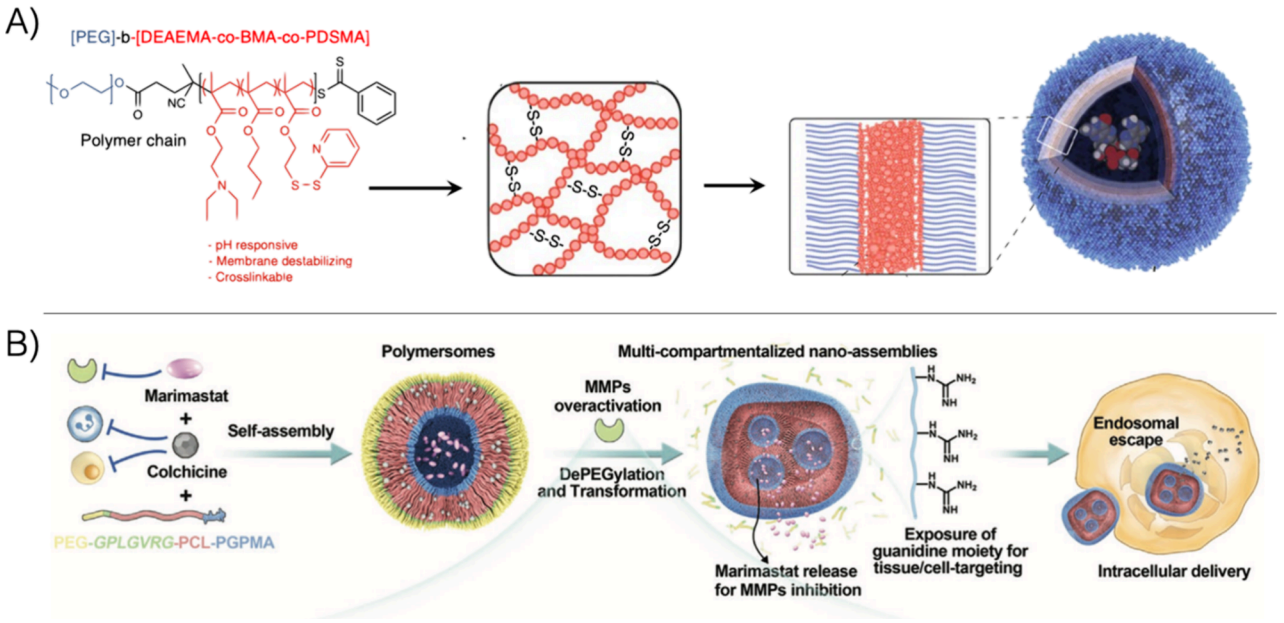

Figure 43. (A) A dual functional PEGylated polymersome that utilizes the redox-responsive disulfide moiety, and a pH-responsive charge shifting monomer DEAEMA, for sensitive nucleotide delivery. (B) A PEGylated PCL-based polymersome design that incorporates peptide−polymer conjugation for tumor targeting, and stimuli-responsive morphological change for enhanced drug delivery. Reproduced with permission from ref. 483, 488. Copyright 2019, Nature (A) and Copyright 2021, Wiley-VCH (B).

charged PAAs have shown potential as PEG replacements. The important functionality of most polymersome designs comes in the form of its hydrophobic block, and biodegradable PAAs and polyesters have received the most attention as hydrophobic sections. Non-biodegradable polymers such as poly(butadiene) (PB), poly(ethyl ethylene) (PEE), PS, and poly(dimethyl siloxane) (PDMS) have also been employed to enhance polymersome mechanical strength and stability relative to liposomes.[480] While most polymersomes are composed of amphiphilic di-/tri-block copolymers, more complex polymer designs have been recently investigated, including star brush and graft architecture. For example, Stayton and co-workers used RAFT polymerization to design a polymersome formed from the self-assembly of PEG-*co*-HEMA polymers grafted with PDMAEMA and PHPMA. Their design encapsulated the antibiotic drug ceftazidime, and displayed the capability to escape the endosome through pH-responsive particle changes.[481]

Recent research has centered around developing polymersomes with greater drug-delivery efficiency and minimal off-target effects. One way to achieve this is to utilize natural differences in the intracellular environment as stimuli for targeted delivery. Polymersomes have been designed to respond to a broad range of such stimuli, including pH, light, temperature, enzyme, and redox environment. Fenghua Meng and co-workers developed a dual pH and redox-responsive polymersome utilizing the charge shifting polymer PDEAEMA and thiol-functionalized poly(acrylic acid).[482] This PDEAEMA-disulfide multi-functional polymersome design was utilized by Shae et al., who was able to encapsulate highly sensitive cyclic dinucleotide cargo inside a polymersome that, through stimuli-responsive endosomal escape, provided a platform for enhanced cancer immunotherapy (Figure 43A).[483] Wei et al. utilized PDEAEMA and poly(methoxyethyl methacrylate) (PMEMA) to form a PEG-*b*-PDEAEMA-*stat*-PMEMA polymersome that responded to both pH and ultrasound stimulation.[484] This polymersome showed superior *in vivo* DOX release upon non-invasive sonication, compared to un-sonicated polymersomes and free DOX. Zhong and co-workers developed a multi-functional, highly cross-linked chimeric polymersome that encapsulated RNA within the hydrophilic core.[485] In their system, the polymersomes comprised a disulfide functionalized PEG-*b*-polycarbonate-*b*-PEI tri-block copolymer conjugated to a tumor targeting peptide. The rapid de-cross-linking of the polymersome in the presence of glutathione facilitated the fast release of RNA in the cytoplasm. Deng et al. synthesized a napthylboronate-based polymersome that responded to endogenous ROS such as H_2O_2.[486] The oxidation of these boronate moieties resulted in the self-immolation of the polymer assembly and the polymersome membrane's switch from hydrophobic to hydrophilic facilitated drug release. Bruns and co-workers developed a light-responsive polymersome functionalized with donor−acceptor Stenhouse adducts.[487] These photochromic compounds are hydrophobic in the dark but become more polar upon irradiation of specific wavelengths (525, 630 nm) yielding a polymersome whose membrane permeability can be efficiently controlled in the presence of light.

The functionality of polymersomes can be even further enhanced by utilizing the high specificity of biomacromolecules through peptide−polymer conjugates. Meng and co-workers developed a BBB penetrating polymersomes formed from PEI and peptide-functionalized PEG, decorated with angiopep2 (ANG) and apolipoprotein E peptide (ApoE).[489] These peptides mediated BBB transcytosis, and in the case of ApoE, yielded polymersomes that crossed the BBB over twice as efficiently as unconjugated polymersomes. Kataoka and co-workers utilized an MMP cleavable peptide and guanidine to create a functionalized cancer targeting PEG-*b*-PCL polymersome, containing the anti-tumor drug, cochicine (Figure 43B).[488] MMP, overexpressed in tumor associated tissue, de-PEGylates the polymersome, inducing a conformational

https://doi.org/10.1021/acs.chemrev.3c00705
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change that exposes the guanidine moieties for improved cell targeting and differentially releases colchicine.

Liu's research group, seeking to design stimuli-responsive degradable polymersomes, focused on functionalizing their polymeric vesicles with self-immolative moieties. They designed a polymersome that is responsive to two different enzymes—penicillin G amidase and β-lactamase (Bla)—produced by the bacteria *S. aureus*.[490] These polymersomes were strain selective, and able to achieve sustained release of antibiotics, with minimized side-effects. Similarly, cytosolic enzyme responsiveness was employed to design a self-immolative polymersome.[491] In the cytosol, this polymersome underwent an enzyme-induced morphological change into a micellular nanoparticle, from where a variety of therapeutic cargo was effectively released. Liu et al. synthesized another enzyme-responsive polymersome based on the self-assembly of PDMA-*b*-PBC-*b*-PDMA tri-block copolymers functionalized with benzyl carbamate moieties.[324] This design, however, was triply stimuli responsive, and underwent self-immolation through both UV and visible light, as well as enzymatic reductive milieu. The polymersomes were termed "self-immolative polymersomes" (SIPsomes), and were able to release a variety of cargo including DOX.

5.4. Nanogels

Nanogels are nanosized, three dimensional networks of highly cross-linked hydrophilic polymers that do not dissolve in water (Figure 44). They have the capacity to swell through the

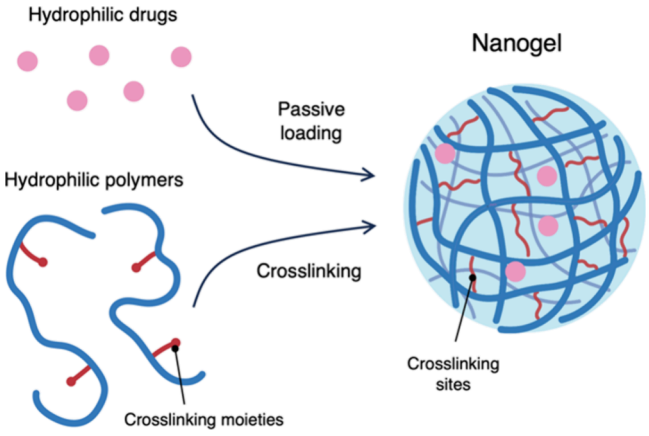

Figure 44. A schematic illustration depicting the self-assembly of nanogels.

absorption of water, and thus combine the advantages of both nanoparticles and hydrogels. Nanogels are typically soft, stable, and based on biodegradable materials with a wide size range (20−200 nm) and a high biocompatibility due to their hydrophilic chemistry as well as their water absorption properties, which mirrors the structure and behavior of tissue.[492] Nanogels are composed of hydrophilic polymers that are highly cross-linked either through chemical covalent bonds or through supramolecular interactions including electrostatic, host−guest, and hydrophobic interactions, as well as hydrogen bonding. This cross-linking allows them to resist destabilization due to dilution during blood circulation.[493,494] RDRP has allowed for the synthesis of covalently cross-linked nanogels with enhanced functionality and structure. For example, Xin et al. utilized RAFT polymerization to synthesize a photocleavable nanogel based on a nitrobenzyl acrylate cross-linker and PEGMA.[495] Importantly, this RAFT method allowed for strong control over the size and dispersity of the nanogels, and resulted in a drug loading efficiency that was correlated with the size and dispersity of the nanogels. Furthermore, nanogels also contain hydrophilic pendant groups, including alcohols, carboxylic acids, and amides, which are particularly well suited to grafting stimuli-responsive and pH-responsive moieties. Nanoprecipitation, aqueous self-assembly, cross-linking, as well as various emulsion techniques are commonly used for the formation of nanogels. Unfortunately, the difficulties in scaling up production, as well as imperfect batch reproducibility limits the applicability of nanogels as drug-delivery vehicles relative to micelles.[493] Nanogels formed through supramolecular interactions typically involve the self-assembly of micelles followed by non-covalent cross-linking. Such nanogels can be formed in mild conditions, but are generally weaker than their covalently cross-linked counterparts.[494]

Nanogel drug loading is typically a passive mechanism, with the drug either transporting into the polymer matrix via osmotic pressure, or becoming encased by the nanogel during self-assembly. Drugs can also be conjugated to the nanogel covalently through drug−polymer conjugates. Nanogels, due to their water solubility and swellability, are able to more efficiently load hydrophilic drugs as opposed to standard micelle configurations; indeed, they are particularly appealing as delivery vectors for hydrophilic macromolecules such as DNA and RNA, which can be loaded at levels >50%.[492,496] RNA cross-linking and DNA/enzyme incorporation into the nanogel are motifs that have gained significant attention in recent years. For example, Ding et al. designed a nanogel that was formed from DNA-*g*-PCL micelles cross-linked with siRNA linkers and coated with a thin layer of PEGylated polydopamine, a photothermal moiety.[497] This 90nm nanogel was able to both protect and deliver siRNA, as well as display endosomal escape and apoptosis inducing capability via a low-temperature photothermal mechanism. De Backer et al. used mini emulsion polymerization to synthesize a siRNA-loaded dextran nanogel cross-linked with the cationic trimethyl ammonium moieties, and stabilized with a commercial pulmonary surfactant.[496] This pulmonary surfactant imbued the nanogel with the ability to target human lung cells, and resulted in greater RNA delivery efficacy relative to uncoated nanogels by a factor of five. Further studies revealed these nanogels could be delivered via aspiration into the lungs as opposed to injection while maintaining their siRNA delivery capability.[498]

As well as nucleic acids, hydrogels have gained attention as a therapeutic protein delivery vehicle due to their hydrophilicity, porosity and biocompatibility.[499] For example, Zhiyuan Zhong's research group have investigated hyaluronic acid-based nanogels for protein encapsulation and stimuli-responsive delivery. In one design, they designed a nanogel based on hyaluronic acid and functionalized with cysteine, a redox-responsive moiety, and the pH-responsive, endosome-disrupting peptide GALA.[500] These ∼80 nm stimuli-responsive nanogels were formed through catalyst free, tetrazole-alkene click cross-linking, and display an endosomal escape capability as well as the ability to load a range of proteins including cyctochrome C, herceptin, immunoglobin G, and bovine serum albumin. Another study employed a similar HA nanogel to load saporin, a clinically active anti-cancer protein.[501] The nanogel displayed strong cellular uptake due to the conjugation

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Chem. Rev. 2024, 124, 5505−5616

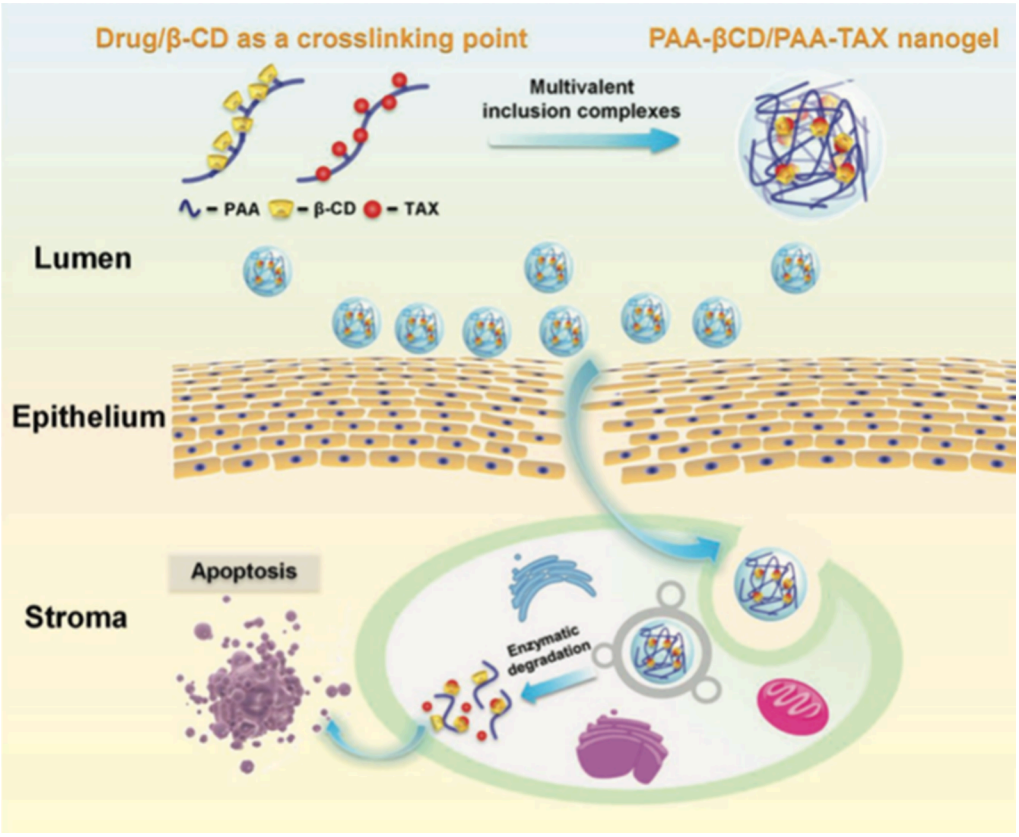

Figure 45. Drug−polymer conjugation was used to design a nanogel that was able to efficiently encapsulate PTX (TAX), a hydrophobic drug. Specifically, PTX was conjugated to poly(acrylic acid), a mucoadhesive polymer, which formed a nanogel when cross-linked with cyclodextrin. The enhanced targeting performance and high loading efficiency of this nanogel yielded strong anti-tumor performance. Reproduced with permission from ref. 503. Copyright 2019, Wiley-VCH.

of the GE11 peptide (a targeting ligand) and demonstrated tumor inhibition activity in mice.

Though less well studied, nanogels have also shown significant potential as hydrophobic drug-delivery vehicles. For example, Song et al. designed a nanogel formed from the combination of two different chitosan derivatives cross-linked with hydroxypropyl-β-cyclodextrin that was able to encapsulate two poorly soluble drugs: a chemotherapeutic agent PTX and an immunotherapeutic agent (IL-2).[502] Qian et al. designed a nanogel that efficiently loaded the hydrophobic drug PTX (TAX) via drug−polymer conjugation with poly(acrylic acid), and cross-linking with cyclodextrin (Figure 45).[503] The inclusion of poly(acrylic acid), a mucoadhesive polymer, yielded a nanogel with strong targeting and anti-tumor performance in a cervical cancer model.

Stimuli-responsiveness is a highly desired trait to increase the therapeutic efficiency of nanogels. This responsiveness expresses itself through the swelling or deswelling of the nanogel due to external environmental changes, including but not limited to variations in pH, temperature, and redox environment. Tian et al. designed a 200 nm redox-responsive nanogel composed of PEG, diglycidyl ether and hyaluronic acid (HA) cross-linked via disulfide bonds.[504] This nanogel showed promise as an anti-cancer delivery system as tumor cells overexpress both HA receptors and GSH, triggering the preferential release of DOX. Qu et al. designed a redox-responsive hydrogel that conjugated camptothecin (CPT), an extremely insoluble anti-tumor drug, to an acrylamide cross-linked methacrylic acid hydrogel via a disulfide linkage.[505] This nanogel combined both redox- and pH-responsive behaviors through the disulfide and methacrylic acid moieties, and showed significant *in vivo* anti-tumor activity with little side effects. Ju et al. synthesized a pH-responsive DOX-loaded nanogel based on *N*-lysinal-*N*′-succinyl chitosan that was able to swell from 200 nm at neutral conditions, to over 2 μm at a low pH (~4.5).[506] This swelling was reversible, and served not only to enhance the endosomal escape capabilities of the nanogel but also to allow for repeated DOX delivery to different tumor cells. The theorized mechanism for this cycling behavior involved: (1) nanogel endocytosis and swelling in the endosome; (2) nanogel release into the cytosol and subsequent contraction due to the neutral cytosolic pH; (3) nanogel exocytosis/escape from the dead tumor cell; and (4) endocytosis of the nanogel into a new tumor cell, resulting in the release of the remaining encapsulated DOX. This is a particularly interesting nanoparticle design as it offers the potential to treat multiple cells with the one nanoparticle and thus increase efficiency. In 2021, Zhang et al. designed a thermoresponsive nanogel whereby the protein BSA was covalently conjugated to the particle via self-immolative carbamate linkages.[507] RAFT was employed to synthesize a copolymer containing PEG, and carbamate functionalized, disulfide containing polymeric component, which formed a nanogel. The nanogel was able to achieve traceless release of BSA in the presence of GSH, which mirrors the reducing conditions of the endosome.

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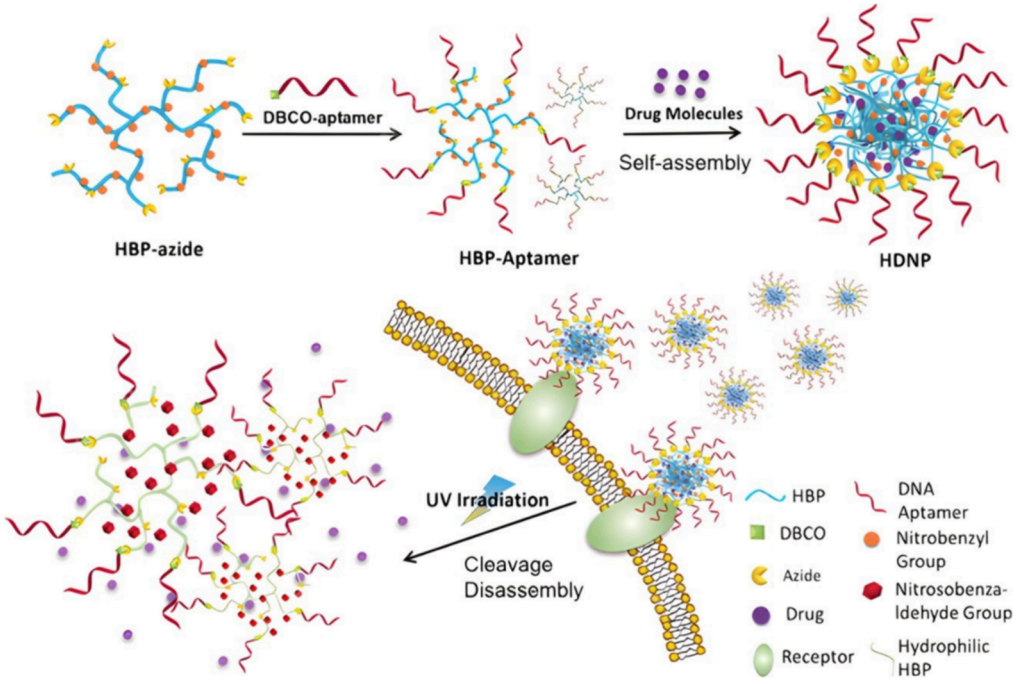

Figure 46. A light-responsive hyperbranched polymer that is able to encapsulate and deliver the insoluble chemotherapeutic drug DOX. This hyperbranched polymer was composed of UV degradable nitrobenzyl groups and stabilized by a DNA−polymer conjugate (aptamer). Cleavage at 365 nm irradiation resulted in controlled drug release and anti-tumor efficacy. Reproduced with permission from ref. 531. Copyright 2018, Wiley-VCH.

5.5. Star and Hyperbranched Polymers

Star polymers and hyperbranched polymers (HBPs) are examples of polymeric systems composed of many "arms" that form a matrix, either by growth from a central core, in the case of stars, or by random irregular ordering in the case of hyperbranched materials. At higher molecular weights, these polymer systems form globular, spherical, or quasi-spherical three-dimensional structures potentially dozens of nanometers in diameter.[508,509] Though not always referred to in the literature as such, stars and hyperbranched polymers are, in the authors' view, a kind of polymeric nanoparticle. As opposed to micelles and vesicles, these kinds of polymeric nanoparticles are sometimes described as unimolecular containers, since they do not rely on self-assembly and hence benefit from robust stability due to their covalent reinforced structure.[510] Furthermore, unlike self-assembly systems, stars and HBPs do not require multi-step fabrication methods, and can instead be synthesized via a one-step approach. Ring-opening and ring-opening metathesis polymerization (ROP/ROMP), as well as the development of RDRP methods such as ATRP and RAFT polymerization, has allowed for the creation of highly controlled and structurally sophisticated polymers, greatly enhancing the power and potential of star and HBPs.[511,512] Stars and HBPs have displayed an efficient drug-delivery capability as unimolecular vectors alone, but they have also been used as building blocks to design a wide variety of functional micelles, core shell particles and vesicles.[513]

Star polymers are polymer architectures composed of multiple "arms" (linear or block copolymers) emanating out of a central core in the shape of a star (Figure 35E). More recent research has focused on asymmetric star polymers with a variety of arms (≥3) with different molecular weights and chemical functionalities. These systems are known as miktoarm stars.[514] Star polymers can be synthesized either through the polymerization and growth of linear polymers from a central multi-functional initiator (core first), or by the formation of linear polymers first, followed by their subsequent grafting/cross-linking/conjugation to a central core to form a star (arm first).[512] In this way star polymers are structurally similar to dendrimers, which are large organic macromolecules formed from a few repeating units (generations), which at their largest (∼5 nm) can form globular structures. However, unlike dendrimers, whose laborious synthesis limits scalability, star polymers can be synthesized via more facile polymerization techniques.[512] Furthermore, the greater size and lower density of star polymers allows for the loading of larger, more diverse therapeutics. We will not include dendrimers in our description of polymeric nanoparticles; however, for the reader's interest, two reviews into dendrimers for drug delivery are presented here.[515,516]

Star polymers are capable of delivering both hydrophobic and hydrophilic drugs. Kostka et al., for example, designed star polymers based on a polyester hyperbranched core grafted with PHPMA arms with tunable size (13−31 nm).[517] DOX was conjugated to the arms via a pH-responsive hydrazone link, and the DOX-stars were able to prevent tumor growth in mice. Teo et al. designed a ∼30 nm star polymer with PEG and PDMAEMA arms cross-linked to form stars via the arms first approach.[518] This star was able to electrostatically complex RNA, and showed therapeutic potential against pancreatic cancer and lung cancer in an aerosol form.[519] Song and co-workers took this design further, synthesizing a miktoarm star polymer based on a β-cyclodextrin core with PEG and PDMAEMA arms.[520] This star was able to encapsulate DOX within its core via host−guest interactions, while complexing RNA to its PDMAEMA arms, resulting in a dual component system with superior anti-tumor efficacy. Nayanathara et al., seeking to understand how star polymers affect nanoparticle

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

behavior, designed a pH-responsive nanoparticle whose core constituted either a charge-shifting star polymer or a charge-shifting linear polymer.[521] This nanoparticle was also able to efficiently encapsulate DOX via drug−polymer conjugation. Interestingly, the star and linear polymers yielded similar physiochemical properties for the nanoparticles, but the linear polymer system had superior toxicity. Qiao and co-workers designed star polymer peptide−polymer conjugate arrays termed "structurally nanoengineered antimicrobial peptide polymers" (SNAPPs).[522] These SNAPPS, containing a poly(amidoamine) (PAMAM) core with PLA and poly(valine) arms, showed the greatest bactericidal properties when functionalized with 8 arms.[523] Durmaz et al. sought to employ stimuli-responsiveness, and designed a pH-responsive cyclodextrin star polymer for gene delivery.[524] pH responsiveness was imbued by hydrazone moieties, with the star able to detach half of its arms in only 1 h at pH 5.8. Zhang et al. designed star polymers based on self-immolative PEtGs.[331] The star polymers underwent highly tunable pH-induced depolymerization, providing a design strategy for both a stimuli-responsive and biodegradable drug-delivery vehicle with reduced off-target effects.

Hyperbranched polymers, as opposed to stars, are matrixes comprising highly branched and randomly distributed polymers that manifest as a three-dimensional globular particle (Figure 35F). HBPs are the smallest kind of polymeric nanoparticle, with sizes usually below 10 nm, and are in some sense the most structurally simplistic. They are characterized by small size, low viscosity, high solubility, and low polymer entanglement, resulting in large intramolecular cavities.[525] Furthermore, the unique topology of HBPs results in the high surface density of functional groups, making subsequent modification and functionalization easier and more powerful. The properties of HBPs are determined by chemical functionality and monomer ratios, MW and dispersity, and the degree of branching.[526] As drug-delivery vehicles, a high surface density of functional groups endows HBPs with significant drug conjugation capability, while the existence of cavities within the matrix allows for drug loading via physical host−guest interactions.[527] Functionalized hyperbranched polyethyleneimines, polyesters, polyethers, polyacrylamides, and β-cyclodextrins have been well studied as vehicles to encapsulate and more efficiently deliver a wide range of hydrophobic and hydrophilic drugs. For example, Wei et al. functionalized nanodiamonds, another promising biotherapeutic agent, with β-cyclodextrin HBPs, resulting in a system with a very high DOX loading capacity.[528] Thurecht and co-workers designed a 25 nm dual pH- and redox-responsive PEGylated HBP that conjugated both DOX, via a pH-responsive hydrazone linkage, and RNA, via a disulfide linkage.[529] Their HBP was able to achieve very high RNA coupling >80%. Wei et al. designed a similar dual-functional HPMA-based HBP, but employed a redox cleavable peptide linkage to load therapeutic cargo.[530] In 2018, Tan and co-workers designed a light-responsive HBP composed of UV degradable nitrobenzyl groups with DNA conjugated to the HBP via an azide linkage (Figure 46).[531] This HBP was also able to conjugate DOX within hydrophobic cavities forming larger 40 nm spherical nanoparticles. Under 365 nm irradiation, this dual component HBP showed controlled drug release and tumor inhibition. Gao et al. sought to imbue a cinnamaldehyde-based HBP with pH responsiveness from its backbone.[421] This was achieved through pH labile aminoethylpiperazine moieties, and it was shown that the resultant biodegraded polymer fragments were able to inhibit the growth of bacteria by generating ROS. ROS responsiveness was also utilized by Zhang et al. who imbued a PEG-based HBP with ROS responsiveness via tellurium.[294] H_2O_2 caused the HBPs to swell from ∼28 to ∼66 nm. The mechanism was posited to be caused by the change in chemical environment of the oxidized tellurium atoms.

By virtue of their tunability, versatility, ability to load a diverse range of drugs, and, most importantly, their unparalleled functional power, polymeric nanoparticles are perhaps the most promising class of non-lipid-based drug-delivery vehicles. Polymeric nanoparticles have shown levels of drug loading efficiency, bioavailability, and targeted delivery unrivalled by other delivery vectors. However, the difference between what can be synthesized by cutting edge research laboratories and what can be produced in a commercially viable manner illustrates the principal reason why polymeric nanoparticles are still relatively rare in clinical medicine. Batch-to-batch consistency, toxicity, cost, and long-term stability are four hurdles polymeric nanoparticles must overcome before they can be considered a force in the drugs market. Furthermore, the diversity of structure, chemical functionality and stimuli-responsive behavior across different nanoparticle designs is vast, and there remains no clear agreement regarding which designs are the most fruitful moving forward. Finally, there remains a surprising dearth of research comparing the various polymeric nanoparticle designs with other drug-delivery vectors, specifically liposomes and lipid nanoparticles. Greater study is required comparing the performance of polymeric nanoparticles to these designs. Nevertheless, polymeric nanoparticles are uniquely suited to address the inevitable future challenges of delivering extremely sensitive or insoluble drugs and minimizing toxic off target drug effects, particularly in the case of cancer therapy. In terms of synthetic simplicity, cost and scalability, micelles show the most promise, and will likely be the first polymeric nanoparticles to significantly impact the market. As drug-based therapies become more complex and demanding of highly precise performance, it is expected that the applicability and importance of polymeric nanoparticles will only increase over time.

5.6. Hybrid Nanoparticles

Hybrid nanoparticles involve the combination of different components to provide a sophisticated, multi-functional design that displays promise as a drug-delivery vehicle. Comprehensive reviews on hybrid nanoparticles that solely comprise organic constituents, such as lipid−polymer hybrid nanoparticles, have been published in the last decade.[532−534] Therefore, this section will focus on polymeric nanoparticles with specific inorganic constituents (Figure 47). By combining the unique properties of diverse materials, these inorganic-based hybrid nanoparticles offer a versatile platform that can be tailored to encapsulate, protect, and efficiently deliver therapeutic agents to their intended targets. However, these hybrid designs are highly complex and the current research is focused on more fundamental aspects of these materials. Though hybrid nanoparticles have displayed strong efficacy in *in vitro* and animal models, more work is needed to translate these benefits to clinical trials and beyond.

5.6.1. Preparation Methods. *5.6.1.1. Surface Modification.* Surface modification involves coating an inorganic core with single/multiple layers of polymers to form a hybrid

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Chem. Rev. 2024, 124, 5505−5616

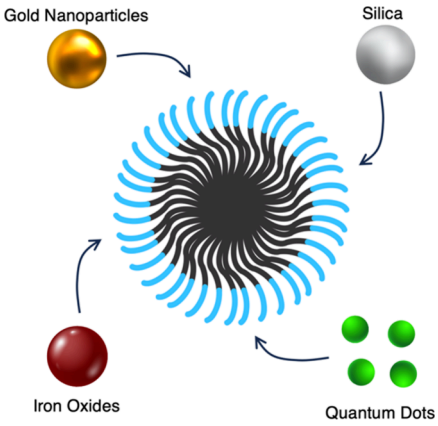

Figure 47. Hybrid nanoparticles are polymeric nanoparticles that incorporate a fraction of inorganic material for a variety of therapeutic purposes. Depicted are four of the most common inorganic materials that have been incorporated within polymeric nanoparticles: gold nanoparticles, silica, iron oxides, and quantum dots.

nanoparticle. These polymers can be deposited onto the surface of the core via two separate methods.[535] The first is through non-covalent bonding, such as hydrophobic interactions and electrostatic attraction. For example, layer-by-layer deposition has been widely used to form highly controlled hybrid nanoparticles by adding charged polymers to a suspension of oppositely charged inorganic particles.[536] The morphology and the thickness of the polymeric layers can be easily adjusted, and this surface modification also serves to enhance biocompatibility and colloidal stability of the inorganic components.[537]

The second method is to graft/grow polymer chains on the surface of the inorganic core through covalent bonding. The grafting approach often involves coupling techniques and requires embedding certain functional groups onto the surface of the inorganic core, allowing subsequent chemical reactions to attach the polymers to the surface to form the polymeric shell. "Click chemistry", such as azide–alkyne addition and thiol–ene reactions, has been widely used to modify the surface of inorganic nanoparticles under mild reaction conditions.[538] Initiating polymerization directly on the surface of the inorganic core is known as a bottom-up approach, and allows for the synthesis of more stable hybrid particles, with higher grafting densities compared to non-covalent adsorption.[539] More advanced polymerization methods yield a high degree of control over polymer density, composition, the thickness of the shell, and even exotic architectures, such as brushes. In this kind of system, specific functional groups need to be pre-anchored to the surface of the inorganic core. These include an immobilized ruthenium catalyst in the case of ROMP[540], immobilized azo initiator groups in the case of RAFT[541], and an immobilized alkyl halide in the case of ATRP.[542]

Surface modification allows polymeric components to encapsulate and protect functional inorganic cores, thus improving their biocompatibility and water solubility. For hybrid nanoparticles prepared via this strategy, the diameter of the inorganic core is usually much larger than the thickness of the polymer shell.

5.6.1.2. In Situ Precipitation. *In situ* precipitation involves the spontaneous self-assembly of amphiphilic block copolymers into polymeric nanoparticles through non-covalent interactions, and provides a cost-effective route for the preparation of structured materials.[543] Smaller inorganic particles are encapsulated into the polymeric nanoparticles during this self-assembly process, and the resulting hybrid materials retain the functionality of both their polymer and inorganic components, while demonstrating synergistic effects that differ from each individual component.[544,545] When compared to surface modification, where the hybrid nanoparticle is grown from a single inorganic core, nanoparticles prepared via this method normally encapsulate multiple smaller inorganic particles.

The distribution of inorganic cargo within these hybrid nanoparticles can be adjusted by the interaction between the cargo and the polymer matrix. Specifically, when the interaction is unfavorable, inorganic cargos tend to form closely packed clusters within nanoparticle cores, whereas they will be more evenly dispersed throughout the particle when the interactions with the polymer matrix are more favorable.[546,547] A series of studies from Park's group have shown that rational design of starting materials and their relative concentrations can govern the distribution of inorganic cargos into different anisotropic arrays.[548,549] One study details a three-layered hybrid nanoparticle composed of CdSe/ZnS interfaces formed during the self-assembly of poly(acrylic acid)-*b*-PS block copolymers and hydrophobic CdSe/ZnS quantum dots (QDs). The distribution of QDs can be regulated by changing the relative concentrations of reactants. An increased polymer concentration led to the radial position of QDs shifting toward the center, which was explained by the smallest possible loss of conformational entropy of polymer chains.[550] In another study, the choice of solvent also affected the cargo locations when QDs were replaced with iron oxide particles. Assemblies in DMF/water generated an organic interface, but assemblies in THF/water produced typical core–shell nanoparticles with a uniform dispersion of iron oxide throughout the polymer matrix (Figure 48).[551]

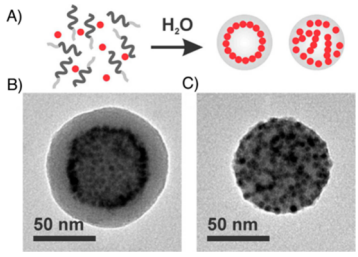

Figure 48. (A) A Schematic illustration of the self-assembly of QDs and amphiphilic copolymers into two distinct nanoparticle assemblies of magneto-core/shell assemblies (left) and magneto-micelles (right). (B) A TEM image of a magneto-core/shell assembly prepared with 2.8 nm iron oxide particles using DMF as the common solvent. (C) A TEM image of a magneto-micelle prepared with 2.8 nm iron oxide particles using THF as the common solvent. Reproduced with permission from ref. 551. Copyright 2013, American Chemical Society.

Loading small inorganic cargos into polymeric nanoparticles through non-covalent interaction is the most widely used strategy for preparing hybrid nanoparticles with unique morphologies and properties. There are, however, notable challenges when utilizing precipitation to form hybrid inorganic–polymeric nanoparticles. For instance, cargo loading efficiency is usually lower than 1% w/w,[552] and cargo leakage

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505–5616

can occur, due to the fact that the cargo is generally bound to the nanoparticle via hydrophobic interactions.[553] Forming a covalently bound conjugate between the inorganic cargo and the polymer is one method to alleviate this problem. Recently, we reported the design of pH-responsive core−shell hybrid nanoparticles that incorporate $[B^{III}W_{11}O_{39}Co^{III}]^{6-}$ cargos. This was achieved by forming a coordination bond between Co^{III} and the pyridyl pendant of the polymer chains. Cryo-EM was conducted on the hybrid nanoparticles at pH 8, 7, and 6 to observe the distribution of $[B^{III}W_{11}O_{39}Co^{III}]^{6-}$ as well as the particle's structural rearrangement in response to acidification.[554] Generally, pre-modification is a feasible strategy to improve the loading efficiency and overall stability of hybrid assemblies. Although it provides a more controlled means of loading and release, more research is needed in terms of better characterization techniques and the incorporation of cleavable bonds between polymer chains and inorganic cargo.

5.6.1.3. In Situ Polymerization. Another preparation method for hybrid nanoparticles is the *in situ* encapsulation of small inorganic cargo during the polymerization process. There are two main routes to attain hybrid nanoparticles by *in situ* polymerization: miniemulsion polymerization and PISA. In miniemulsion polymerization, nucleation occurs within monomer droplets, as opposed to micelles in conventional emulsions. Generally, inorganic particles are modified to become hydrophobic nucleation sites within monomer droplets, from where they become part of a hybrid nanoparticle following polymerization. Emulsifying inorganic cargo in monomer droplets pre-polymerization is a central challenge of this process, as droplets containing inorganic cargo are often highly viscous and abrasive.[535,555] Utilizing high pressure in both the monomer feed step and during homogenization can successfully break up particle-loaded droplets, leading to a more efficient preparation process.[556]

PISA allows for the synthesis of polymer−inorganic hybrid nanoparticles with very high solids content.[552] As previously discussed, the formation of block copolymers and their self-assembly into nanoparticles occurs at the same time during PISA. Nanoparticle morphology generally evolves from small spherical micelles to linear wormlike intermediates as the polymerization progresses. The final stages of PISA yield highly branched networks and partially coalesced worms, which eventually enclose to form vesicles with almost 100% monomer conversion.[557] Given the vesicles are hollow nanospheres with hydrophilic cores, it is possible to encapsulate hydrophilic inorganic particles into these polymersomes via PISA. Some studies have reported the preparation of hybrid vesicles with more than 10% w/w inorganic content by a one-pot PISA approach, encapsulating up to hundreds of silica nanoparticles per vesicle.[558] For example, Tan et al. used photoinitiated PISA to prepare hybrid vesicles with 25% w/w silica. The silica nanoparticles (20 nm) were added before the PISA reaction and loaded *in situ* into the polymeric vesicles. TEM and SEM images confirmed the successful encapsulation of silica into the lumen of vesicles.[559] Overall, PISA is an attractive strategy to synthesize polymer-inorganic hybrid nanoparticles. However, for now, only SiO_2 and TiO_2 have been loaded into polymeric vesicles via PISA.

5.6.2. Inorganic Cargos. Inorganic particles and scaffolds are a promising candidate for the design of more sophisticated drug-delivery nanoparticles, due to their diverse biological functionality. For a comprehensive summary of these inorganic materials, the reader is directed to these recent publications.[560−562] This section aims to highlight an important subclass of polymeric nanoparticles where inorganic materials are encapsulated or integrated within a greater polymeric matrix. Currently, the most commonly studied inorganic cargos are silica, QDs, gold nanoparticles, and metal oxides. Hybrid nanoparticles that can encapsulate these kinds of cargo are of high interest for biological applications, since they usually demonstrate higher solubility, better cytotoxicity, and more sensitive stimuli-response compared with their individual starting materials.

5.6.2.1. Silica. Silica is a useful platform for many drug-delivery applications due to its extensive surface area, porous structure, low toxicity, and biodegradability.[563] However, the usefulness of silica is strongly diminished via unfavorable interactions with red blood cells (hemolysis), due to the silanol group on its surface.[564] Silica-based hybrid nanoparticles are a feasible strategy to solve this problem. Polymer-modified mesoporous silica nanoparticles (MSNs) are the subject of significant interest due to their outstanding stability under extreme environments and strong encapsulation capability, and are the focus of a number of comprehensive reviews.[565,566]

Zhao et al. described an ultra-small silica−polymer hybrid nanoparticle, prepared by the self-assembly of PEG-*b*-PPG-*b*-PEG tri-block polyoxamers and a silica precursor. The diameter of the silica core was <5 nm and the total size of the hybrid nanoparticle was 14 nm. This particle comprised a brush-like PEG corona as its shell, which yielded superior stealth and non-specific binding properties when compared to linear PEG-modified silica dots. More importantly, animal experiments indicated that brush PEG-modified particles could be excreted faster compared to the linear PEG-modified silica dots. Specifically, more than 90% of injected nanoparticles with the brush-like PEG shell were excreted within 5 days, along with a prolonged blood-circulation half-life of 19 h. These features benefit tumor targeting through the EPR effect, displaying great potential for further biomedical applications.[567]

Modifying the surface of MSNs via covalently conjugated polymers is another widely used strategy to prepare hybrid nanoparticles. For example, Wang and co-workers utilized enzymatic radical polymerization to prepare hybrid nanoparticles with redox responsive polymeric shells and MSN cores. The MSNs were first modified with a coupling agent (3-aminopropyltriethoxysilane) to obtain amine groups on the surface. These amines were then further reacted with *N*-acryloyloxy succinimide to obtain vinyl-functionalized MSNs. Finally, the hybrid nanoparticles were prepared via laccase-mediated polymerization of dimethylacrylamide and a redox-responsive bis(acryloyl)cystamine cross-linker. During this preparation, the diameter of particles was observed by TEM and DLS to increase from 55 to 180 nm. *In vitro* drug loading and release tests indicated that DOX was encapsulated into the particles with a high loading capacity (∼34%). The hybrid nanoparticles showed significant DOX release under physiological reducing conditions.[568] Similarly, Ribeiro et al. designed a thermoresponsive hybrid nanoparticle composed of a fluorescent MSN core and a poly(2-(2-methoxyethoxy)ethyl methacrylate)-*co*-(oligo(ethylene glycol)methacrylate) shell. The surface of MSNs was functionalized with a RAFT agent to undergo RDRP, allowing for control over the density and thickness of the polymeric shell. Sulforhodamine B was then used as a model cargo to test the nanoparticles' loading and release behavior over different temperatures. At low temper-

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Chem. Rev. 2024, 124, 5505−5616

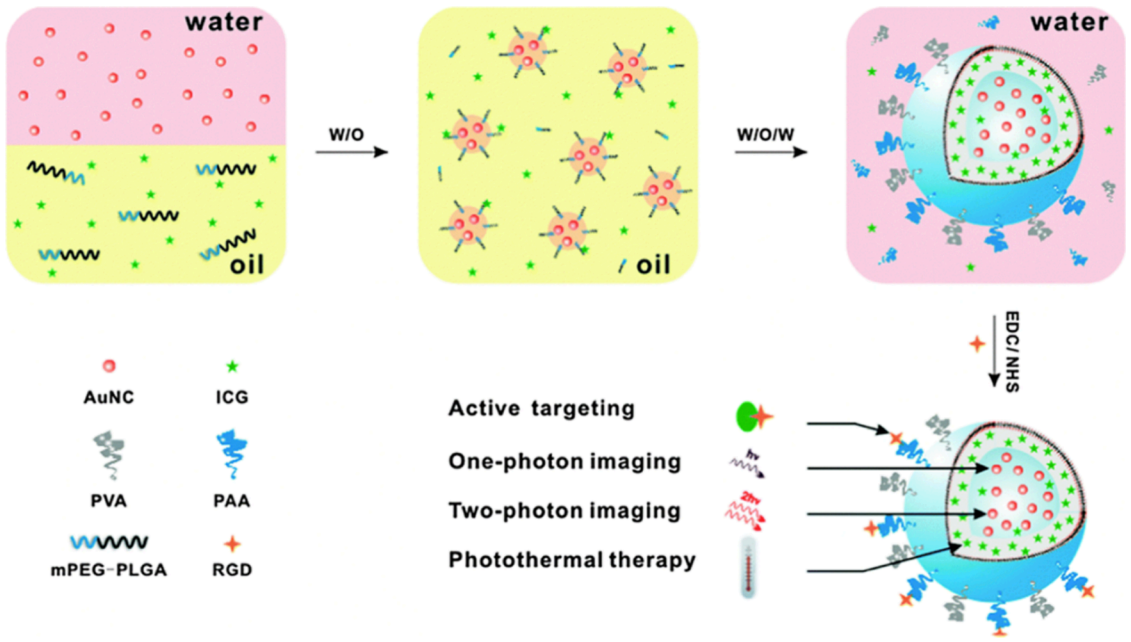

Figure 49. A Schematic representation of the formation of RGD-functionalized Au NPs-loaded hybrid polymersome via a double emulsion process (w/o/w). Reproduced with permission from ref. 583. Copyright 2016, Royal Society of Chemistry.

atures, the fluorescent cargo successfully diffused into the polymer shell, to be released at a high temperature above the polymer's LCST (37° C). More work needs to be done to increase the LCST to better mimic the higher temperatures associated with the tumor microenvironment.[569]

5.6.2.2. Quantum Dots. Quantum dots (QDs) are semiconducting nanoparticles 2−10 nm in size, with size-dependent optical and electronic properties.[570] Usually, ∼5−6 nm QDs emit longer wavelengths of visible light (red or orange), while ∼2−3 nm QDs emit shorter wavelengths (blue and green). QDs exhibit notable advantages when compared with traditional organic dyes, such as a narrow emission spectrum, high resistance to photobleaching and a high photoluminescence quantum yield.[571] However, QDs generally exhibit poor water solubility, cytotoxicity, and a tendency to aggregate in aqueous solutions. Thus, encapsulation in hybrid nanoparticles is a vital method to convert QDs into promising bioimaging and theranostic tools.

QDs with NIR fluorescence have been actively studied mainly for cancer imaging due to their high quantum yields and tunable emission. Wang et al. reported an indium phosphate core/zinc sulfide shell (InP/ZnS) QD-loaded micelle that was modified with anti-epidermal growth factor receptor (EGFR) nanobodies. This hybrid micelle was designed to target EGFR, which is overexpressed in cancers. The surface of the InP/ZnS QDs was functionalized with carboxyl groups, and PEG-*b*-PLA block polymers were grafted to the QDs via esterification. Then, the anti-EGFR nanobodies were selectively conjugated to the end of the PEG arm through a thiol-maleimide reaction. In subsequent *in vitro* and *in vivo* tests, the QD cores showed stable NIR fluorescent signals, helping to monitor the localization of the hybrid nanoparticles.[572]

As well as imaging, QDs are also promising theranostic agents due to being donors for the Forster resonance energy transfer (FRET) process.[573,574] Recently, $CdSe_xS_{1-x}$/ZnS QDs and zinc(II) phthalocyanines (photosensitizers) were loaded into polymeric nanoparticles via a solvent/evaporation method. The shortening of the QD's fluorescence lifetime confirmed that the average distance between QDs and phthalocyanines inside the hybrid nanoparticles was suitable for FRET even without chemical linkage. This successful FRET generated ROS from the photosensitizers upon NIR irradiation, which is an important stimulus for many drug-delivery applications.[575]

5.6.2.3. Gold Nanoparticles. Gold nanoparticles (Au NPs) have been widely investigated across a variety of medical applications due to their unique electronic and optical properties, as well as their biocompatibility. Modification of Au NPs with organic ligands under physiological conditions occurs via the Au−S bond. Given that this bond is responsive under endogenous redox conditions, specifically due to the presence of GSH in the cytoplasm of cells, Au NPs are a very attractive drug-delivery vector.[576]

Plasmonic nanostructures possess the ability to efficiently transform incident light within the spectral range of surface plasmon resonance (SPR) into thermal energy, resulting in the localized heating of the surrounding medium. Particularly for *in vivo* applications, nanostructures exhibiting SPR bands within the NIR spectral window are desirable, as this spectral range experiences comparatively minimal light attenuation by blood and soft tissue. Therefore, Au NPs have emerged as promising candidates for photothermal applications, given their capacity to readily adjust their longitudinal plasmon resonance into the NIR region through alterations in their aspect ratio.[577] Duan and co-workers have designed a class of hybrid plasmonic vesicles assembled from polymer brush coated Au NPs. These hybrid nanoparticles were conjugated with a hydrophilic PEG brush shell, as well as both ATRP and ROP initiators through the Au−S bond, allowing for highly controlled surface modification.[578] The obtained hybrid vesicles displayed the optical and spectroscopic properties of gold nanoparticles, as well as an enclosed cavity structure similar to polymersomes.[579] These novel vesicles showed promise as theranostic platforms,[580] traceable intracellular drug

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carriers,[581] and for imaging-guided photothermal/photodynamic therapeutics.[582]

Gu et al. reported a facile approach to encapsulate Au NPs and indocyanine green into polymeric nanocarriers based on a double emulsion process (w/o/w). Hydrophilic Au NPs were loaded into the vesicle cavity, while hydrophobic indocyanine green was loaded into the polymeric shell. The surface of this hybrid polymersome could be further functionalized by biotargeting agents such as RGD peptides, facilitating targeted delivery to the tumor cells. These hybrid nanoparticles demonstrated strong tumor imaging performance (Figure 49).[583]

Hyperbranched nanoparticles are attractive drug carrier candidates due to their modifiable surfaces and inherent internal cavities.[584] Au NPs loaded into dendrimers have been developed and systematically studied, showing excellent biocompatibility and promising imaging capability.[585−587] For example, Wang et al. developed a GSH-triggered drug-delivery system based on dendrimer-encapsulated Au NPs. Drugs that contained a thiol or could be post-modified with a thiol were covalently conjugated to the dendrimer interiors via the Au−S linkage, exhibiting controlled drug release behavior in response to thiol-reducing agents, such as GSH.[588]

5.6.2.4. Iron Oxide. Magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) are two common iron oxides that display superparamagnetic properties at sizes below 20 nm, and are widely employed in the preparation of hybrid nanoparticles.[570] In the presence of an applied magnetic field, these iron oxides can be used for a variety of biomedical applications, including targeted therapy, hyperthermal therapy, contrast agents for magnetic resonance imaging (MRI), and the ability to induce ferroptosis.[589] However, superparamagnetic nanoparticles tend to aggregate into micro-size clusters, especially in the presence of an external magnetic field, which severely limits their bioapplicability.[590] Modification with polymeric materials is one of the most promising approaches to radically enhance the biocompatibility and water solubility of iron oxide particles.

Ling et al. successfully encapsulated small iron oxide nanoparticles (~3 nm) into pH-responsive self-assembled nanoparticles by forming coordination bonds with catechol ligands. These hybrid magnetic nanoparticles demonstrated two-stage pH responsiveness: surface charge reversal and nanoparticle swelling at pH 7.0−6.5 (from 60 nm to 70 ± 5 nm); and disassembly and drug release below pH 6.5. During this process, the particle's fluorescence signal and photoactivity were turned on after the disassembly, and MRI contrast was quenched at pH 7.4, but recovered at pH 5.5. The following *in vivo* tests of these hybrid nanoparticles demonstrated effective tumor diagnosis and greater therapeutic efficacy in both human colorectal carcinoma xenografts and highly heterogeneous drug-resistant tumors.[591]

Because of the inherent magnetic properties of iron oxide particles, applied ultrasound and magnetic fields have imbued the resultant hybrid nanoparticles with targeted drug-delivery capabilities. One study has shown that core−shell nanoparticles made from PVA and magnetic nanoparticles displayed strong magnetothermal chemotherapy, while releasing a drug when exposed to a high frequency magnetic field.[592] Beyond this, magnetic PLGA nanoparticles have been shown to actively accumulate around tumor tissue under an applied magnetic field, leading to an increased concentration of the drug in the targeted region. This approach exhibited excellent anti-tumor activity for ultrasound accessible tumors with perfused vascularity, such as colon cancer.[593] Kim et al. designed a nanoparticle whereby DNA block copolymers self-assembled to form a shell around Fe^{III} ions.[594] These DNA−polymer−iron particles were highly tunable and displayed efficient cellular association and endosomal escape, allowing for enhanced siRNA delivery.

6. NON-SPHERICAL NANOPARTICLES

Polymer nanoparticles exhibiting diverse shapes and exotic architectures are commonly referred to as non-spherical or anisotropic nanoparticles, and have garnered increasing attention over the past decade (Figure 50).[595−597] These diverse particle morphologies offer the ability to enhance the drug-delivery capability through superior internalization, circulation, and targeting. However, the majority of studies on non-spherical nanoparticles, given the relative novelty of the area, focus on fundamental properties concerning fabrication and intracellular behavior. Thus far, only a few non-spherical nanoparticles have entered early clinical trials, and none have been approved for clinical use.[598] Recently, scientists have published several proof-of-concept studies that demonstrate the unique advantages of non-spherical particles for combination chemotherapy, cancer immunotherapy, and vaccination. Herein, we outline the various architectural designs of polymeric nanoparticles currently under investigation and evaluate the emerging applications of these non-spherical nanoparticles. To provide a perspective on the emerging utility of non-spherical particles in disease treatment, we explore how the shape of nanoparticles influences drug delivery.

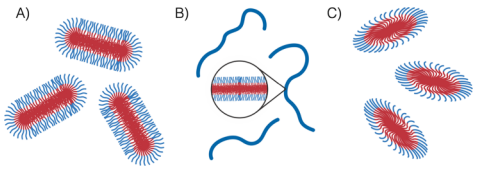

Figure 50. A selection of non-spherical polymeric nanoparticle designs consisting of (A) rod-like architecture, (B) worm-like architecture, and (C) disk-like architecture.

6.1. Preparation Methods

Various top-down and bottom-up methods have been proposed to design non-spherical nanoparticles. Generally, bottom-up approaches are cost-effective and easy to handle, but they show relatively weak control of nanoparticle morphology and size distribution. In contrast, top-down approaches are more reproducible and demonstrate strong control over shape, but usually require sophisticated instruments and processing techniques. Detailed descriptions of the preparation and characterization techniques for non-spherical organic and inorganic nanoparticles can be found in various reviews.[599,600]

6.1.1. Self-Assembly for Non-spherical Nanoparticles. Self-assembly is a widely used bottom-up method for fabricating non-spherical nanoparticles. A myriad of non-spherical morphologies can be obtained through block copolymer self-assembly, such as rods, lamellas, cones, fibers and other multi-lamellar assemblies. As previously described, the packing parameter, $p = v/al$, mainly determines the morphology of the assemblies.[601,359] Self-assembly provides a straightforward method to synthesize non-spherical nanoparticles under mild conditions, which allows for a wide variety

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Chem. Rev. 2024, 124, 5505−5616

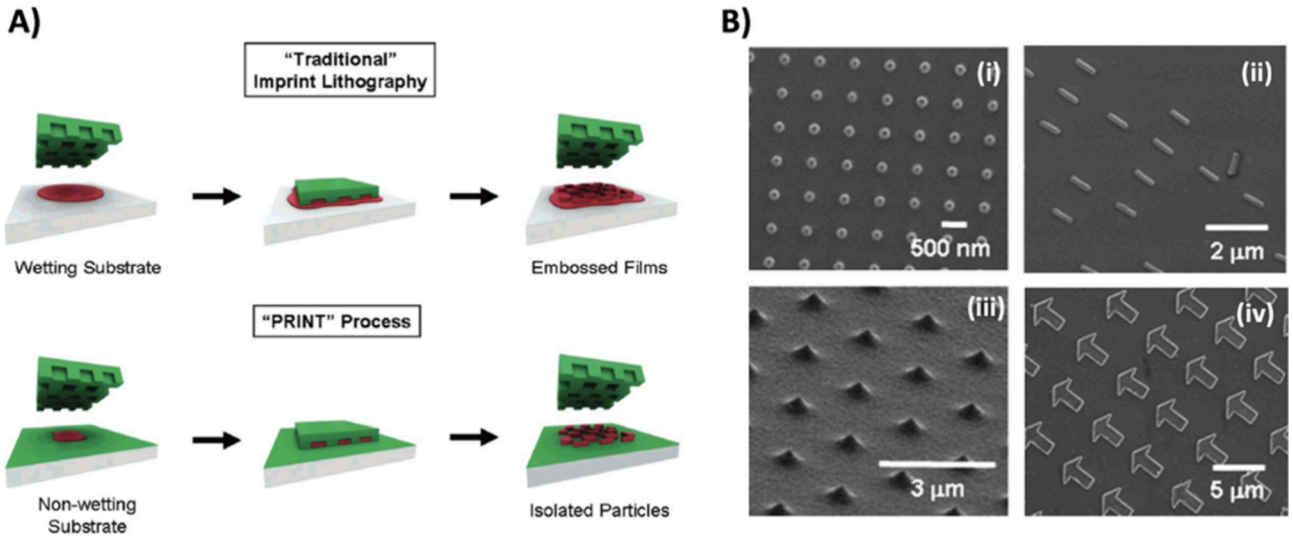

Figure 51. (A) A Schematic diagram of the PRINT process compared to traditional imprint lithography. (B) Different types of morphologies that are obtained by PRINT: (i) trapezoidal PEG particles, (ii) bar PEG particles, (iii) conical PEG particles, (iv) arrow PEG particles. In PRINT, the use of a non-wetting substrate allows for the generation of isolated particles. Reproduced with permission from ref. 609. Copyright 2005, American Chemical Society.

of delicate therapeutic cargo to be loaded, such as proteins and nucleic acids. However, nanoprecipitation, the most common self-assembly method, often results in batch-to-batch inconsistency and a relatively broad size distribution, which limits its clinical potential somewhat. Moreover, because the polymer chains are bound together mainly by the hydrophobic effect rather than stronger covalent bonds, the stability of nanoparticles can be suspect, depending on the different external environments.[602]

6.1.2. Mechanical Deformation. In the fabrication of non-spherical nanoparticles, mechanical deformation serves as a critical technique, particularly within the framework of top-down methodologies.[603] This approach involves the application of macroscopic manipulations to environments already containing nanoscale objects, facilitating the production of particles with diverse shapes and morphologies.[604] In one such study, PS nanoparticles were dispersed within a PVA solution. Subsequently, the dispersion underwent solvent evaporation to form a PVA thin film containing spherical PS nanoparticles, and from this starting formulation varying shapes can be formed via two different methods. The first method involves melting nanoparticles either by heating them above their glass transition temperature (T_g), or dissolving them in a suitable solvent. They can then be stretched in one or two directions to form different shapes. The second method involves first creating small voids by stretching the PVA film, and then adding extra liquid PS, either heated above its melting point or dissolved in an organic solvent into these voids. After reaching determined aspect ratios and shapes, PS nanoparticles are formed either by cooling or solvent evaporation. Finally, the non-spherical nanoparticles are obtained by dissolving the supporting substrates, often yielding a highly uniform morphology.[605] A series of shapes can be achieved by this means, which includes but is not limited to rods, worms, disks, and ellipses.[598]

The T_g and the solubility of the component polymers are the two key parameters that allow the soft particles to set into new shapes. Optimizing these two parameters also represents a major limitation of this technique. Therefore, although mechanical deformation can produce highly uniform non-spherical nanoparticles, most studies have thus far focused either on PS or PLGA.[598]

6.1.3. Molding Techniques. Photolithography, microfluidic fabrication,[606] and nanoimprint lithography[607] are three commonly used top-down molding techniques to fabricate non-spherical polymeric particles. The first two approaches normally yield microscale particles (>20 μm) due to limitations associated with both the equipment and manufacturing process.

Nanoimprint lithography involves "imprinting" polymer solutions or precursors into the holes of a template. Over time the nanoparticles solidify and are collected following the removal of the template. The resulting particles are non-spherical, and can be tailored to a variety of shapes using this technique. Nanoimprint lithography is generally regarded as a low-cost and efficient molding technique, while also allowing for a diverse set of particle morphologies. Residual scum layers, however, represent a bottleneck for this technique, and can result in an embossed film instead of separate nanoparticles. Significant research has been undertaken to solve this problem.[608] Particle replication in non-wetting templates (PRINT), for example, represents a breakthrough in this endeavor. PRINT was first reported in 2005 by Rolland et al.,[609] and it has been used to prepare uniform nanoscale particles with a range of morphologies such as cylinders, cubes, and rods (Figure 51).[610] The major novelty of PRINT is the use of photocurable perfluoropolyether (PFPE) molds instead of traditional polydimethylsiloxane molds. Highly fluorinated molds are non-wetting and non-swelling to both organic and inorganic liquids, which eliminates the residue layer between products and enables the production of isolated nanosized non-spherical particles.[611] PRINT has been used to encapsulate a range of cargo, from small molecules and prodrugs to biological macromolecules and nucleic acids.[612]

6.2. Impact of Nanoparticle Shape on Therapeutic Delivery

Non-spherical particles have gained attention in recent years as drug-delivery vehicles. In general, studies suggest that particle

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

morphology is a key parameter affecting drug-delivery performance. Thus far, numerous nanoparticle morphologies and architectures have been designed and synthesized via the methods mentioned above. These designs have demonstrated an enhanced ability to migrate various biological barriers, including biological distribution, metabolism and clearance, cellular internalization, and cytotoxicity.[613] Inorganic nanoparticles, such as gold nanoparticles and silica nanoparticles, are often employed to study the impact of shape on drug delivery *in vivo* because of their well-defined morphologies, and these proof-of-concept studies have been reviewed in detail.[614,615] Therefore, this section will introduce and discuss some recent progress in non-spherical nanoparticles and shape-shifting nanoparticles based on polymeric materials in the field of drug delivery. However, it is premature to claim non-spherical nanoparticles represent an obviously superior platform for drug delivery based on the current body of research. Notable challenges, such as synthesis complexity and the need for sophisticated characterization methods, significantly limit their widespread applicability. Moreover, the majority of explorations remain at the *in vitro* or cellular experimental stage. The mechanisms by which different nanoparticle shapes influence their performance *in vivo* are not yet fully elucidated, nor is it clear whether they can demonstrate enhanced therapeutic effects in general. Therefore, a comprehensive understanding of the physicochemical properties of different nanoparticles (such as rigidity, aspect ratio, surface area, and surface charge) is essential. Further exploration into the interactions and biotoxicity between various nanoparticles and cells in practical scenarios is crucial, which will provide a solid foundation for designing more effective nanoparticles.

6.2.1. Rods. As one of the most common non-spherical nanoparticles, rod-like nanoparticles have been widely studied in recent years. Rod-like morphology has yielded nanoparticles with increased cellular internalization, enhanced specific binding, and prolonged circulation.[602]

During the last decade, Mitragotri and co-workers investigated the role of nanoparticle shape and size in drug delivery and immune response. They showed that antibody coated polystyrene nanorods exhibited higher affinity and specificity toward the endothelium compared with spherical polystyrene nanoparticles (Figure 52).[616] This effect was not

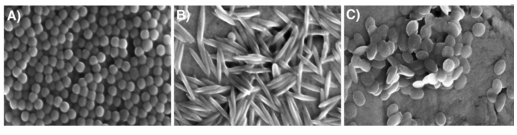

Figure 52. SEM images of nanoparticles with different shapes: A) spheres, B) rods, and C) discs. These non-spherical nanoparticles were prepared from polystyrene spherical particles using the mechanical deformation process discussed in Section 6.1.2. Reproduced with permission from ref. 616. Copyright 2016, Elsevier.

only observed in synthetic microvascular networks, static cell cultures, and *in vivo* distribution, but was also described by a shape dependent mathematical model of particle−surface interactions.[49] The same group employed carboxylate polystyrene nanorods with different surface coating and compared them to their spherical counterparts, examining oral drug-delivery capability and immune responsiveness. In both cases, the rod-shaped nanoparticles showed unique characteristics, which suggests that nanoparticle morphology needs to be considered in tandem with size and surface chemistry for the rational design of drug carriers.[616,617] Most recently, Mitragotri and co-workers reported that macro-sized rod particles demonstrated better injectability and penetrability than spherical macro particles, along with diminished cardiotoxicity on cells when loaded with DOX.[618]

Chilkoti and co-workers developed a simple approach to prepare cylindrical micelles from high molecular weight elastin-like polypeptides (64 kDa) by introducing a short (1.5 kDa) hydrophobic amino acid block to one end of the polypeptides.[619] In their following work, a cysteine-rich segment was added as the third block to provide eight thiol groups for conjugating small molecules. This asymmetric tri-block polypeptide amphiphile self-assembled into rod-like nanoparticles, and hydrophilic chemotherapeutics were loaded into the core via covalent conjugation with the added thiol groups. Their study showed that mice treated with the free drug exhibited a tumor volume three times higher than mice treated with the drug-loaded nanorods 12 days after incubation. Moreover, mice treated with the free drug had a median survival time of 21 days, while the nanorods increased survival to 30 days.[620]

Wu et al. designed and synthesized a brush-type polymer with a cleavable polyacetal backbone and biodegradable PCL-*b*-PEG side chains. This polymer self-assembled into rod-shaped nanoparticles with an average length of 200 nm and a diameter of 80 nm. DOX was encapsulated into the rods via hydrophobic interactions with the PCL side chain, and the drug-loaded nanorods exhibited cellular uptake efficiency twice that of free DOX.[621]

6.2.2. Disks. Polymeric nanoparticles with a disk morphology are known as nanodisks, and are inspired by disk shaped lipid carriers in the blood stream, such as high-density lipoproteins (HDLs). Ideally nanodisks can make use of the biogenicity of HDLs to more effectively avoid the immune system and increase circulation time in the blood. Nanodisks may also improve microvascular adhesion and cell internalization.[622]

Synthetic high-density lipoprotein (sHDL) nanodisks have been prepared with peptide-based cancer vaccines and chemotherapeutic drugs in mind. Recently, sHDLs loaded with both antigen peptides and adjuvants were reported to have dramatically improved the drug-delivery capability to lymphoid organs, as well as enhanced presentation on dendritic cells.[623] These nanodisks triggered broad-spectrum anti-tumor T cell responses, resulting in the ultimate elimination of tumors. Such a strategy provides the opportunity for personalized vaccines, due to the simple preparation of the nanodisks, as well as the robust therapeutic efficacy. The same group also synthesized a pH-cleavable lipid−DOX conjugate that was successfully loaded into sHDLs via co-incubation in PBS (pH 7.4) for 5 min at 37 °C. DOX-carrying sHDLs showed a 2.8-fold increase in the cellular uptake of DOX within tumors, compared with free DOX treatment. Generally, the sHDL-DOX treatment exhibited significant anti-tumor efficacy without any overt side effects. Advanced murine tumor models were utilized to test the therapeutic efficacy of sHDL-DOX treatment, demonstrating that 80 to 88% of established tumors were eliminated after the combination treatment with sHDL-DOX and immune checkpoint inhibitors.[624] A similar strategy was exploited for chemo-immunotherapy against glioblastoma multi-forme. DTX and CpG, a Toll-like receptor 9 (TLR9) agonist, were loaded into sHDLs for targeted drug

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

delivery and tumor regression. Combination treatment with these drug-loaded nanodisks and radiation resulted in an effective anti-tumor response and also prevented glioblastoma multi-forme recurrence.[625]

Lin et al. successfully loaded DOX into nanodisks composed of organoalkoxysilane and dihexanoyl phosphatidylcholine.[626] This hybrid assembly was thought to provide higher stability than conventional phospholipid bicellular disks owing to their siloxane surface.[627] Their nanodisks showed a pH-responsive drug release behavior, high cytotoxicity, and strong stability. In addition, *in vitro* and *in vivo* analysis showed that the drug-loaded nanodisks passively accumulated in tumors and successfully inhibited tumor growth. In a further study, PEGylated nanodisks were compared to non-PEGylated nanodisks, with the former demonstrating superior biocompatibility and improved anti-tumor efficacy.[628] The drug release rate was observed to increase with a higher ratio of PEG. Ge et al. reported a hydrophobic guest transport system based on biogenic macrocycle nanodisks to deliver hypocrellin B, a hydrophobic, photodynamic, poorly water-soluble drug. The nanodisks exhibited strong biocompatibility and internalization performance, while retaining the inherent photodynamic therapy activity of hypocrellin B.[629] This design showed strong theranostic potential.

6.2.3. Worms and Fibers. While nanorods and nanodisks comprise the two most highly studied non-spherical polymeric nanoparticles, worm-like nanoparticles (nanoworms) and nanocubes are two other morphologies that have recently garnered significant attention as drug-delivery vehicles. The high aspect ratio of nanoworms has been shown to improve specific accumulation within cells. This was demonstrated in early work by Geng et al, showing worm-like micelles demonstrated better biodistribution than spherical counterparts.[630] Later work showed this led to increased specificity for localization within a tumor, potentially due to improved biodistribution and being entrapped within the tumor environment more effectively via the EPR effect.[631]

Block copolymers are utilized to prepare different morphologically asymmetric assemblies, such as nanoworms, through rational molecular engineering. For example, PEG-*b*-PDLLA can assemble into spherical micelles in PBS and then transform into nanoworms through exposure to high salt concentrations (≥5 mM NaCl). The length of these worms can be further adjusted by varying the electrolyte concentration. Introducing azido-modified copolymers allows these nanoworms to be functionalized through surface modification using bioorthogonal "click" chemistry.[632] Another design introduced quaternary ammonium as a third block to achieve an ionically induced morphology switch from nanospheres to nanoworms of different aspect ratios. DOX was efficiently loaded into these nanoworms, and their worm-shape allowed for selective interactions with cancer cells and increased tumor penetration.[633]

Borteh et al. synthesized ribbon-like fibrous nanometer scaffolds composed of acetylated dextran, a biodegradable polymer. These scaffolds were loaded with the drug resiquimod, and their degradation rate (hydrolysis) was tuned by varying both the cyclic acetal coverage of the polymers and the molecular weight of dextran.[634] Recently, the same group also used dextran scaffolds to encapsulate PTX and resiquimod for the treatment of glioblastoma and vaccine applications, respectively. In both cases, the dextran scaffolds displayed high tunability and strong biocompatibility.[635,636]

6.2.4. Shape-Shifting Nanoparticles. As research into the impact of nanoparticle shape on drug-delivery efficiency has progressed, it has become evident that nanoparticles of different shapes exhibit distinct characteristics during circulation, accumulation, penetration, and cellular internalization.[637,638] However, it is challenging to identify a single nanoparticle shape that consistently outperforms all other designs as there are many factors that affect drug-delivery efficiency. Therefore, rather than compromising on certain needs, such as extending circulation time at the expense of cell uptake efficiency, recent research has focused on the development of a promising new type of shape-shifting drug-delivery system.[130,639] By triggering the transformation of nanoparticles at an appropriate time or location via a suitable mechanism, it is possible to enhance drug delivery and therapeutic efficiency. Currently, there are three main stimuli used to induce shape changes in nanoparticles: endogenous pH, enzymes, and exogenous light.[640] These stimuli disrupt the kinetic or thermodynamic equilibrium of the original nanoparticle assembly, altering covalent/non-covalent intermolecular or intramolecular interactions, thus driving the formation of a new equilibrium state.

pH-responsive shape-switching nanoparticles undergo changes in their intra- and intermolecular forces in environments with varying pH levels. These alterations can pertain to electrostatic interactions, hydrophilicity/hydrophobicity, and hydrogen bonding modification, yielding different structures and shapes. For example, Han et al. developed a chimeric peptide that responds to the acidic environment outside tumor cells and undergoes a change in shape to enhance its uptake into tumors.[641] The peptide, modified with dimethylmaleic anhydride and composed of the sequence (Ala-Glu-Ala-Glu-Ala-Lys-Ala-Lys)$_2$, spontaneously forms spherical nanoparticles under normal physiological conditions. Upon encountering an acidic environment, the removal of the dimethylmaleic anhydride moiety leads to the self-assembly of the peptide into rod-like nanoparticles, driven by electrostatic interactions among the polypeptide chains. This transformation from spheres into rods significantly increases peptide tumor uptake, resulting in improved photodynamic therapy effectiveness and minimal side effects both *in vitro* and *in vivo*.

Due to the abundance of abnormal enzymatic activity within the tumor microenvironment, enzyme-responsive polymeric nanoparticles have emerged as prominent candidates for enhanced cancer therapy. MMPs are overexpressed in various tumors to facilitate invasion and metastasis, and have been widely used to design tumor-targeted delivery systems. Kalafatovic et al. introduced a category of enzyme-responsive micelles formed by peptides (PhAc-FFAGLDD) through hydrophobic interactions.[642] These micelles can be hydrolyzed by MMP-9, resulting in a shift in their amphiphilic balance, leading to a shape transition from micelles into nanofibers. The nanofibers formed after this transformation exhibited enhanced capabilities for sustained drug release compared to the free drug, yielding significantly higher effective drug concentrations and therapeutic outcomes.

Light, as a non-invasive exogenous stimulus utilized in drug-delivery systems, is categorized into three main types based on its wavelength: ultraviolet (UV) (200−400 nm), visible light (vis) (400−700 nm), and near-infrared (NIR) (700−1000 nm). UV and visible light have limited tissue penetration and the former's high energy contributes to its phototoxicity, making NIR-responsive nanoparticles a central focus of

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

Table 2. List of Clinically Approved Polymer-Nanoparticle-Based Therapeutics for Cancer Therapy

Trade Name [Company]	Drug	Polymer	Indication	Clinical stage
Genexol-PM [Samyang Biopharmaceuticals]	PTX	mPEG-*b*-PDLLA	Breast cancer, non-small cell lung cancer	Approved in South Korea (2007)
Paclical/Apealea [Osmia Pharmaceutical]	PTX	Surfactant-based derivative of all-trans retinoic acid (XR-17)	Ovarian cancer	Russian Federation (2015) and EMA (2018) approved

research. Recently, nanoparticles based on amphiphilic aza-BODIPY dyes have been developed that self-assemble into nanofibers with a diameter of approximately 27 nm under physiological conditions, facilitating prolonged circulation in blood.[643] These nanofibers transitioned into nanoparticles with a diameter of 20−30 nm upon NIR laser stimulation, enhancing their ability to penetrate tumors. Benefiting from this *in situ* shape transformation strategy, these nanoparticles offer a promising therapeutic strategy for extended blood circulation and deep tumor penetration.

7. APPLICATIONS

Owing to the versatility of polymeric materials to design more sophisticated systems with diverse functionalities, polymeric nanoparticles have exhibited greater potential in overcoming specific biological barriers associated with individual diseases. This requires designing nanoparticles that combine the ability to migrate generic barriers for all nanoparticle delivery systems as described above, with functionality that can target specific disease conditions. The target locations for different diseases are varied as are the types of cargo that are required to achieve therapeutic outcomes and thus these factors need to be considered when designing a nanoparticle to target a specific disease. Here, we will provide a detailed description of different drug-delivery applications of polymeric nanoparticles that have been reported recently and highlight how they can overcome biological barriers associated with individual diseases.

7.1. Cancer

Cancer is perhaps the most burdensome class of disease affecting humanity worldwide, with a severe mortality rate, and an absolute death toll that continues to increase year over year. According to Global Cancer Observatory, almost 10 million deaths occurred in 2020 alone, along with 19.3 million estimated new cases, which is expected to grow to almost 40 million by 2040.[644] Cancer is characterized by uncontrolled cellular growth and multiplication that occurs due to the mutation of proto-oncogenes and tumor suppressor genes, which are responsible for controlling cell division. Consequently, abnormal masses of defective cells (tumors) are created. Metastasis occurs when these cells grow and spread into the other parts of the body.[645] As previously described, a tumor's microenvironment is a complex structure defined by numerous blood vessels and different types of cells enclosed within a protein-rich extracellular matrix. These cells include proliferating cancer cells and non-malignant stromal cells, fibroblasts, endothelial cells, immune cells, and cancer stem cells. In addition, the composition of this tumor microenvironment varies according to the type of tumor, and continuously changes with the progression of cancer.[646,647] Therefore, development of effective cancer therapies remains a significant challenge due to the complexity and heterogeneity of different types of tumors. Although the administration of unmodified anti-cancer drugs is the primary method for cancer treatment, most of these free therapeutics have their own limitations, including low specificity toward tumor tissues, poor solubility, unfavorable drug pharmacokinetics, and undesirable side effects.[134,648] Therefore, creating novel strategies that can promote selective delivery of these drugs by navigating biological barriers is essential for more effective cancer treatment.

The recent progress of nanomedicine has opened up new opportunities for the development of targeted and safe drug-delivery carriers for cancer therapy.[649,650] There are various types of nanoparticles that have been employed for cancer treatment, including lipid nanoparticles, polymeric nanoparticles, inorganic nanoparticles, and protein nanoparticles.[10,134] Among these designs, polymeric nanoparticles have shown tremendous potential in cancer therapy owing to their sophistication and high degree of control over important particle properties, which allows for more selective delivery of therapeutics while avoiding off-target toxicity in healthy cells.[651] Specifically, the physicochemical properties of polymers can be easily tuned to design nanoparticles that can transport a wide range of anti-cancer drugs including hydrophobic and hydrophilic drugs, as well as larger macromolecular cargo such as peptides, proteins, and nucleic acids.[6,193,652] Moreover, the ease of surface modification of polymeric nanoparticles offers the ability to more efficiently target tumor tissue, increasing the selective accumulation of therapeutics without affecting healthy cells.[653] As a result, a significant amount of clinical and pre-clinical studies have been reported that utilize a diverse and sophisticated range of polymeric nanoparticle designs.

7.1.1. Clinical Translation of Polymeric Nanoparticles in Cancer Therapy. Though the pre-clinical research into polymeric nanoparticles is vast and growing, only a few nanoparticle formulations have been approved for anti-cancer clinical trials, let alone approved for commercial consumption. Most of these designs are simple polymeric micelles, prepared via the self-assembly of amphiphilic block copolymers comprising a hydrophilic PEG shell and various hydrophobic core polymers. Specifically, biodegradable polymers such as polyesters (PGA, PDLLA) and PAAs (PGlu, PAsp) comprise the majority of hydrophobic blocks, owing to their reduced toxicity in physiological conditions. Only two polymeric nanoparticles are currently on the market as anti-cancer drug-delivery vehicles (Table 2). However, neither of these are approved by FDA and both are still undergoing phase II/III clinical trials. Genexol-PM is a micelle formed from a PEG-*b*-PDLLA block copolymer that loads the chemotherapeutic drug paclitaxel (PTX) and has been approved for the treatment of metastatic breast cancer and advanced non-small cell lung cancer in South Korea. Genexol-PM has demonstrated strong anti-tumor efficacy, improved pharmacokinetic properties and lower toxicity, with a maximum tolerated dose (MTD) 40 times higher than conventional PTX.[10,134,654] Apealea, known as Paclical in Russia, is another micelle that loads PTX, and has been approved by European Medicines Agency (EMA) in 2018 for the treatment of ovarian cancer. It is formulated with a novel-surfactant-based derivative of retinoic acid (XR-17),

https://doi.org/10.1021/acs.chemrev.3c00705
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which is a mixture of two isoforms of *N*-retinoyl-L-cysteic acid methyl ester sodium salt.[10,655,656] Conventional PTX is a poorly water-soluble anti-cancer drug. Therefore, by incorporating PTX into micelles (Genexol-PM and Paclical), its solubility and pharmacokinetic performance is radically enhanced.

There are also a growing number of polymeric nanoparticles in clinical trials. NC-6300 is a promising micellular design whereby the drug epirubicin is covalently conjugated to the block copolymer PEG-*b*-PAsp via a pH-responsive hydrazone linkage. This design forms a micelle with pH-responsive drug release capability. Furthermore, NC-6300's polymer backbone is partially modified with benzyl groups to improve the stability of its micellar structure. *In vitro* drug release experiments confirmed the stability of NC-6300 in blood conditions (pH 7.4) and accelerated drug release in acidic conditions due to the pH-responsive nature of the hydrazone linkage.[657] Thus, in preclinical studies, NC-6300 demonstrated superior anti-tumor activity with less side effects owing to selective and efficient drug release in acidic conditions of the endosome and lysosome of cancer cells.[657,658] In Japan, Phase I trials found that NC-6300 was well tolerated in patients with advanced and recurrent solid tumors, and the patients displayed less side effects compared to free epirubicin.[659] NC-6300 is currently undergoing phase I/II trials to investigate the anti-tumor activity and tolerability in patients with soft tissue sarcoma. As well as NC-6300, several other polymeric nanoparticles have been translated into human clinical trials to evaluate their safety and efficacy for various types of cancers (Table 3). The majority of these nanoparticles are micelles that encapsulate small chemotherapeutic drugs such as DOX, PTX, cisplatin, and docetaxel. These micelles offer several advantages over the delivery of free drugs, including enhanced solubility, longer circulation time in the blood, higher tumor accumulation, and reduced toxicity. CALAA-01 is the only polymeric nanoparticle that has been approved for clinical trials regarding the delivery of siRNA. The clinical history of these nanoparticles (Table 3) can be found in recently published review articles with detailed information regarding their chemical structures, preparation methods, clinical outcome, and challenges.[10,11,112,134,660]

7.1.2. Site-Targeted Drug Delivery. Polymeric nanoparticles are ideal candidates for delivering drugs to specific target sites due to their tunable physiochemical properties and the ability to incorporate sophisticated functionality, including the opportunity for efficient targeting capability. Selective targeting offers an enhancement over traditional anti-cancer drug treatment, as it bears superior therapeutic efficacy and, just as importantly, reduces side effects and off-target toxicity. Furthermore, the selective accumulation of anti-cancer drugs within tumor sites improves the unfavorable drug pharmacokinetics of conventional chemotherapeutics.[55,651,653] To date, there is a tremendous ongoing research effort regarding polymeric nanoparticles with tumor targeting properties. The following section will outline the recent progress of polymer nanoparticles that have been used in targeted drug delivery for cancer therapy.

7.1.2.1. Passive Targeting. Passive targeting is the selective accumulation of nanoparticles within the tumor microenvironment based on the EPR effect. This is possible due to the distinct pathophysiological features associated with a tumor's microenvironment. For example, tumor growth requires an adequate supply of nutrients and oxygen to ensure rapid proliferation of cells. In order to meet this nutrient uptake demand, new blood vessels form via a process called angiogenesis. These new vessels, however, are structurally and functionally abnormal, and contain leaky pores due to their incomplete endothelial lining or basement membrane.[678,679] The result is a leaky vasculature with increased permeability, allowing nanoparticles to extravasate into the tumors through this permeable tumor vasculature. Moreover, nanoparticles can be retained in the tumor due to impaired lymphatic drainage. This phenomenon is referred to as EPR effect, which was first described by Matsumara and Maeda in 1986, and forms the basis of passive tumor targeting.[680−682] The EPR effect is mainly governed by certain physicochemical properties of nanoparticles, including size, shape and surface properties.[56] However, more recent literature claims that the EPR effect is obscure in humans, despite its consistency across small animal models.[683,684] One study utilized canine tumor models, which closely resemble human tumors, to investigate variations in the EPR effect across different tumor histologies.[685] The findings revealed that liposomal nanoparticles exhibited excellent accumulation in most carcinomas but not in soft tissue sarcomas, indicating that tumor histology significantly impacts the efficiency of the EPR effect. Nevertheless, a recent study demonstrated a substantial EPR effect in human renal tumors using the *ex vivo* perfusion model, and validated a positive correlation with *in vivo* rabbit models. However, the EPR effect was still heterogeneous in humans across various factors such as development stage, tumor size, and the gender of patients.[686]

Primarily, nanoparticle size is the most crucial factor that determines the efficacy of passive accumulation in tumors. For this purpose, it has been found that the optimum particle size is roughly between 10 and 200 nm. This size range yields enhanced tumor accumulation via the EPR effect, along with prolonged blood circulation and reduced clearance by the immune system.[687,688] Kataoka and co-workers reported that PEG-*b*-PGlu polymeric micelles with sizes between 50 and 100 nm displayed superior penetration in permeable hypervascular tumors compared to micelles smaller than 50 nm, which only penetrated through poorly permeable tumors.[689] Recently, Kang et al. reported smaller size PEG nanoparticles (<20 kDa, 12 nm) that showed enhanced tumor accumulation via the EPR effect and reduced nonspecific uptake. Larger PEGylated nanoparticles accumulated in major organs such as the lungs, liver, and pancreas.[690] Thus, the exact size of nanoparticles required to fully maximize the EPR effect and to avoid clearance mechanisms is still somewhat unclear, with studies yielding conflicting results over the past few years. This is likely due to other nanoparticle properties that also play a role in localization, such as rigidity and surface chemistry. Surface charge plays a significant role in determining the blood circulation time and tumor accumulation. A slightly negative or neutral surface charge maximizes blood circulation, as foreign cationic materials are rapidly cleared by the immune system, and simultaneously improves the tumor accumulation, as more nanoparticles extravasate through the leaky vasculature of tumor tissues via the EPR effect.[14,691] Therefore, to maximize circulation time, polymeric nanoparticles are often engineered with stealthy hydrophilic polymers in their shell, including PEG and other biocompatible polymers. Kataoka and co-workers demonstrated longer circulation times for anionic and neutral micellar surfaces, while anionic micelles resulted in lower uptake into liver and spleen, suggesting that slightly negatively charged micellar surfaces could avoid non-specific

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

Table 3. List of Polymer-Nanoparticle-Based Therapeutics in Clinical Trials for Cancer Therapy

Trade Name [company]	Drug	Polymer composition	Indication	Clinical Phase	References/ ClinicalTrials.gov Identifier
Polymeric micelles					
Genexol-PM [Samyang Biopharmaceuticals]	PTX	mPEG-*b*-PDLLA	Bladder cancer, ureter cancer, ovarian cancer, breast cancer	II/III	NCT01426126
					NCT05300828
					NCT00876486
Paclical/Apealea	PTX	Surfactant derived from all-trans retinoic acid (XR-17)	Epithelial ovarian cancer, primary peritoneal cancer, fallopian tube cancer	III	NCT00989131
NK-911 [Nippon Kayaku]	DOX	PEG-*b*-PAsp	Solid tumors	I	661
NC-6300 [NanoCarrier]	Epirubicin	PEG-*b*-poly(aspartate-hydrazone) (pH responsive)	Solid tumor, soft tissue sarcoma, metastatic sarcoma	I/II	657, 658
					NCT03168061
NC-4016 [NanoCarrier]	Oxaliplatin	PEG-*b*-PGlu	Advanced cancer lymphoma	I	NCT03168035
NK-105 [Nippon Kayaku]	PTX	PEG-*b*-poly(4-phenyl-1-butanoate-L-aspartamide) PEG-*b*-P(PPBA)	Breast cancer	III	NCT01644890
NK-012 [Nippon Kayaku]	SN-38 (active metabolite of CPT-11 (irinotecan)	PEG-*b*-PGlu	Small cell lung cancer,breast cancer, solid tumors	II	NCT00951613
					NCT00951054
NC-6004 (Nanoplatin) [Nanocarrier]	Cisplatin	PEG-*b*-PGlu	Pancreatic cancer, solid tumors -	II/ III	NCT00910741
					NCT02043288
					NCT02240238
					NCT03771820
SP1049C [Supratech Pharma]	DOX	Mixture of Pluronic block copolymers (1:8 w/w ratio of Pluronic L61 & F127)	Advanced adenocarcinoma	II/III	662−664
Nanoxel-M/ Nanoxel-PM [Samyang Biopharmaceuticals]	Docetaxel	mPEG-*b*-PDLLA	Breast cancer, non-small cell lung cancer, metastatic cancer, miscellaneous cancers	I/III	660, 665
					NCT04066335
					NCT05207514
Nanoxel [Fresenius Kabi Oncology Ltd.]	PTX	pH-sensitive (PVP-*b*-PNIPAm) copolymer	Advanced breast cancer	I	NCT00915369
Cripec [Crystal therapeutics]	Docetaxel	mPEG-*b*-poly[*N*-(2-hydroxypropyl) methacrylamide-lactate]	Solid tumor, metastatic cancer, ovarian cancer	I/ II	11, 650
					NCT03712423
					NCT02442531
					NCT03742713
Polymeric nanoparticles					
CALAA-01 [Calando Pharmaceuticals]	siRNA	Transferrin receptor- targeted Cyclodextrin-PEG copolymer	Solid tumors	I	666−669
					NCT00689065
CRLX101 [Cerulean Pharma)	Camptothecin	CPT conjugated cyclodextrin-PEG copolymer	Non-small cell lung cancer, solid tumor, renal cell carcinoma, ovarian cancer	I/ II	670, 671
					NCT01380769
					NCT02648711
					NCT02187302
					NCT02389985

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

Table 3. continued

Trade Name [company]	Drug	Polymer composition	Indication	Clinical Phase	References/ ClinicalTrials.gov Identifier
BIND-014 [BIND Therapeutics]	Docetaxel	PSMA-targeted PEG-*b*-PLGA	Prostate cancer, non-small cell lung cancer, metastatic cancer, solid tumors	I/II	672−674
					NCT01812746
					NCT01792479
					NCT01300533
					NCT02283320
Docetaxel-PNP [Samyang Biopharmaceuticals]	Docetaxel	PEG-*b*-PLGA	Solid tumors, prostate cancer	I/II	NCT02274610
					NCT02494921
DHAD-PBCA-NP	Mitoxantrone	Poly(butylcyanacrylate)	Hepatocellular carcinoma	II	675
BA-003, Transdrug (Livatag) [BioAlliance Pharma]	DOX	Poly(isohexylcyanoacrylate)	Hepatocellular carcinoma	III	676, 677

organ uptake.[692] Despite the fact that most studies conclude that anionic and neutral nanoparticles are highly efficient at penetrating tumors, some research has claimed that positively charged nanoparticles exhibit superior tumor penetration and cellular uptake, resulting in enhanced anti-tumor efficacy. In one interesting study, Wang and co-workers demonstrated that cationic PEGylated nanoparticles, composed of a PDLLA core, are more effective in tumor penetration and inhibiting tumor growth than their anionic or neutral counterparts.[53] Thus, the correlation between surface charge and anti-tumor efficacy should be carefully considered to maximize the therapeutic effect while avoiding non-specific uptake by the immune system.

PEGylation, the most common method to imbue nanoparticles with higher levels of stealth activity, can result in poor uptake by cancer cells due to the steric hindrance of the PEG segments, leading to inefficient therapeutic delivery. This is known as the "PEG dilemma".[58] Shedding the stealthy PEG layer upon association with cancerous cells (dePEGylation) is an attractive approach to promote cellular uptake by reducing steric hinderance. One method to achieve this is by adding a detachable PEG layer that is responsive to the intrinsic pathophysiological features of a tumor microenvironment. This strategy of shedding PEG has been comprehensively reviewed.[58,693] Wang and co-workers developed PEG detachable polymeric nanoparticles by incorporating a pH-cleavable DMMA linkage for siRNA delivery.[257,694] They designed a functionalized maleimide acid amide derivative, 2-propionic-3-methylmaleic anhydride, to fabricate a PEG-cleavable nanoparticle for siRNA delivery that was responsive to the acidic environment associated with tumors.[695] The amphiphilic copolymer PEG-*Dlink*$_m$-R9-PCL was synthesized by incorporating a degradable bridged bond (*Dlink*$_m$), CDM in between PEG and a cell-penetrating peptide containing non-arginine residues (R9). This polymer can self-assemble into micelles and complex with siRNA to form a micelleplex delivery system (Figure 53). PEG was rapidly released at pH 6.5 (nearly 60% within 20 h) with minimal non-specific release at pH 7.4 (less than 20%), demonstrating the cleavability of CDM linker at the lower pH of the tumor microenvironment. Pharmacokinetic profiles demonstrated this micelleplex had a prolonged blood circulation time and extended the half-life ($t_{1/2}$) of siRNA to nearly 12 h (for both nanoparticles with and without *Dlink*$_m$). However, the nanoparticle with *Dlink*$_m$ displayed a superior tumor accumulation in A549 tumor-bearing mice, yielding pronounced tumor growth inhibition. It is postulated that the presence of the outer PEG layer supports longer blood circulation of the micelleplex, and tumor acidity triggers the loss of PEG to expose the R9 layer, yielding enhanced cellular uptake and more effective siRNA delivery. However, these types of delivery systems based on pH-cleavable maleic acid amide chemistry are only studied on primary tumors, and their activity on metastatic cancers is not fully understood.[257]

As an alternative to PEGylation, zwitterions have been employed in designing stealth nanoparticles for anti-cancer drug delivery. Zwitterions exhibit superior surface hydration due to their ability to bind with water molecules via strong electrostatic interactions, as opposed to PEG, which relies on hydrogen bonding. Thus, zwitterionic polymeric nanoparticles have demonstrated higher resistance to non-specific protein adsorption, leading to an increase in blood circulation time.[58,696] In particular, Duvall and co-workers demonstrated the impact of different surface properties by developing a

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

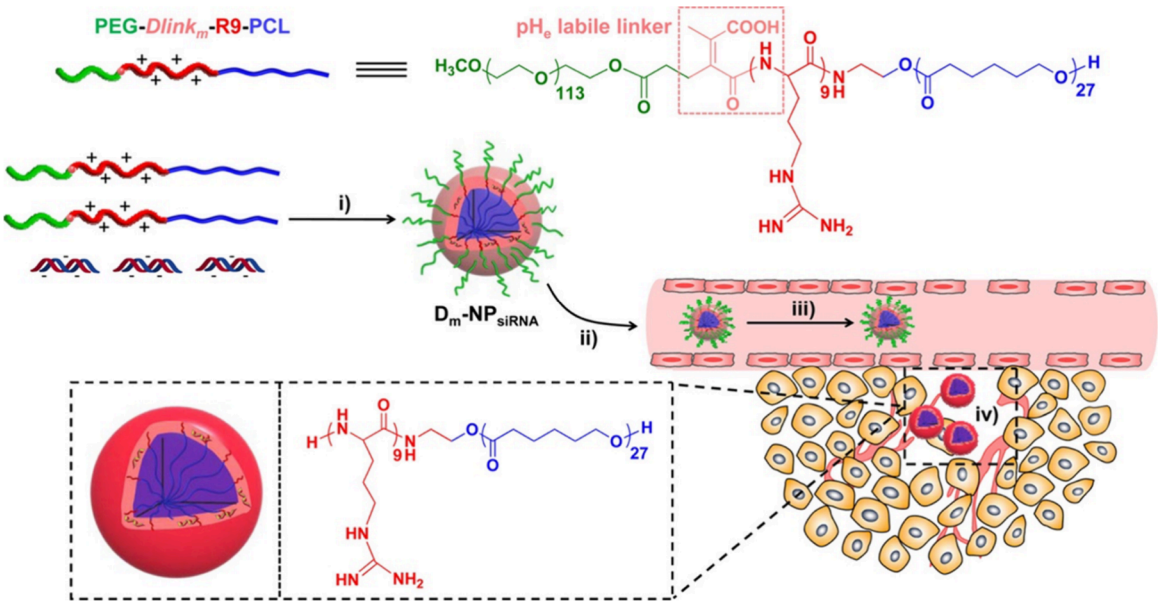

Figure 53. A schematic illustrating the self-assembly of PEG-*Dlinkm*-R9-PCL into PEG detachable polymeric micelleplexes for siRNA delivery. (i) Self-assembly of PEG-*Dlinkm*-R9-PCL into nanoparticles in aqueous solution and binding with siRNA to form micelleplexes (D_m-NP_{siRNA}). (ii) Systematic administration of D_m-NP_{siRNA}. (iii) Prolonged circulation of micelleplexes with the protection of stable PEG layer until reaching the targeted tumor site. (iv) Recognition of D_m-NP_{siRNA} by tumor cells and *Dlink$_m$* undergoes degradation when exposed to low pH of extracellular environment to increase the cellular uptake. Reproduced with permission from ref. 695. Copyright 2015, American Chemical Society.

library of siRNA polyplexes with the same core composition (PDMAEMA-*co*-PBMA), but with varied shell compositions: PEG (5 and 20 kDa), brush-like poly (oligo (ethylene glycol) methyl ether methacrylate) (POEGMA) (10 and 20 kDa), and zwitterionic phosphorylcholine-based polymers (PMPC) (10 and 20 kDa).[697] Both the PMPC and PEG (20 kDa) polyplexes exhibited improved pharmacokinetic properties with longer half-lives of ∼25 min. These half-lives were higher than those of all other polyplexes ($t_{1/2}$ <10 min), while material properties in terms of size and surface charges were kept similar. *In vivo* studies showed a higher tumor uptake (2-fold higher than 20 kDa PEG) and significantly increased luciferase gene knockdown (roughly 80%) for polyplexes with zwitterionic shells (20 kDa) compared to PEG shells. Thus, high molecular weight zwitterionic shells were found to provide enhanced tumor cell uptake for siRNA polyplexes rather than traditional PEG-based surfaces, due to their improved association with cell membranes. In general, zwitterionic moieties offer a promising strategy to develop nanoparticles with improved pharmacokinetic properties and superior tumor accumulation.[58,698−700] However, the development of zwitterionic polymer-based nanoparticles is still in its infancy owing to the challenges associated with their controllable, reproducible, and scalable synthesis.[701]

Polymeric micelles such as Genexol-PM, NK-105, NC-6004, NK-911, NC-6300, and NC-4016 are capable of passive targeting and have displayed promising performance in clinical trials. These nanoparticles all encapsulate chemotherapeutic drugs in their core, have a size range of 10−100 nm, are imbued with stealth properties to prolong blood circulation, and display controlled drug release within the tumor cells.[11,112] Furthermore, there is an extensive body of preclinical research that focuses on the passive targeting capability of polymer nanoparticles. Most of these systems trigger drug release in response to specific stimuli present within tumor tissue, such as pH, redox potential, and the presence of specific enzymes.[6] We will highlight these systems in Section 7.1.2.3.

Presently, passive targeting represents the primary method by which polymeric nanoparticles, particularly micelles, accumulate at tumor sites and thus perform their anti-cancer therapy. However, it is important to underscore that there are notable limitations associated with passive targeting. For instance, passive targeting is highly dependent on tumor biology, specifically the permeability of the tumor vasculature, the efficiency of lymphatic drainage, blood perfusion rates, interstitial fluid pressure, the nature of the extracellular matrix, and tumor cell density.[680,702] Furthermore, tumors are highly heterogeneous, and certain solid tumors do not exhibit EPR effect.[703] In fact, the challenges associated with physiological barriers of tumor microenvironments and their heterogeneity within and between different tumors have had a significant impact on the clinical development of the passively targeted polymeric nanoparticles.

7.1.2.2. Active Targeting. Active targeting has the potential to offset some of the limitations associated with passive targeting. Active targeting involves synthesizing nanoparticles with one or more targeting ligands. These targeting ligands can bind to specific receptors that are overexpressed in tumor cells, thereby improving the retention and selective internalization of nanoparticles within targeted tumor cells. Moreover, targeting ligands can be employed to promote the accumulation of nanoparticles within tumor vasculature by targeting angiogenic endothelial cells of tumor blood vessels.[55,56] Therefore, functionalizing polymeric nanoparticles with targeting moieties is a useful strategy to enhance the selective delivery of anti-cancer therapeutics while minimizing off-target toxicity. However, it is also crucial to maintain control over fundamental nanoparticle properties such as size, shape and charge, to achieve an optimum therapeutic outcome. Nanoparticles must also remain stable and include stealth properties to avoid non-specific interactions with the immune system and

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

Table 4. Comprehensive List of Targeting Ligands Employed in Polymeric Nanoparticle Designs for Anti-cancer Therapy

Targeting ligand	Targeting site/receptor	Nanoparticle formulation/payload	Ligand attachment	Activity compared to non-targeted system	Ref.
Transferrin	Transferrin receptors	PLGA nanoparticles/DOX	EDC-NHS coupling	N/A	706
Transferrin	Transferrin receptors	PEG-chitosan nanoparticle/ PTX	Esterification reaction	*In vitro*: Higher cellular association in HOP-62 cells.	707
Transferrin	Transferrin receptors	Chitosan- or PLGA-coated MSN/ gemcitabine	EDC-NHS coupling	*In vitro*: Higher cytotoxicity in MIA PaCa-2 cells.	708
Lactoferrin	Lactoferrin receptors	PNIPAM-*co*-AA nanoparticles/ honokiol	Carbodiimide coupling	*In vitro*: 2.7-fold higher cytotoxicity compared to honokiol in MCF-7 cells. *In vivo*: 3-fold higher suppression of VEGF-1 expression compared to honokiol.	709
Lumretuzumab (anti-HER3)	HER3 receptors (breast cancer)	PEG-based Hyperbranched polymer/DOX	Conjugation through PEG	*In vitro*: Higher cytotoxicity BT474 breast cancer cells (IC_{50}:17.6 μg/mL)	710
Trastuzumab	HER2 receptors	mPEG-polyester dendron micelles/docetaxel	Amidation reaction	*In vitro*: 3-fold higher toxicity that is comparable to docetaxel in SK-OV-3 cell line	711
Sgc8 aptamer	PTK7 receptor (HCT 116 colon cancer)	HPMA PISA nanoparticle/ photosensitizer	Click reaction	*In vitro*: Higher cellular uptake in HCT116 tumor cell line	712
A10 aptamer	PSMA receptors	PEG-PLA nanoparticle/DOX	Carboxylate-amine coupling reaction	*In vitro*: Higher cytotoxicity in cHSA cell line. *In vivo*: Higher cellular uptake in subcutaneous macroscopic SB-HSA tumors in SCID/beige mice. 2-fold higher necrosis and 70% reduction in macroscopic SB-HSA tumor endothelial cells	713
AS1411 aptamer	Nucleolin receptors	PLGA-lecithin-PEG nanoparticles/PTX	EDC-NHS coupling	*In vitro*: Enhanced cellular uptake, association and cytotoxicity in MCF-7 cells	714
XQ-2d aptamer	CD71 receptors on pancreatic cancer cells	PCL-*b*-PEO micelles/DOX	EDC-NHS coupling	*In vitro*: Higher cellular uptake in Panc-1 cells and better tumor penetration in multi-cellular 3D spheroids of Panc-1 cells	715
AS1411 aptamer	Nucleolin receptors	Pluronic F127-cyclodextrin-PEG-PLA nanoparticles/DOX	EDC-NHS coupling	*In vivo*: Higher tumor growth inhibition MCF-7 tumor bearing mice.	716
Mannose	Mannose receptors	Albumin nanoparticles/DOX	Thiol-maleimide reaction	*In vitro*: Enhanced cytotoxicity in U87MG glioma cells and enhanced cellular uptake in bEnd.3 cells.	717
Glutamate urea	Prostate-specific membrane antigen (PSMA) (prostate cancer cells)	PEG-based hyperbranched polymer/DOX	Covalent binding to RAFT agent	*In vivo*: Significantly higher tumor growth inhibition (90%) in subcutaneous LNCaP tumors	718
Angiopep2 (ANG)	Low-density lipoprotein receptor-related protein 1 (LRP1) receptor (glioma cells)	Polyprodrug star unimolecular micelles/CPT	Click reaction	*In vitro*: 18-fold higher cytotoxicity in on C6 tumor cells. *In vivo*: Higher antiglioma efficacy compared to CPT and non-targeted micelles.	719
APT_{EDB} peptide	Fibronectin extra domain B (EDB) (glioma neovasculature endothelial cells and glioma cells)	PEG-*b*-PLA nanoparticle/PTX	Maleimide-thiol coupling reaction	*In vitro*: 3-fold higher cytotoxicity in U87MG glioma cells. *In vivo*: Higher tumor growth inhibition rate in subcutaneous U87MG tumor xenograft mode.	720

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

maximize blood circulation time. Furthermore, it is critical to better understand the impact of the protein corona on targeting efficiency, and ultimately develop strategies to tune this impact using specific targeting approaches. One strategy to achieve this is to employ releasable PEG, which de-shields a targeting ligand only at the target site. Therefore, how specific targeting ligands are arranged on the surface of nanoparticles, as well as their density, must be considered to avoid the non-specific clearance by immune system.[650,653]

A wide range of ligands have been employed to imbue polymer nanoparticles with tumor targeting performance, a selection of which are listed in Table 4. These ligands include proteins such as antibodies, transferrin, lactoferrin, antibody fragments and growth factors, peptides such as cyclic arginine-glycine-aspartic acid (cRGD), aptamers (A10 and AS1411), polysaccharides, and small biomolecules such as folic acid and biotin.[55] Targeting ligands can be attached to the surface or shell of polymeric nanoparticles either by conjugation with the amphiphilic polymer backbone prior to self-assembly, or by direct conjugation to the outer surface of the preformed nanoparticle. Click chemistry is the most common synthetic approach for this purpose, and has been extensively reviewed by Moreau and co-workers.[704] A useful targeting ligand should be chosen to bind with specific receptor sites that are overexpressed in tumor cells but relatively absent in healthy cells. Moreover, choosing a specific targeting site is mainly governed by the mechanism of action of therapeutic cargo that needs to be delivered. In addition, recent research has focused on targeting tumor vasculature in order to enhance the retention and accumulation of nanoparticles within the tumor site. The vascular endothelial growth factor receptor (VEGFR), integrin $\alpha_v\beta_3$ and vascular cell adhesion molecule-1 (VCAM-1), are the most common tumor vascular endothelium receptors that have been considered in the design of tumor vasculature-targeting polymeric nanoparticles.[705]

Small biomolecules such as folic acid (vitamin B9) and biotin (vitamin B7) have been widely employed as targeting ligands for cancer therapy.[721−724] They are readily available, non-toxic, inexpensive, non-immunogenic, and easy to modify and characterize. Folic acid binds to the glycosylphosphatidylinositol-linked folate receptor, which is overexpressed in tumor cells compared to healthy cells.[55,725,726] Liu et al. developed a folic acid-modified chitosan-based polymeric micelle loaded with both DOX and all-trans-retinoic acid. *In vivo* studies indicated that these targeting micelles resulted in 85.5% tumor inhibition in 4T1 tumor bearing mice, which was an improvement compared to non-targeted micellar formulations.[727] Zhao and co-workers designed a folic acid-conjugated pH-responsive polymeric nanoparticle based on a DOX prodrug and encapsulating a NIR dye (IR825) for combined photothermal-chemotherapy.[728] Confocal laser scanning microscopy (CLSM) images revealed that DOX was successfully delivered to the cytoplasm of HeLa cells. *In vitro* experiments showed much lower half maximal inhibitory concentration (IC_{50}) values with NIR light irradiation on both DOX-sensitive HeLa cells and DOX-resistant A2780/DOX^R cells (2.0 and 1.7 μg/mL, respectively) compared to no NIR irradiation (6.7 and 12.6 μg/mL, respectively). Moreover, *in vivo* studies demonstrated significantly reduced tumor volume (50% over 1 day) confirming the combinational therapeutic efficacy of these IR825-loaded DOX prodrug nanoparticles. Unfortunately, folate receptor expression is also higher in the normal healthy cells of the liver and kidneys, and this could result in off-target toxicity. Giorgio and co-workers addressed this issue by developing a dual MMP7-activated and folate receptor targeted micellar nanoparticle comprising a pH-responsive core (PDMAEMA-*b*-PDMAEMA-*co*-PBMA-*co*-poly(propylacrylic acid)) and a PEG shell with matrix metalloproteinase-7 (MMP7) cleavable peptide and folic acid functionality for siRNA delivery.[729] This system was designed to deliver siRNA via two stages. PEGylation enhanced the tumor accumulation of the nanoparticles by extending their circulation time in the blood. Following tumor accumulation, the PEG shell was removed by the action of MMP7 enzyme, a type of enzyme that is overexpressed in highly aggressive and metastatic cancers. This resulted in the exposure of folic acid to bind with the folate receptors, thereby enhancing the cellular uptake in targeted tumor cells and minimizing the off-target effects. This nanoparticle design showed limited cellular uptake in an MDA-MB-231 breast cancer cell line without MMP7, but MMP7 pretreated cells yielded higher nanoparticle uptake, highlighting folate receptor-dependent accumulation. Furthermore, both MMP7 activation and folate receptor engagement resulted in significant knockdown (greater than 50%) of a model gene, luciferase, demonstrating the efficiency of dual-targeting nanoparticle formulations. This highlights the advantages of a novel dual-targeting method to improve the cellular uptake of polymeric nanoparticles while minimizing the off-target effects in healthy cells.

Small peptide molecules have also gained significant attention as targeting agents owing to their scalable and facile synthesis, low production cost, and resistance to enzymatic degradation and the immune system.[730−732] The cRGD peptide is one of the more promising targeting ligands in the design of tumor targeting polymeric nanoparticles. cRGD has a higher binding affinity with integrin $\alpha_v\beta_3$ receptors that are overexpressed on both activated endothelial cells in tumor neovasculature and many types of solid tumor cells.[733] Chen and co-workers designed cRGD-modified pH-responsive polymeric nanoparticles for targeted delivery of DOX to neovascular cells and tumor cells.[734] The DOX-loaded nanoparticle was prepared via the self-assembly of cRGD conjugated PEG-*b*-poly(2,4,6-trimethoxybenzylidene-pentaerythritol carbonate) (PEG-*b*-PTMBPEC). The cRGD-targeted nanoparticle with a ligand density of 10% exhibited higher *in vitro* cytotoxicity in B16 and HUVEC cells compared to a non-targeted nanoparticle control. *In vivo* studies showed significantly enhanced tumor growth inhibition for the cRGD-targeted nanoparticle compared to the unfunctionalized control. In 2016, Zhong and co-workers designed a cRGD-functionalized, redox-responsive, shell-sheddable, and biodegradable PEG-SS-PCL micelle for the enhanced delivery of DOX.[735] The conjugation of cRGD significantly improved the cellular internalization and association of DOX by a factor of 2.3 compared to a non-targeted control in $\alpha_v\beta_3$ integrin receptor overexpressed tumor cells. There was no difference in $\alpha_v\beta_3$ negative MCF-7 cells for both targeted and non-targeted micelles. The *in vivo* anti-tumor efficacy was evaluated on U87MG glioma bearing nude mice, and revealed that RGD-targeted micelles had greater potential to suppress tumor growth compared to non-targeted micelles. In another study, Zhong and co-workers developed DOX-loaded cRGD-modified polymersomes with a disulfide cross-linked vesicular membrane as a targeted nanomedicine for the treatment of lung cancer.[736] The polymersomes were prepared by self-

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Chem. Rev. 2024, 124, 5505−5616

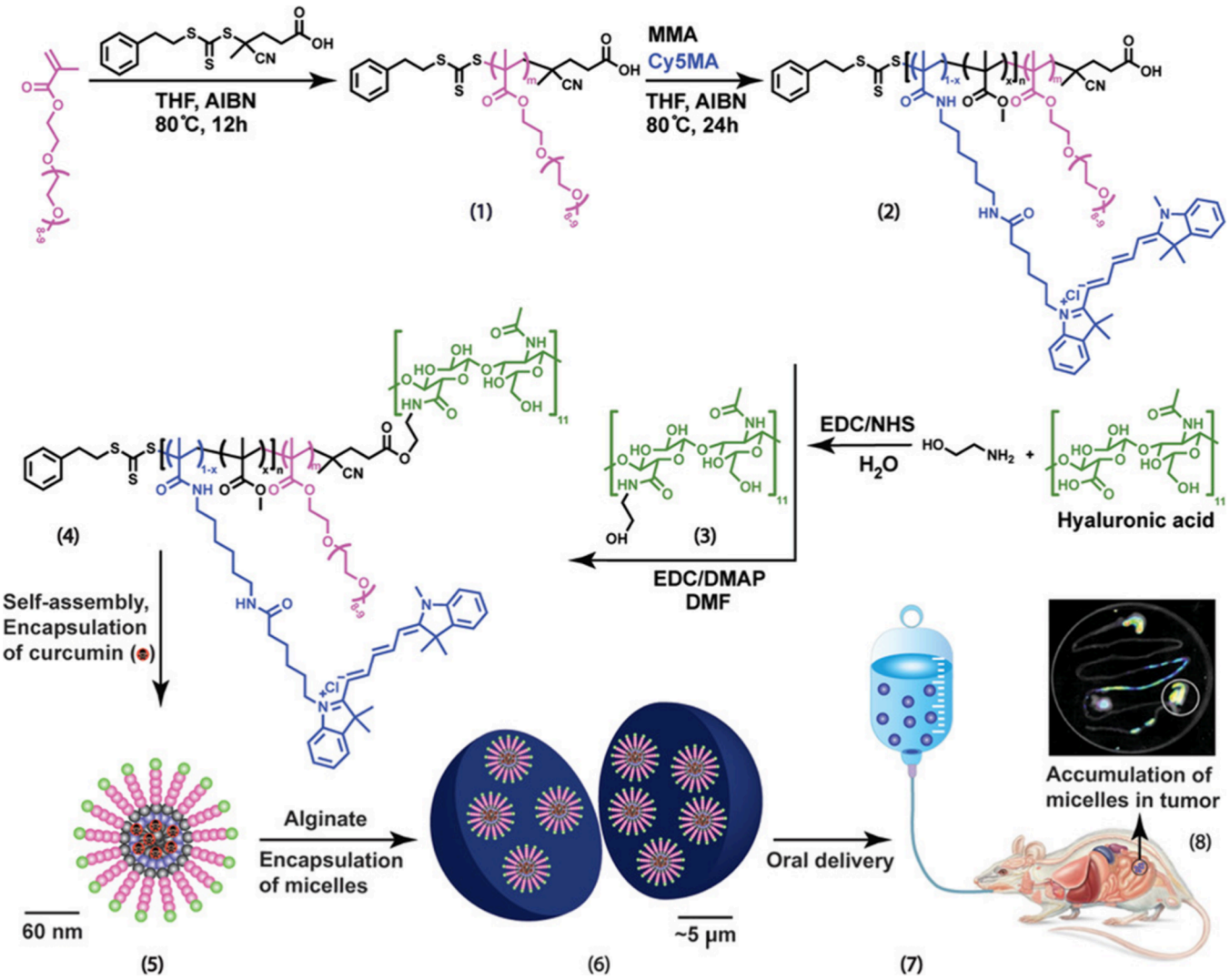

Figure 54. A schematic representation for the synthesis of HA-PPEGMA-*b*-P(MMA-*co*-Cy5MA) block copolymer (**1**−**4**), formation of curcumin-loaded HA-modified micelles via self-assembly (**5**), formation of multi-component drug-delivery system encapsulating curcumin-loaded HA-modified micelles into an alginate microcapsule (**6**), oral delivery for the site-specific drug release at tumor cells (**7**, **8**). Reproduced with permission from ref. 747, 749. Copyright 2020, Wiley-VCH.

assembling two block copolymers: PEG-*b*-poly(trimethylene carbonate-*co*-dithiolane trimethylene carbonate) (PEG-*b*-P(TMC-*co*-DTC)) and cRGD-functionalized PEG-*b*-P(TMC-*co*-DTC). The average hydrodynamic diameter was around ∼100 nm for both targeted and non-targeted polymersomes. *In vitro* experiments confirmed that both polymersomes had rapid drug release behavior (more than 70% in 24 h) in the presence of GSH. The cRGD-targeted polymersomes exhibited higher cytotoxicity toward $\alpha_v\beta_3$ integrin overexpressed human lung cancer cells, with an IC_{50} of 3.2 μg/mL, which was 4.1-fold lower than an unfunctionalized polymersome control. In comparison with the non-targeted control, the targeted polymersome showed a 2-fold enhanced tumor accumulation, and *in vivo* studies in lung-tumor bearing mice demonstrated higher tumor growth inhibition for the cRGD-targeted design, with minimal side effects at a DOX dose of 12 mg/kg.

Another promising approach to design tumor targeting polymeric nanoparticles is to employ monoclonal antibodies, which are highly specific and have high affinity toward certain receptors. Epidermal Growth Factor Receptor (EGFR) is a cell surface receptor protein that is overexpressed in several types of solid tumors, such as pancreatic cancer, breast cancer, ovarian cancer, kidney, prostate, and non-small cell lung cancer. It is responsible for cell signaling pathways that control cell proliferation and survival.[737] The anti-EGFR monoclonal antibody cetuximab (CTX) has the ability to inhibit the EGFR signaling pathway by blocking binding of EGFR ligands to their receptor site. Thus, CTX has been investigated as a specific targeting molecule in the search for more efficient drug-delivery designs. Mondal et al. developed an EGFR targeted, gemcitabine (GEM)-conjugated, miRNA complexed micelle for enhanced codelivery of GEM and miRNA (miR205) in the treatment of pancreatic cancer.[738] These micelles were functionalized with cetuximab (C225) to target EGFR receptors, and 30% (w/w) of the micelles resulted in significantly higher uptake compared to non-targeted micelles. Moreover, the same concentration of micelles showed enhanced tumor suppression against a pancreatic tumor model, compared to non-targeted micelles. In a previous study, the same researchers used a GE11 peptide as their EGFR targeting ligand to prepare micelles for the delivery of GEM to EGFR-overexpressing pancreatic cancer.[739] These

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Chem. Rev. 2024, 124, 5505−5616

GE11-conjugated micelles demonstrated significant tumor growth inhibition, indicating the significance of EGFR targeting for superior pancreatic cancer treatment. McDaid et al. reported a CTX-functionalized polymeric nanoparticle for the treatment of CTX-resistant pancreatic cancer cells that express mutated Kirsten rat sarcoma (KRAS).[740] The CPT-loaded, CTX-functionalized, PEGylated PLGA nanoparticles were prepared with a size of approximately 200 nm. These CTX-functionalized nanoparticles induced cell apoptosis more efficiently than non-targeted nanoparticles in mutant KRAS cell line, PANC-1. *In vivo* results showed enhanced anti-tumor efficacy for CTX-targeted nanoparticles in a PANC-1 xenograft model, demonstrating effective and efficient targeting ability of CTX-conjugated nanoparticles for CTX-resistant cancers. Trastuzumab is another specific monoclonal antibody that has been used to target the human epidermal growth factor (HER2) receptor, which is overexpressed in breast cancers. Hoang et al. achieved a 5-fold increase in tumor uptake for trastuzumab-functionalized PEG-*b*-PCL block copolymer micelles in HER2 overexpressed BT-474 tumors, compared to unfunctionalized control micelles.[741] An interesting extension to targeted nanoparticles is the use of dual targeting. Koul and co-workers reported that dual-targeting nanoparticles displayed superior cellular uptake and apoptosis compared to individually targeted formulations.[742] They designed a trastuzumab, and folic acid-conjugated redox-responsive polymersome based on a PEGMA-*b*-PCL-ss-PCL-*b*-PEGMA tri-block copolymer for receptor-mediated DOX delivery. These dual-functional polymersomes exhibited higher cellular uptake in BT-474 and MCF-7 breast cancer cell lines compared to singly targeted or non-targeted polymersomes. *In vivo* studies showed an ∼82% reduction in tumor volume in mice compared to a free DOX control (∼42% tumor regression), along with reduced toxicity toward major organs (heart, liver, kidney).

Hyaluronic acid (HA) is a natural polysaccharide that can bind to the CD44 receptors overexpressed in various types of cancers including ovarian, lung, and breast cancers.[743] Due to its excellent biocompatibility and biodegradability, HA has been extensively utilized for developing polymeric nanoparticles for targeted delivery of anti-cancer drugs.[744−746] Thurecht and co-workers developed what they termed a multi-component drug-delivery system by encapsulating CD44-targeting micelles within an alginate microcapsule for targeted treatment of colorectal cancer.[747] The alginate capsule acted as a protective sheath to overcome the multiple harsh obstacles encountered within the stomach following oral administration. The encapsulated curcumin-loaded micelles were prepared through the self-assembly of HA-conjugated PEGMA-*b*-PMMA. These functionalized micelles exhibited a 6-fold higher cellular association than non-targeted micelles in CD44 positive HCT-116 cells, but no distinct difference was observed in CD44 negative Caco-2 cells (Figure 54). Moreover, the HA-targeted micelles yielded improved toxicity in HCT-116 cells, implying that the HA targeting functionality improved the delivery of curcumin. *In vivo* studies demonstrated site-specific degradation properties for the alginate microcapsule in an orthotopic tumor bearing mouse model, and the HA-modified micelles showed enhanced tumor accumulation and targeting efficiency compared to a non-targeted micelle control. Zhong et al. developed an acid-responsive PTX prodrug micelle with an HA shell based on HA-*b*-dendritic oligoglycerol block copolymers (HA-dOG-PTX-PM). This micelle was designed for active targeting of breast cancers overexpressed with CD44 receptors.[748] HA-shelled micelles displayed a higher cell killing efficiency against MCF-7 compared to a PTX control, with a low IC_{50} value of 0.93 μg/mL compared to PTX (IC_{50} ∼ 1.63 μg/ml). The *in vivo* pharmacokinetics of these HA-shelled micelles demonstrated significantly longer circulation time than free PTX, resulting in enhanced tumor suppression with minimal side effects in a mouse model.

Functionalizing polymeric nanoparticles with a wide variety of tumor targeting ligands is a promising strategy to enhance the selective tumor accumulation and therapeutic efficacy, while minimizing the off-target toxicity of chemotherapeutics. These designs, however, are still in their infancy in regard to clinical application, as only two actively targeted polymeric nanoparticles (CALAA-01 and BIND-014) have been approved for clinical trials (Table 2). CALAA-01 is a cyclodextrin-based polymeric nanoparticle functionalized with a transferrin ligand, and was the first polymeric nanoparticle to be designed with active targeting functionality. BIND-014 is a PEG-*b*-PLGA nanoparticle tailored for docetaxel delivery, and employs a ligand targeting the prostate-specific membrane antigen (PSMA), a protein specific for prostate cancer.[56,725] It should be noted that most of the preclinical studies are limited to *in vitro* investigations, focusing on nanoparticle design and their interactions with specific cell lines, rather than assessing the *in vivo* therapeutic efficacy. Additionally, some of these receptors overexpressed in disease sites are also expressed in normal healthy cells, limiting the effectiveness of active targeting.[18] Moreover, the tumor mice models used *in vivo* studies do not fully resemble human cancers, and this heterogeneity will also limit the clinical investigation of these actively targeted nanoparticles.[55] The existence of a protein corona, which is generated *in vivo*, is also likely to impact the efficacy of targeting, and the extent of this effect is still poorly understood.

Most preclinical research has focused on designing polymeric nanoparticles that target individual tumor cells or their intracellular organelles to radically enhance nanoparticle uptake. However, the presence of dormant cancer cells (DCCs) and cancer stem cells (CSCs) plays a crucial role in cancer metastasis, recurrence, tumor heterogeneity and multi-drug resistance, and can lead to poor therapeutic outcomes.[750−752] Thus, targeting dormant cancer cells and cancer stem cells is a promising approach for cancer treatment. CSCs are a small subpopulation of cancer cells that show resistance to most drugs and have the ability to self-renew, differentiate, and proliferate. DCCs, on the other hand, usually remain in a non-dividing quiescent state within the tumor, but can become active after a certain period, initiating tumor recurrence.[750,753] Currently, nanoparticle-mediated targeting of CSCs is an active research area, with a primary focus on targeting specific biomarkers (e.g., CD123, CD44, CD133, CD90, ALDH, and EpCAM) and signaling pathways, such as Notch, Hedgehog, and transforming growth factor-β (TGF-β).[754−756] In one interesting study, Rao et al. investigated the application of chitosan-decorated Pluronic F127-cross-linked DOX-encapsulated polymeric nanoparticles to target CD44 receptors on CSCs.[757] These nanoparticles (IC_{50} = 0.35 μg/mL) exhibited a 6-fold increase in cytotoxicity compared to free DOX (IC_{50} = 2.0 μg/mL) for eliminating $CD44^+$ CSCs residing in 3D mammary tumor spheroids. The authors claimed that chitosan can target CD44 receptors on CSCs to enhance their anti-

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Chem. Rev. 2024, 124, 5505−5616

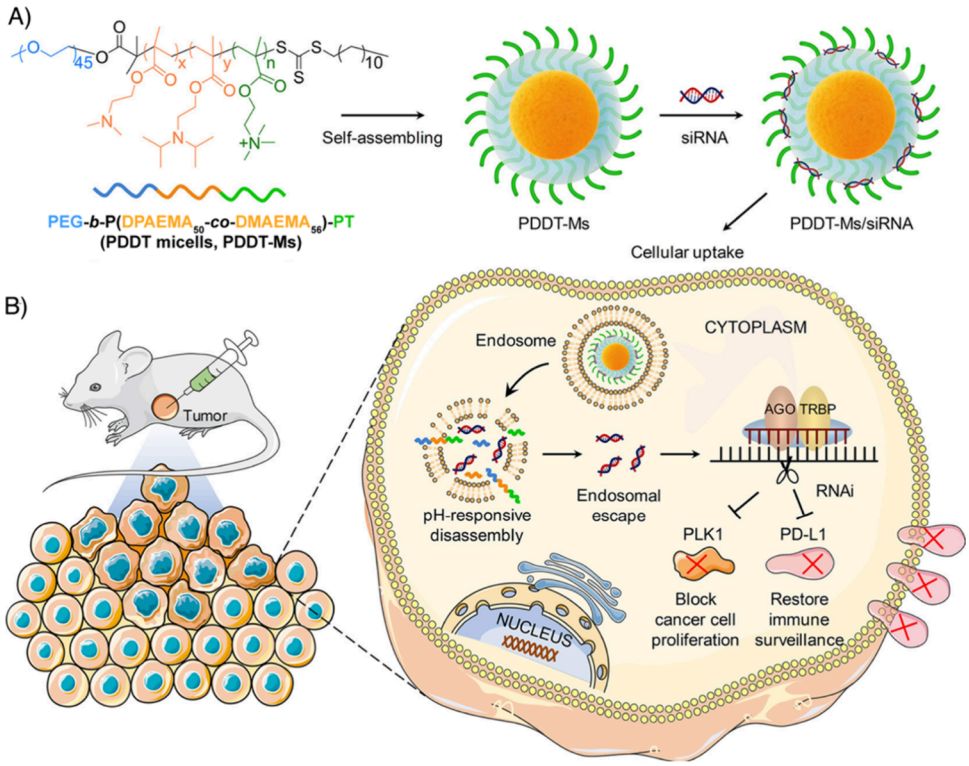

Figure 55. (A) Schematic representation of self-assembly of tri-block copolymer (PDDT) composed of PEG, pH-sensitive copolymer ($P(DPAEMA_{50}$-*co*-$DMAEMA_{56})$), and positively charged poly(*N*,*N*,*N*-trimethylammonium ethyl methacrylate) (PT, also known as PTDMAEMA) forming pH-responsive polymeric polyplexes (PDDT-Ms/siRNA) for siRNA delivery. (B) After cellular uptake, PDDT-Ms/siRNA polyplexes undergo pH-induced disassembly within the acidic pH of endosome resulting in cytosolic release of siRNA to block the cancer cell proliferation. Reproduced with permission from ref. 764. Copyright 2021, American Chemical Society.

tumor efficacy, as chitosan partially resembles the chemical structure of HA, which is the most common targeting ligand for CD44 receptors. CSC targeting designs have been comprehensively discussed in recent reviews.[754,758] Thus, additional research efforts should focus on designing efficient drug-delivery systems that not only target solid tumors but also selectively eliminate metastatic tumor cells, drug-resistant tumor cells, and cancer stem cells.[55]

7.1.2.3. Stimuli-responsive Release. Both active and passive targeting can only enhance the accumulation of nanoparticles at a tumor site by altering their pharmacokinetic properties. However, despite the incorporation of targeting functionality, uncontrollable drug release is a major challenge that limits the therapeutic efficacy of many anti-cancer nanoparticle designs. Premature or non-specific release of encapsulated therapeutics can result in dangerous off-target toxicity. Moreover, insufficient intracellular release generally reduces the therapeutic efficacy of anti-cancer drugs. Over the past few decades, stimuli-responsive nanoparticles combined with either active or passive targeting functionalities have garnered significant interest because they can be designed to provide site-specific "on-demand" drug release in response to a given stimulus.[759] Generally, stimuli-responsive nanoparticles utilize a wide variety of functional moieties that undergo structural or conformational change in response to certain stimuli, yielding more efficient drug release and reduced off-target toxicity.[703] A wide range of stimuli have been employed to develop polymeric nanoparticles for cancer therapy. These include endogenous stimuli such as pH, redox environment, and enzymatic environment, or exogenous stimuli including temperature, light, ultrasound, and a magnetic field.[315] Section 3.9 provides a detailed description of the respective functional moieties that provide this stimuli-responsiveness. Many stimuli-responsive polymeric nanoparticles have been investigated in pre-clinical research and are the subject of multiple systematic reviews.[759,760]

Nanoparticles that take advantage of the pH variation inherent in a tumor environment (6.4−6.8) compared to the blood environment (~7.4) are a promising strategy to enhance cancer therapy. There are two main strategies to induce pH-triggered drug release from polymeric nanoparticles: 1) use of charge-shifting polymers that can undergo solubility or conformational change in response to pH variation; and 2) conjugating drugs to a nanoparticle via an acid labile linkage, which can be cleaved depending on the pH, resulting in controllable drug release.[761] Increasingly, such systems are being used to load multiple therapeutics for improved therapeutic efficacy. Nanoparticles that utilize combination therapy by co-delivering both siRNA and chemotherapeutics are a promising strategy to combat multi-drug resistance.[762] Shuai and co-workers developed a pH-responsive polymeric nanoparticle from a tri-block copolymer, PEG-*b*-PLL-*b*-PAsp functionalized with a pH-responsive diisopropylaminoethyl moiety. This particle co-loaded both DOX and BCL-2 siRNA to treat multi-drug resistant hepatic carcinoma.[763] At pH 5 (endosomal pH), DOX was rapidly released due to the protonation of the tertiary amine group. *In vitro* cellular uptake studies showed efficient co-delivery of siRNA and DOX in both HEPG2 and HEPG2/ADM cells. In comparison to scrambled siRNA complexed nanoparticles (D/SCR-CP), nanoparticles with BCL-2 siRNA (D/siR-CP) exhibited higher *in vitro* toxicity in HEPG2/ADM cells. The authors suggested

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Chem. Rev. 2024, 124, 5505−5616

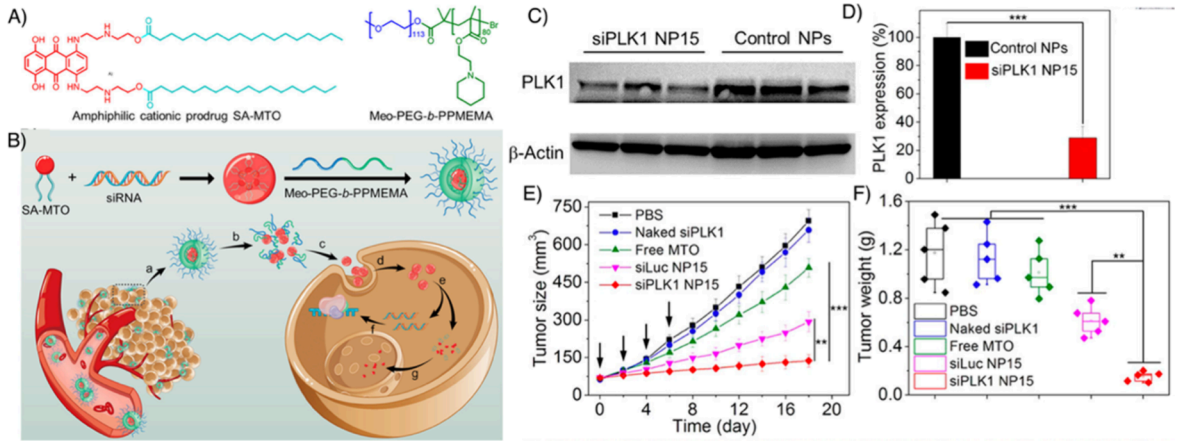

Figure 56. A schematic representation of the chemical structures of amphiphilic cationic prodrug SA-MTO and pH-responsive polymer MeO-PEG-*b*-PPMEMA (A), formation of pH-responsive polymer−prodrug hybrid nanoparticle for combinational cancer therapy using siRNA and MTO delivery (B), Western blot (C, D) analysis of PLK1 expression in the tumor tissues of the MDA-MB-231 xenograft tumor bearing nude mice treated with siLuc NP15 (control NPs) or siPLK1 NP15 (siPLK1-loaded nanoparticle). Tumor size (E) and tumor weight (F) of the MDA-MB-231 xenograft tumor-bearing nude mice treated with PBS, naked siPLK1, free MTO, and siLuc NP15 (control NPs), and siPLK1 NP15. Reproduced with permission from ref. 765. Copyright 2019, American Chemical Society.

that the downregulation of the BCL-2 gene improved the therapeutic efficacy of DOX to achieve a synergistic anti-cancer effect. Furthermore, *in vivo* studies demonstrated enhanced tumor suppression for siRNA complexed nanoparticles in tumor bearing mice, illustrating the efficacy of a pH-responsive co-delivery system for the treatment of multi-drug resistant hepatic carcinoma.

pH-responsive polymeric nanoparticles formulated with cationic functionalities have displayed potential in delivering anionic RNA for the treatment of cancer. Huang and co-workers developed a quaternary ammonium-based pH-responsive polymeric micelle for the efficient delivery of siRNA.[764] The micelles (PDDT-Ms) were formed by self-assembly of a tri-block copolymer (PEG_{45}-*b*-P($DPAEMA_{50}$-*co*-$DMAEMA_{56}$)-PT_{53}) composed of positively charged poly(*N*,*N*,*N*-trimethylammonium ethyl methacrylate) (PT, also known as PTDMAEMA), a pH-sensitive copolymer (P($DPAEMA_{50}$-*co*-$DMAEMA_{56}$)) and hydrophilic PEG. Negatively charged siRNA was complexed via electrostatic attraction to highly positively charged quaternary ammonium moieties (Figure 55). The pH was tuned by tailoring the ratio of charge-shifting monomers DPAEMA and DMAEMA, with particle disassembly occurring at pH 6.5−6.8. This stimuli-responsive morphological change released siRNA, yielding 86.9% gene silencing of a polo-like kinase 1 (PLK1) proto-oncogene. In addition, these particles exhibited strong tumor growth inhibition in liver cancer models, underscoring the enhanced anti-tumor efficacy of pH-responsive micellar nanoparticles for siRNA-mediated cancer treatment. Xu and co-workers developed a pH-responsive polymer−prodrug hybrid nanoparticle for combinational cancer therapy through both siRNA-mediated gene silencing and the release of the anti-cancer drug mitoxantrone (MTO).[765] The amphiphilic, cationic, MTO-based prodrug interacted with negatively charged siRNA to form a siRNA−prodrug polyion complex. This complex was assembled with a pH-responsive polymer, methoxyl-poly(ethylene glycol)-*b*-poly(2-(pentamethyleneimino)ethyl methacrylate) (mPEG-*b*-PPMEMA). The polymer−prodrug hybrid nanoparticles were able to disassemble at pH 6.8, highlighting their potential to release siRNA−prodrug complexes in response to the lower pH of a tumor microenvironment. Furthermore, the overexpressed esterase in the tumor hydrolyzed the amphiphilic prodrug structure, inducing the destabilization of the siRNA−prodrug complex for efficient release of both siRNA and MTO in tumor cells. *In vivo* analysis revealed longer blood circulation for siRNA-loaded nanoparticles ($t_{1/2}$ ∼ 1 h) compared to naked siRNA or free MTO ($t_{1/2}$ ∼ less than 10 min). In addition, the nanoparticles yielded a >7-fold increase in tumor accumulation for tumor-bearing nude mice as well as superior gene silencing efficiency (70% knockdown of PLK1 gene expression). Ultimately, these hybrid nanoparticles yielded high tumor growth inhibition compared to both naked siRNA and free MTO (Figure 56). These systems highlight the potential use of pH-responsive nanoparticles for efficient siRNA delivery, and their careful optimization into clinical studies would address major challenges associated with other nanoparticle designs, such as poor endosomal escape and cytosolic delivery.

Reactive oxygen species (ROS) can be overproduced in cancer cells, resulting in higher ROS (up to 100×10^{-6} M) levels than in normal tissues (20×10^{-9} M). ROS are chemically reactive, single electron reduction products of oxygen, and include superoxide ($O_2^{\bullet -}$), nitric oxide ($NO^{\bullet}$), hydroxyl ($^{\bullet}OH$) radicals, hydrogen peroxide (H_2O_2), and singlet oxygen ($^1O_2$). Endogenous ROS in cancer cells are mainly linked with an increase in metabolic activity, mitochondrion dysfunction due to hypoxia, and oncogene activity.[766,767] Thus, ROS-responsive polymeric nanoparticles have been extensively investigated to achieve site-specific drug delivery in response to higher ROS levels in cancer cells.[767,768] Ge and co-workers designed polymersome nanoreactors with a pH-permeable membrane to activate a cascade reaction for cooperative cancer therapy.[769] The polymersome was prepared from a PEGylated block copolymer prodrug, PEG-*b*-P(CPTKMA-*co*-PEMA), which comprises ROS-responsive thioketal-linked CPT methacrylate (CPTKMA) and pH-responsive 2-(pentamethyleneimino)ethyl methacrylate (PEMA). Glucose oxidase (GOD) was encapsulated within the inner aqueous cavity, while ultrasmall iron oxide nanoparticles were encapsulated in the polymersome's membrane.

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Chem. Rev. 2024, 124, 5505−5616

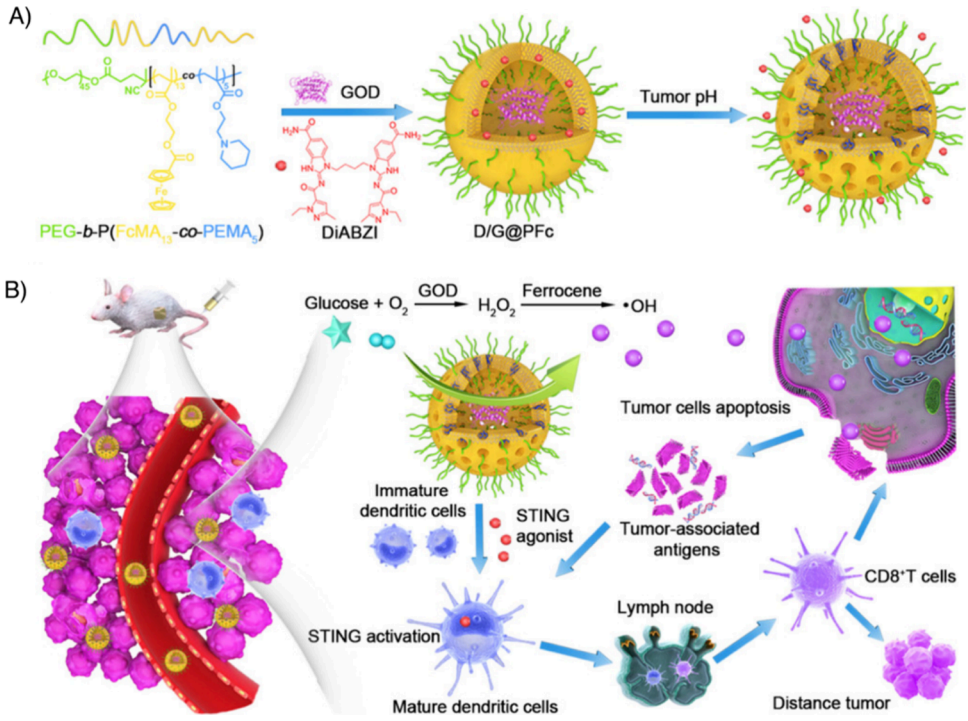

Figure 57. (A) A schematic representation for the preparation of GOD and DiABZI co-loaded polymersome nanoreactor (D/G@PFc) via self-assembly of block copolymer, poly(ethylene glycol)-*b*-poly(2-(methacryloyloxy) ethyl ferrocene-carboxylate-*co*-2-(piperidin-1-yl)ethyl methacrylate) (PEG-*b*-P(FcMA-*co*-PEMA)) in an aqueous solution at pH 7.4. (B) The cascade reactions pathway to enhance anti-tumor immunity via combination of chemodynamic-immunotherapy. Reproduced with permission from ref. 770. Copyright 2021, Wiley-VCH.

The authors suggested that within the acidic tumor microenvironment, a sequence of cascade reactions is initiated following the enhancement of membrane permeability through the protonation of PEMA moieties. These reactions are: 1) glucose consumption to generate H_2O_2 under the catalysis of GOD; 2) acid-triggered release of $Fe^{2/3+}$ions; 3) production of $^{\bullet}OH$ radicals through the Fenton reaction between H_2O_2 and $Fe^{2/3+}$ions; and 4) $^{\bullet}OH$-triggered release of CPT via cleavage of ROS-responsive thioketal linkers. *In vivo* anti-tumor studies demonstrated higher tumor growth suppression in A549 tumor-bearing mice indicating the suitability of this system for cooperative cancer therapy involving chemotherapy, chemodynamic therapy and starvation therapy.

Recently, there has been extensive exploration of how to activate the protein stimulator of interferon genes (STING) to enhance anti-tumor immunity. This includes promoting dendritic cell maturation, increasing the presence of tumor-infiltrating antigen-presenting cells and $CD8^+$ T cells, and enhancing the cytotoxicity of natural killer cells. In one study, a ferrocine-containing polymersome nanoreactor (D/G@PFc) was engineered by co-loading STING agonist, symmetry-linked amidobenzimidazole (DiABZI) and GOD to enhance anti-tumor immunity through STING activation and combination chemodynamic-immunotherapy (Figure 57).[770] The authors revealed that upon intravenous administration, tumor acidity triggered the membrane permeability of the polymersome, owing to the protonation of PEMA moieties, initiating a series of cascade reactions. Thus, H_2O_2 was generated through the catalysis of GOD, which was then transformed into the highly toxic $^{\bullet}OH$ via the Fenton reaction through the catalysis of ferrocene moieties. $^{\bullet}OH$ promoted cell apoptosis as well as the release of tumor-associated antigens and fragmented DNA, reversing the immunosuppressive tumor microenvironment and promoting STING activation. Simultaneously, released DiABZI was internalized by dendritic cells to activate the STING pathway, which promoted the maturation of dendritic cells and finally recruited $CD8^+$ T cells to enhance the anti-tumor immunity via synergistic chemodynamic-immunotherapy. *In vivo* anti-tumor studies revealed significantly enhanced tumor growth inhibition in primary and metastatic tumors when treated with polymersomes co-loaded with both GOD and STING agonist, as opposed to individually loaded systems, demonstrating the synergistic effect of STING agonist and chemodynamic therapy. However, given the complexity of these designs, scalability and cost are clear challenges hampering clinical applications. Primarily, greater emphasis on nanoparticle stability is necessary before reaching the targeted tumor site; otherwise, the initiation of non-specific reactions may compromise therapeutic efficacy.

Advances in nanomedicine and materials science have led to the design of polymeric nanoparticles that are responsive to external stimuli. These stimuli can be controlled in a precise way to trigger drug release at the targeted site, achieving both a more efficient therapeutic outcome, as well as reducing toxicity in parts of the body not exposed to such stimuli. Photodynamic therapy is one of the most widely investigated exogeneous stimuli-responsive strategies employed in cancer treatment. However, most biologically relevant and safe wavelengths of light have low tumor penetration and lack the energy needed to cleave chemical bonds, which hinders the application of light-responsive systems. To address these challenges, and to achieve light-controlled drug release, photosensitizers that can induce the formation of singlet oxygen ($^1O_2$) species have been applied to polymeric nanoparticle systems. Lin and co-workers developed a singlet oxygen-responsive polymeric nanoparticle by introducing a

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Chem. Rev. 2024, 124, 5505−5616

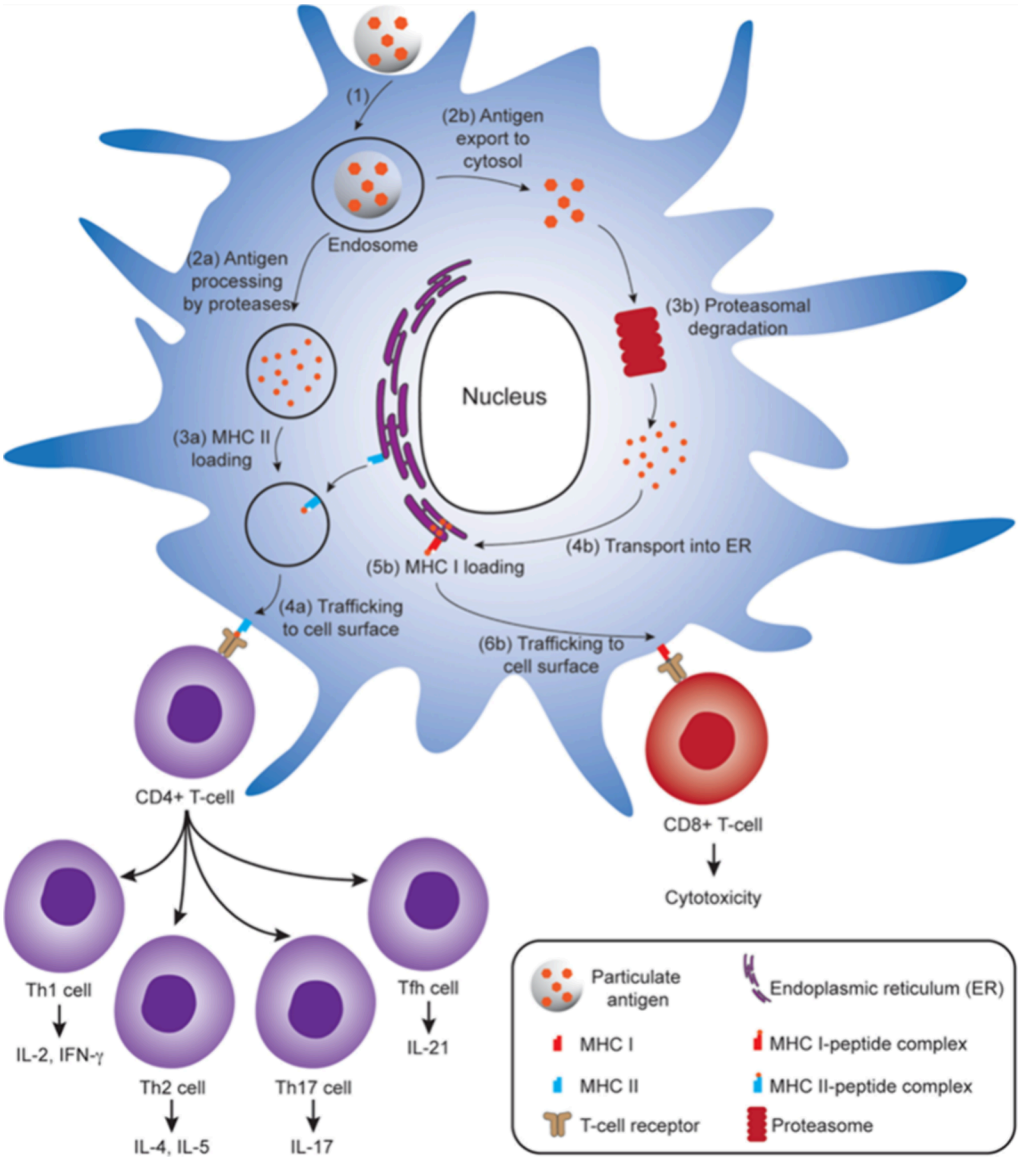

Figure 58. A schematic illustration of the antigen processing and presentation pathway in a dendritic cell leading to the activation of $CD4^+$ T cells (left), and $CD8^+$ T cells (right). $CD4^+$ T cells can be differentiated into Th1, Th2, Th17, and Tfh cells, which release various cytokines such as interferon-γ (IFN-γ) and interleukins (IL-2, IL-4, IL-5, IL-17, and IL-21), to stimulate both humoral and cellular immune response, and activation of $CD8^+$ T cells leads to the killing of mutated or infected cells. Reproduced with permission from ref. 778. Copyright 2021, Elsevier.

singlet oxygen-responsive aminoacrylate linker to a mPEG-*b*-PCL block copolymer. Boron dipyrromethene (BDP), a photosensitizer, and the anti-cancer drug PTX were co-loaded.[771] The nanoparticles showed enhanced $^1O_2$ generation under light irradiation, confirming that the photosensitivity of BDP was retained even after encapsulation within a nanoparticle. Moreover, these particles exhibited light-triggered disassembly and enhanced PTX release (~50%) after 1 h of laser light irradiation (660 nm, 5 mW cm^{-2}), underscoring their light-responsive drug release behavior. *In vitro* cell viability studies demonstrated a higher cell killing efficiency for nanoparticles co-loaded with both BDP and PTX. Furthermore, *in vivo* studies revealed that the nanoparticles, upon light irradiation, yielded more potent tumor inhibition in tumor bearing mice compared to a control nanoparticle without a light-responsive linker. The mechanism suggested for this strong cancer performance was that upon light irradiation, the photosensitizer generates singlet oxygen species, which cleaves the aminoacrylate linker, releasing PTX to kill the cancer cells via a synergistic effect from both chemotherapy and photodynamic therapy.

Stimuli-responsive polymeric nanoparticles display very promising anti-cancer performance, alas their clinical translation remains elusive. The complex chemistry involved in these highly sophisticated systems do not easily lend themselves to scalability or low-cost mass production, and likely also negatively affect reproducibility and batch-to-batch consistency. In addition, endogenous stimuli often slightly vary between preclinical and clinical tumor models, as well as between patient populations, which are inherently heterogeneous. External triggers can be precisely controlled, but poor tumor penetration and non-specific exposure also limit the applicability of nanoparticles that utilize these triggers. The next step in applying multi-functional systems that combine both targeting functionalities and stimuli-responsiveness involves reproducible designs whose preparation is facile.[703,772]

https://doi.org/10.1021/acs.chemrev.3c00705
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7.2. Vaccines

Vaccination plays a critical role in preventing infectious diseases by providing long-lasting acquired immunity.[773] In the last half-century, vaccines have contributed to controlling the spread of many infectious diseases including smallpox, measles, tetanus, and polio, and have played a significant role reducing the morbidity of influenza and the corona virus (SARS-CoV-2) disease (COVID-19). Live attenuated vaccines, which employ a weakened form of the virus (antigen) that can still replicate, and inactivated vaccines, which utilize the destroyed genetic material of the antigen, are the most common vaccine formulations that have been developed thus far. However, both can cause adverse side effects due to their insufficient inactivation processes, and the fact that "dead" viruses can sometimes revert to their pathogenic forms. To tackle these safety issues, subunit vaccines have been developed by utilizing a specific antigenic component of the pathogens, such as a particular protein, peptide, or polysaccharide.[774] However, poor immunogenicity remains a major obstacle that can hinder the therapeutic efficacy of these subunit vaccines when using antigens alone. Thus, these kinds of vaccines have been formulated with delivery systems and adjuvants to enhance their antigen-specific immune response. Adjuvants are substances that stimulate the immune response of co-delivered antigens by activating the immune system and enhancing the durability of an immune response.[775] Thus, the development of more efficient delivery systems and adjuvants can induce a strong immune response by improving the immunogenicity of antigens while reducing the vaccine dosage and production cost.[776]

It is critical to understand the mechanism and pathways of antigen-specific immune responses when designing an effective delivery system for subunit vaccines. Vaccination aims to provide long-term protection by triggering the adaptive immune response. Humoral immunity and cellular immunity are the two main mechanisms of the adaptive immune response. The humoral immune response is primarily driven by B-lymphocytes and produces antigen-specific antibodies in response to extracellular pathogens. However, cellular immune response does not depend on antibodies and is primarily mediated by mature T cells, macrophages, and the release of cytokines in response to intracellular pathogens. Adaptive immunity is slowly developed against an infection, but is ultimately highly specific to the invading pathogen, providing long-term protection. Upon vaccine administration, the antigen is first taken up by the antigen presenting cells (APCs). Dendritic cells (DCs) are the most potent APCs, and are responsible for antigen uptake and transport through the lymphatic system. Inside the lymph nodes, antigens are processed to form major histocompatibility complex (MHC) molecules that are then transported to the surface of DCs to induce interaction with T-lymphocytes (T cells). DCs with antigen-MHC I molecules activate the $CD8^+$ T cells to kill the infected/mutated cells, whereas MHC II molecules activate the $CD4^+$ T cells (Figure 58).[777] Activated $CD4^+$ T cells can be differentiated into T-helper (Th) type cells (Th1, Th2, Th17) and T follicular helper (Tfh) cells).[778] Th1 cells produce various cytokines to stimulate the cellular immune response and activated Th2 cells interact with B-lymphocytes (B cells) to stimulate the humoral immune response. Plasma cells and memory cells are two types of B cells that are vitally important to long-term immunity. Plasma cells are capable of producing antibodies against specific antigens, whereas memory cells can memorize characteristics of previously encountered antigens, thus providing an immune response against any future infections along with long-term protection.[779]

Polymeric nanoparticles have shown enormous potential in subunit vaccine development, as they can optimize the immune response by controlling the antigen release at APCs. Both synthetic and natural polymers such as PLGA, HA, chitosan, and alginate have been widely explored in vaccine preparation due to their biocompatibility and non-toxic nature.[780] Polymeric nanoparticles have the potential to deliver a wide range of antigens including proteins, peptides, or nucleic acids via encapsulation or covalent conjugation. Such encapsulation protects the antigen from enzymatic degradation, while enhancing blood circulation time to reach DCs. Furthermore, polymer nanoparticles can be easily functionalized with targeting moieties that recognize the specific receptors present on the surface of DCs to enhance site-specific antigen uptake and activate specific immune-response pathways.[778] Polymer nanoparticles also have self-adjuvanting properties, and they can act as adjuvants to enhance the immune response of co-loaded antigens.[779,781] Thus, polymeric nanoparticles can be easily manipulated to deliver a lower dose of antigen and adjuvants, while generating a comparatively strong immune response with minimal side effects. However, the field of polymeric nanoparticles for application in vaccine development is still relatively new, and only a few nanoparticle formulations have shown promise regarding clinical trials. DermaVir, a mannosylated PEI polyplex vaccine loaded with DNA-encoded HIV antigens, has completed phase I/II clinical trials for HIV immunotherapy. In addition, cancer vaccines based on PLGA, such as WDVAX, a PLGA scaffold vaccine for melanoma, and PRECIOUS-01, a PLGA nanoparticle loaded with natural killer T cell activators and tumor antigens for the treatment of solid tumors, are currently in phase I clinical trials.[782,783]

7.2.1. Mucosal Vaccines. Oral, nasal, rectal, or vaginal mucosal surfaces are the basic entry points for the majority of pathogens. Mucosal tissue is composed of highly compartmentalized mucosa-associated lymphoid tissue (MALT) that is responsible for providing a mucosal immune response. Antigens delivered via mucosal vaccines can interact with MALT to induce both a mucosal and systematic immune response. Thus, they can neutralize the pathogens at mucosal sites before a serious infection progresses.[784,785]

Mucosal vaccines based on biodegradable polymeric nanoparticles have shown tremendous potential to induce humoral, cellular, and mucosal immune responses. In addition, they can both control and prolong the release of antigens at mucosal sites and protect the stability of antigens against degradation. PLGA and PLA are the most well-studied, FDA approved biodegradable polymers that have been used in antigen delivery.[776,786] It has been reported, however, that PLGA nanoparticles are not as successful for nasal vaccination due to their lack of mucoadhesiveness, coupled with their rapid nasal clearance. Thus, to reduce the mucosal clearance of PLGA nanoparticles, chitosan and glycol chitosan derivatives are often functionalized to their surface.[787] Pawar et al. designed chitosan and glycol chitosan coated PLGA nanoparticles to understand the mucosal immune response for nasal vaccine delivery.[788] These glycol chitosan coated PLGA nanoparticles demonstrated a relatively strong immune response due to their enhanced mucoadhesive properties. In addition, PLGA- and PLA-based nanoparticles can encapsulate hydrophobic mole-

https://doi.org/10.1021/acs.chemrev.3c00705
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cules such as pattern recognition receptor (PRR) ligands that are capable of specifically stimulating DCs that act as the bridge between innate and adaptive immune responses. Pavot et al. prepared a PLA nanoparticle to enhance the delivery of nucleotide-binding oligomerization domain (NOD) ligands, a type of cytosolic PRR ligand, which are responsible for stimulating DCs to provide immune response.[789] Each PLA nanoparticle was coated with HIV-1 gag p24 antigen, and NOD-loaded PLA nanoparticles exhibited enhanced HIV-specific T cell activation in HIV positive patients. In addition, enhanced p24-specific immune responses, both systemic and mucosal, were observed following both mucosal and parenteral administration.

Chitosan has also been widely applied in mucosal vaccine development. Chitosan is cationic in nature, and chitosan-based nanoparticles can increase the cellular uptake efficiency of antigens by interacting with anionic nasal epithelial cells. Moreover, chitosan has shown adjuvant properties in vaccine formulations, improving both humoral and cellular immune response.[790] However, poor solubility at physiological pH is one of the major limitations of chitosan for pharmaceutical applications. Thus, chitosan is often modified with other functional groups to overcome this solubility problem, thereby enhancing its effectiveness as a mucosal vaccine strategy. Nanoparticles prepared from chitosan derivatives are some of the most promising designs to enhance mucosal immunity.[791,792] To evaluate the adjuvant properties and mucosal immune response of chitosan derivative nanoparticles, Zhao and co-workers developed bovine serum albumin (BSA)-loaded *N*-2-hydroxypropyl trimethyl ammonium chloride chitosan/*N*,*O*-carboxymethyl chitosan nanoparticles (N-2-HACC/CMCS/BSA NPs).[793] Both *in vitro* and *in vivo* studies revealed enhanced BSA antigen uptake in dendritic cells for these chitosan nanoparticles, as opposed to the antigen alone. The nanoparticles exhibited prolonged antigen retention in mucosal tissues even after 8 h post immunization, confirming the antigen-protective quality of the nanoparticle. Moreover, the nanoparticles exhibited a higher ratio of activated DCs ($CD11c^+$) in the splenocytes of mice, together with a greater level of $CD4^+$ and $CD8^+$ T cells. This suggests that chitosan (N-2-HACC/CMCS NPs) nanoparticles have a greater ability to promote antigen presentation in DCs, and yield an enhanced mucosal and systematic immune response.

PEI is a well-studied cationic polymer, which is employed to deliver a wide range of cargo, including nucleic acids and proteins. It has been recently reported that polycationic PEI can form nanocomplexes that are capable of simultaneous delivery of adjuvants and antigen molecules to induce cross-protective influenza immunity. Wang and co-workers fabricated PEI nanoparticles (PEI-H3/CpG) incorporating both an influenza vaccine antigen hemagglutinin (H3), and the adjuvant CpG.[794] PEI-H3/CpG nanoparticles demonstrated a considerably enhanced local and cellular immune response, which did not decay even after 6 months post-immunization. Furthermore, in comparison to PEI/H3, the PEI-H3/CpG nanoparticle exhibited a multi-faceted immune response, ensuring improved cross-protection against influenza infection. In a recent study, Lei et al. investigated the effectiveness of cationic nanocarriers—PEI, chitosan, and *N*-[1-(2,3-dioleoyloxy)propyl]-*N*,*N*,*N*-trimethylammonium chloride (DOTAP)—as adjuvants for the recombinant S-RBD vaccine for SARS-CoV-2. Anionic and neutral liposomes were used as controls.[795] This study reported enhanced cellular and humoral immune responses for cationic nanoparticles, especially PEI cationic nanoparticles, which exhibited significantly improved antigen uptake and activation of dendritic cells compared to chitosan and other control nanoparticles. However, the choice of PEI and chitosan in mucosal delivery may depend on several other factors, such as the targeted mucosal site, the type of antigen to be delivered, and the administration route.[796] PEI may show efficient transfection compared to chitosan, however, high molecular weight PEI can be more cytotoxic, limiting its clinical applicability.[797−800] Polymeric nanoparticulate-based vaccines have also been developed to treat bacterial infections. Hu and co-workers published a thorough review of various nanomaterial-based antibacterial vaccines against bacterial infections.[801]

7.2.2. Cancer Vaccines. Despite the considerable progress of traditional cancer treatment methods, cancer immunotherapy has recently emerged as a promising treatment choice for various types of cancers. Cancer immunotherapy involves boosting the body's inherent immune system to attack cancer cells via natural mechanisms. Vaccination is one of the most promising immunotherapy strategies, as it can induce a tumor-specific immune response, as well as bestow long-term immunity to suppress the tumor growth, recurrence, and metastasis.[802−804] Prophylactic cancer vaccines are administered as a preventive measure to reduce the development of cancer by initiating a specific immune response. In contrast, therapeutic vaccines are administered to an established tumor, aiming to induce an immune response for tumor regression, establish lasting anti-tumor memory, and avoid non-specific adverse reactions.[805,806] Therapeutic cancer vaccination normally involves the delivery of antigens and appropriate adjuvants to APCs, followed by the activation of APCs and the presentation of antigens to tumor-specific T cells, capped-off by the trafficking of tumor specific T cells into tumors, which eradicate the cancer cells.[807,808] However, it is evident that there are numerous challenges that need to be overcome to improve the immune response of conventional subunit vaccine formulations. The poor activation of APCs and the ineffective presentation of antigens to T cells can prevent the effective clinical translation of these conventional cancer vaccines.

Nanoparticle-based vaccines have shown enormous promise as vaccine delivery systems, as they can more efficiently deliver antigens and adjuvants to provide tumor-specific immunity, and establish long-term immune response that prevent tumor reoccurrence.[808−811] Due to their highly tunable characteristics and potential for functionally sophisticated designs, nanoparticles can more efficiently promote site-specific delivery, thereby improving the activation of DCs to enhance the cross-presentation of antigens to T cells, ensuring enhanced tumor suppression.[811,812] Following the successful delivery of antigens to DCs, they are processed and presented to the $CD8^+$ T and $CD4^+$ T cells via MHC I and MHC II molecules, respectively. Activation of $CD8^+$ T cells into cytotoxic T lymphocytes initiates a cellular immune response and promotes the elimination of antigen specific tumor cells.[813]

Optimizing the delivery of antigens to DCs is essential for polymeric nanoparticles to yield a more efficient immune response. To achieve this, the surface of polymer nanoparticles can be modified with specific ligands that bind to receptors overexpressed on DCs. Upon excretion into lymph nodes, the particles can bind with these specific receptors on DCs to improve their cellular uptake and thereby enhance the antigen delivery. Different types of receptors such as Fc receptor

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

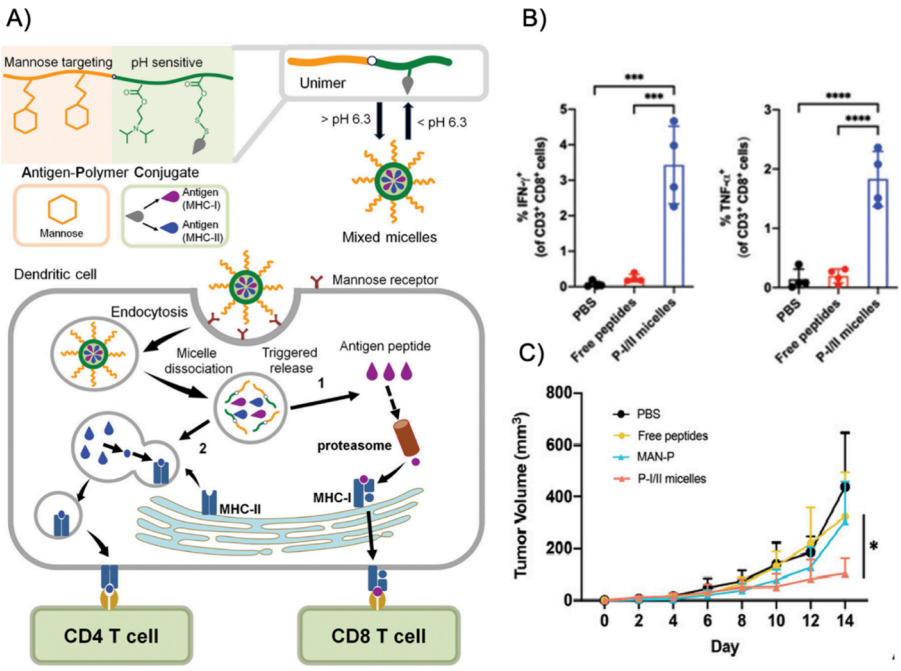

Figure 59. A) Schematic representation of mannosylated polymer nanoparticles (P-I/II micelles) for the delivery of both MHC-I and MHC-II epitopes to DCs. B) Percentage of IFN-γ^+ and TNF-α^+ CD8$^+$ T cells in the spleen after restimulation with SIINFEKL peptide; P-I/II micelles induced a significant increase in the number of IFN-γ- and TNF-α-producing CD8+ T cells in the splenocytes when stimulated with SIINFEKL compared to phosphate buffer saline (PBS) control and free peptide. C) Tumor growth inhibition curve of B16F10 tumor-bearing mice treated with PBS, free peptides, control mannosylated polymer without antigen conjugation (MAN-P), and P-I/II micelles. Reproduced with permission from ref. 819. Copyright 2022, Wiley-VCH.

(FcR), mannose receptor, DEC-205, CD40, and CD11c receptors have been employed in engineering DC-targeted nanoparticles.[814−817] Conniot et al. designed two PLGA/PLA nanoparticles, one non-mannosylated, and the other mannosylated, for the efficient co-delivery of a melanoma-associated antigen and Toll-like receptor (TLR) agonist to DCs.[818] Unsurprisingly, the targeted, mannosylated nanoparticle exhibited higher cellular internalization compared to the non-mannosylated nanoparticle. In combination with ibrutinib and αPD-1/αOX40, the mannosylated nanoparticle demonstrated distinct remission of tumor growth and prolonged survival in tumor bearing mice compared to its unfunctionalized counterpart. These results suggest that mannose receptor targeting is a useful strategy for enhancing antigen cross-presentation and the activation of tumor-antigen specific T cells. Recently, Pun and co-workers reported a mannosylated polymer nanoparticle (P-I/II micelle) for anti-cancer peptide antigen delivery (Figure 59).[819] The amphiphilic polymer was designed with a hydrophilic mannose methacrylate block and a hydrophobic pH-responsive PDPAEMA block, and MHC-I and MHC-II antigens were conjugated to the pH-responsive block via reversible disulfide linkages to initiate selective delivery of peptide antigens after DC internalization. The micelles were stable at physiological pH but disassembled in the acidic environment of the endosome (pH < 6.5−6.6) demonstrating enhanced endosomal delivery of antigens. *In vivo* studies revealed both the enhanced retention of the mannosylated nanoparticle within lymph nodes, as well as improved DC internalization in CD11c$^+$ and MHC11$^+$ cells compared with free peptide and non-targeted particles. Moreover, enhanced DC (CD8$^+$) activation was observed with the targeted nanoparticles, inducing significant increase in the number of IFN-γ- and TNF-α-producing CD8$^+$ T cells in the splenocytes demonstrating the correlation of DC maturation and T cell activation. Thus, these results emphasized the significantly enhanced anti-tumor performance bestowed by mannosylated nanoparticles as opposed to the free antigen, further reinforcing the significance of targeting functionalities for efficient delivery of peptide cancer vaccines.

TLR agonists are potent immune stimulators that have been employed in cancer vaccines.[820,821] TLRs, however, can cause severe side effects when administrated in their free form, and they are also prone to elimination very quickly by the circulatory system. Thus, polymeric nanoparticles have been developed to improve the accumulation of TLR agonists in lymph nodes.[822−824] Moreover, nanoparticles can be designed to deliver TLR agonists to their receptor sites, located at the inner endosomal membrane. Xia et al. reported a pH- and enzyme-responsive TLR7/8 agonist conjugated nanoparticle that could activate the TLR7/8 signaling pathway to achieve robust cancer immunotherapy.[825] The selected TLR7/8 agonist, imidazoquinoline (IMDQ), was covalently conjugated to the pH-responsive PEG-*b*-PDPAEMA block copolymer via an enzyme-responsive linkage GLy-Phe-Leu-Gly (GFLG), and the antigen OVA was physically loaded within the nanoparticle during self-assembly. Upon nanoparticle internalization within DCs, pH induced disassembly into unimers occurred, and the degradation of GFLG linkage released IMDQ, stimulating the TLR7/8 receptors. *In vivo* studies demonstrated an excellent anti-tumor immune response against both mouse melanoma and colon cancer, owing to the controlled delivery of TLR7/8 agonist to its receptor sites at the endosomal membrane.

Antigen cross-presentation to CD8$^+$ T cells via MHC I molecules is essential for activating a cytotoxic T cell response.[157] However, nanoparticles become trapped in endosomes following internalization within DCs. It is essential

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

to develop strategies to improve the endosomal escape of nanoparticles, as the cytosolic delivery of antigens is necessary for efficient antigen cross-presentation to T cells.[808] Thus, engineering pH-responsive nanoparticles that are able to escape the endosome is a promising strategy to improve the cytosolic delivery of antigens.[74,81] Stayton and co-workers reported a pH-responsive micellar nanoparticle with endosomolytic activity to control the cytosolic delivery of an antigen while enhancing $CD8^+$ T cell response.[826] The micellar structure comprised a pH-responsive PDMAEMA core, propylacrylic acid, PBMA and a hydrophilic HPMA shell containing pyridyl disulfide moieties for the conjugation of an antigen. Protonation of the pH-responsive polymer block disrupted the endosomal membrane, enhancing the cytosolic delivery of the antigen. These antigen-conjugated pH-responsive nanoparticles exhibited significantly enhanced antigen-cross presentation relative to a non-responsive control, free antigen, and physical mixture of antigen and the particle. Furthermore, the antigen-conjugated pH-responsive nanoparticles demonstrated enhanced antigen specific $CD8^+$ T cell responses compared to the non pH-responsive control nanoparticles. In addition, pH-responsive polymer nanoparticles have been investigated to enhance the co-delivery of neoantigens and STING agonists for tumor immunotherapy, as their stimuli-responsiveness enhances the release efficiency and cytosolic delivery of these therapeutics.[827] These types of sophisticated stimuli-responsive polymeric nanoparticles notably enhance the precise delivery of antigen and adjuvants to their targeted sites, indicating their potential for clinical translation.

7.3. Antimicrobial Therapy

Despite the discovery and utility of antibiotics in the early 20th century, treating bacteria remains a challenge to global health. The efficacy of conventional antibiotic treatment is seriously threatened by the recent emergence of antimicrobial resistance, as well as the various barriers that lower the efficiency of medication, including biofilms and hard-to-reach infection sites. Therefore, there is a strong incentive in medical research to develop new platforms that can better overcome these challenges. Polymeric nanoparticles are one of the more promising platforms in this regard, primarily due to their sophisticated design capability, which allows for enhanced targeting, penetration and drug loading, as well as the addition of functionality and stimuli-responsiveness.

7.3.1. Intracellular Infections. Phagocytes, including neutrophils, macrophages, and dendritic cells, are activated by the immune system in response to foreign microorganisms (pathogens). These pathogens are then eliminated through phagocytosis, which involves the phagocytes "ingesting" and ultimately destroying the pathogens. During this process, phagosomes acidify, generate reactive oxygen and nitrogen species, and release antimicrobial proteins and peptides that together eliminate pathogens. However, certain intracellular bacteria are able to survive this process.[828] These bacteria can be divided into two groups: obligate intracellular bacteria, which encompasses many species of *Anaplasma*, *Chlamydia*, *Coxiella burnetiid*, etc; and facultative intracellular bacteria, which includes *Staphylococcus aureus*, *Listeria monocytogenes*, and *Legionella pneumophila*. The former category requires a eukaryotic host to replicate, while the latter can replicate both inside and outside host cells. Once inside a host cell, intracellular bacteria can eventually exit through extrusion or lysis.[829] This intracellular penetration can result in a persistent bacterial infection, which, in the case of *Helicobacter pylori* in gastric mucosa, can be life-long.[830] *S. aureus*, one of the most prevalent kinds of bacteria, can survive phagocytosis by secreting protective substances inside phagosomes such as α-toxin, which induces endosomal escape. *S. aureus* is also able to manipulate the cell death pathways of neutrophils to exit the host cell and cause a local infection. Moreover, antibiotics such as β-lactams and glycopeptides are not capable of entering eukaryotic cells, and other antibiotics such as rifampicin become less effective due to the acidic environment within phagolysosomes. Intracellular *S. aureus* can therefore be protected from antibiotics by its own host.[831] In order to overcome this major problem, significant research has centered on a myriad of intracellular antibiotic drug-delivery vectors, including polymeric nanoparticles that are described in detail below.

In one study, phosphatidylcholine-chitosan nanoparticles loaded with gentamicin (a bactericide) were designed, and effectively killed *L. monocytogenes* and *P. aeruginosa* in RAW264.7 cells. This is due to the fact that the nanoparticles were effectively engulfed by phagocytes, resulting in higher intracellular concentration of gentamicin.[832] Jiang et al. used PLGA nanoparticles to passively target intracellular *Klebsiella pneumoniae*. By using a w/o/w emulsion formulation, high loading of gentamicin (135 μg per mg PLGA) was achieved. The nanoparticles killed intracellular bacteria more effectively compared to free gentamicin, and also reduced inflammatory responses.[833]

Given that phagocytes play a vital role in eliminating pathogens, modulating the physical properties of nanoparticles for preferential uptake by phagocytes is a common strategy employed to increase the therapeutic efficacy of antibiotics. Research suggests that particle sizes from 500 to 1000 nm promote uptake by phagocytes. For example, Elnaggar et al. synthesized a 600 nm PLGA nanoparticle modified with an iron-tannic acid supramolecular complex. The nanoparticles were loaded with pexiganan (a cationic antimicrobial peptide) and silver (Ag) nanoparticles (famous for their antimicrobial activity) via attachment to the supramolecular complex. These nanoparticles displayed preferential uptake by macrophages, enhancing intracellular Ag accumulation and pexiganan release.[834] Pei et al. synthesized an 800 nm nanoparticle consisting of PLGA, PEG-*b*-PLGA, Eudragit E 100—a cationic polymer based on PDMAEMA—and a modified zwitterionic chitosan derivative (ZWC). Vancomycin was loaded through electrostatic attraction with Eudragit E 100, and was released in an acidic environment via the charge shifting properties of the modified ZWC. Due to the selective uptake of 500 to 1000 nm nanoparticles by macrophages, and the pH-responsive release of vancomycin, these nanoparticles achieved a ten-fold increase in the concentration of vancomycin inside macrophages. This yielded strong antibacterial activity against a series of intracellular bacteria.[835]

Phagocytes utilize receptor-mediated internalization. Sugar moieties are a useful strategy to target such receptors and thus increase intracellular accumulation, and include mannose, HA, and galactose. The mannose receptor, a transmembrane glycoprotein from the C-type lectin family, can recognize and bind to a variety of bacteria that are coated with mannose-containing structures, while also functioning as an endocytic receptor, making it an attractive target for intracellular delivery.[836] Yang et al. used a mannosylated exosome

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

(intracellular membrane-based vesicles secreted by cells) for delivery of both lysostaphin (antimicrobial enzyme) and vancomycin. According to flow cytometry, mannosylated exosomes showed a high uptake in RAW264.7 cells, while uptake was poor in the case of unmodified exosomes and in A549 cells (human bronchial epithelial cell that has no expression of mannose receptor). Pretreatment with D-mannosamine to inhibit the receptor resulted in no uptake, which further emphasized that the selective internalization of nanoparticles was through the interaction of the modified mannose on the surface. Using mannosylated exosomes to deliver both lysostaphin and vancomycin resulted in a significant reduction of intracellular methicillin-resistant *Staphylococcus aureus* (MRSA) due to multiple bactericidal mechanisms involved.[837] Lunn et al. used surfactant-free emulsion polymerization to synthesize a nanoparticle composed of a tri-block copolymer containing mannopyran-1-oxyethyl acrylamide, PDPAEMA, and diacetone acrylamide-hydrazone-isoniazid. The uptake of these mannose-functionalized nanoparticles was significantly enhanced compared to a PEG-functionalized control, due to preferential endocytosis of mannose. After endocytosis, the nanoparticle disassembled due to the protonation of PDPAEMA, and isoniazid was then released by acidic hydrolysis of the hydrazone linker. These nanoparticles showed improved activity against intracellular *Mycobacterium bovis* BCG.[838]

Functionalizing nanoparticles with HA offers a promising strategy to enhance their cell targeting capabilities and thus improve therapeutic efficacy.[839] Zhang et al. modified a tetracycline-loaded zeolitic imidazolate framework-8 (ZIF-8) with a HA coating via conjugation between the coordination bond of Zn^{2+} and the carboxyl group on HA. The HA-functionalized nanoparticles were found to enter macrophages at a significantly higher level than particles without any HA. Once inside the cell, the pH-responsive ZIF-8 then released a combination of antibiotics and zinc ions, resulting in a 98% clearance of intracellular *S. aureus*.[840]

Macrophage galactose-type calcium-type lectin (MGL) is a type 2 transmembrane glycoprotein that has a calcium-dependent carbohydrate recognition domain. These proteins are expressed exclusively on macrophages and dendritic cells. As opposed to mannose-specific lectins, these lectins recognize galactose and *N*-acetylgalactosamine.[841] A clarithromycin-loaded nanoparticle was designed that comprised a hydrophilic mannose- and galactose-modified shell polymer, and a PCL block copolymer core functionalized with phenylboronic acid groups and glycosyl groups. This nanoparticle displayed strong uptake capability in cells with mannose and galactose receptors, as well as specific interaction with bacterial membranes, attributed to the phenylboronic acid groups. Degradation of the PCL core released clarithromycin, resulting in strong bactericidal activity against *S. aureus* both *in vitro* and *in vivo*.[842]

Cell membranes are biocompatible, and can also be employed to target intracellular pathogens. Gao et al. coated a PLGA nanoparticle with extracellular vesicles of *S. aureus*. These nanoparticles showed enhanced uptake compared to PEGylated and lipid-based vehicles in both *S. aureus* infected phagocytes and *E. coli* infected macrophages. This suggests that the proteins on bacterial membranes are critical for bacteria-host and bacteria-bacteria interactions. Furthermore, these nanoparticles were loaded with either vancomycin or rifampicin, and displayed significantly improved antimicrobial efficacy in kidneys and lungs.[843] Li et al. encapsulated an amphiphilic antibiotic conjugate of triclosan and ciprofloxacin with a membrane from mouse J774A.1 cells. The resultant nanoparticles showed superior engulfment by infected mouse J774.1 macrophages compared to liposomes. Moreover, the nanoparticles were selectively engulfed by infected macrophages rather than sterile macrophages. Finally, these nanoparticles showed significantly higher antimicrobial efficiency in *S. aureus* infected mouse cells *in vivo* compared to ciprofloxacin alone.[844]

To identify peptides targeting *S. aureus*, *in vivo* screenings of phage-display peptide libraries were employed. A 9-amino acid cyclic peptide (CARGGLKSC) was synthesized, based on this screening, which could bind to *S. aureus in vitro*. Vancomycin-loaded porous silicon nanoparticles coated with the peptide showed >4-fold higher accumulation in the infected lung with a 10-fold increase of vancomycin efficacy against intracellular *S. aureus*.[845]

During phagocytosis, the phagosome becomes more acidic over time, reaching pH levels as low as 4.5 in the phagolysosome. Utilizing this pH change, Su et al. synthesized a streptomycin-loaded polymer−liposome hybrid nanoparticle that included PDEAEMA for pH responsiveness, and a mannose-functionalized methacrylate monomer for enhanced targeting. Upon a pH decrease, PDEAEMA shifted from hydrophobic to hydrophilic, disrupting the lipid bilayer and causing a burst release of streptomycin. Overall, these nanoparticles yielded a 13-fold increase in the elimination of intracellular *F. novicida* compared to a control.[846] Li et al. functionalized a moxifloxacin-loaded mesoporous silica nanoparticle using a nanovalve consisting of a 1-methyl-1-*H*-benzimidazole stalk ($pK_a \sim 6$) and β-cyclodextrin. The stalk was covalently attached to the pore entrance of silica and capped by cyclodextrin through hydrophobic interactions. When the pH dropped below 6, the stalk became protonated and the interaction declined, leading to nanoparticle disassembly. These nanoparticles displayed a 2- to 4-fold increase in antibiotic efficacy compared to free moxifloxacin in *F. tularenisis* infected macrophages in the lung.[847] Feng et al. fabricated a cascade targeting rifampicin-loaded nanoparticle composed of poly(α-*N*-acryloyl-phenylalanine)-*b*-(β-*N*-acryloyl-D-aminoalanine) conjugated to mannose via a pH-responsive linker (Figure 60).[848] Mannose acted as a targeting ligand, promoting the internalization of nanoparticles into phagosomes. pH-triggered cleavage of mannose exposed the D-aminoalanine moieties, which allowed the nanoparticle to escape into the cytoplasm and specifically bind to methicillin-resistant *S. aureus* (MRSA). Through this targeting, the nanoparticles outperformed a myriad of nanoparticle controls, as well as free rifampicin both *in vivo* and *in vitro*.

Enzymes such as phosphatase, lipase, and esterase can also be employed as a stimulus to trigger antibiotic drug delivery through nanoparticle disassembly. For example, Xiong et al. synthesized a vancomycin-loaded PPE cross-linked nanogel with a mannose-conjugated PEG shell. Phosphatase and phospholipase secreted by MRSA stimulated the degradation of the nanogel, leading to the release of vancomycin. The nanoparticles showed a 50-fold increase in the elimination of intracellular MRSA in RAW264.7 macrophages compared to a control.[849] Chen et al. synthesized a nanoparticle comprising a mannose-modified poly(ethyl-bis[2-(acryloxy)-ethyl] phosphate-*co*-2-propenoic acid tetraphenylethylene ester) and encapsulating an antibiotic conjugate of ciprofloxacin and

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

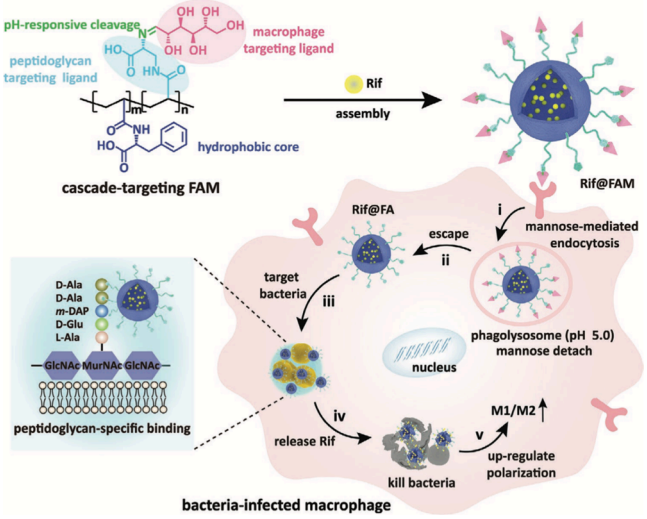

Figure 60. A stimuli-responsive, bacteria targeting dual functional nanoparticle for the delivery of rifampicin against *S. aureus*. Targeted delivery was achieved via the incorporation of mannose receptors for macrophage internalization, and the pH triggered exposure of aminoalanine moieties for intracellular bacteria targeting. Reproduced with permission from ref. 848. Copyright 2022, Wiley-VCH.

deferoxamine complexed with Fe^{3+} ($D_{Fe}C$). After internalization through mannose-mediated phagocytosis, the polymer was degraded by lipase and phospholipase enzymes secreted by bacteria, which resulted in the release of $D_{Fe}C$. These nanoparticles eliminated intracellular *S. aureus in vivo*, such that infected mice survived.[850] Su et al. designed an inhalable polymeric prodrug (drugamer), which featured mannose for enhanced alveolar macrophage uptake, and a prodrug of ciprofloxacin with a protease-cleavable valine-citrulline (VC) linker. This VC linker was designed to rapidly hydrolyze by human liver cathepsin B enzyme at lysosomal pH. When investigated in an airborne *F. novicida* infection experiment *in vivo*, these drugamers displayed a strong retention time and strong antimicrobial performance.[851]

The redox environment is another well studied endogenous stimuli for the design of antimicrobial polymeric nanoparticles. Zhang et al. synthesized a vancomycin-loaded redox-responsive nanoparticle by employing cystine dimethacrylate as a cross-linker. Red blood cell (RBC) membranes were employed both as a nanoreactor and also as a coating material. These RBC membranes were posited to neutralize toxins secreted by bacteria and to promote nanoparticle uptake. The nanoparticles rapidly released vancomycin, which resulted in superior antibacterial activity compared to both the free drug and non-responsive control.[852] Kang et al. designed a multifunctional redox-responsive nanoparticle for tumor-resident intracellular *E. coli*. This nanoparticle featured HA for tumor receptor targeting, guanidine functionality for tumor penetration and membrane destabilization activity, redox-responsive disulfide bonds on its core polymers, and a loaded photothermal agent along with gemcitabine, an antibiotic. Overall, these nanoparticles achieved very high levels of therapeutic efficacy on tumor-resident bacteria through the combination of chemotherapy, phototherapy, and stimuli-responsiveness.[853]

Instead of directly killing bacteria, drug-delivery systems that promote antimicrobial immunity have also received the attention of researchers. For example, Pi et al. synthesized mannose-conjugated, chitosan stabilized selenium nanoparticles that encapsulated isoniazid—an antimicrobial drug. The nanoparticles were specifically internalized through mannose-receptor dependent and clathrin-mediated endocytosis, and released isoniazid in the lysosome. These particles could not only kill the intracellular *Mycobacteiaum tuberculosis* (Mtb) by direct contact, but also induce antimicrobial immunity.[854]

7.3.2. Biofilm Infection. Biofilms are a survival strategy adopted by bacteria to provide a surface for growth and protection from hostile environments.[855] Biofilms are mainly formed by extracellular polymeric substances such as exopolysaccharides, extracellular proteins, and DNA.[856] Due to their protective properties, biofilms render bacteria resistant against antibiotics due to a variety of different mechanisms.[857] Therefore, traditional antibiotics generally fail to treat bacteria in biofilms, and very high concentrations of antibiotics are usually required to achieve therapeutic efficacy. Roughly 60% of bacterial infections involve biofilms, which is of significant concern, and incentivizes the development of antibiotic strategies that are targeted for this environment.[858] Polymer nanoparticles are a potential solution to this problem, given their sophisticated functionality and site-specific targeting capability.

To penetrate biofilms, ideal polymeric nanoparticles are generally small and positively charged, given the anionic nature of biofilms.[859] However, nanoparticles that are stimuli-responsive, shifting from stealth to positively charged, can be even more effective as they allow greater penetration through the biofilm before binding. Horev et al. developed a pH-responsive nanoparticle for the treatment of oral biofilms. Their nanoparticle was loaded with farnesol, and composed of PDMAEMA-*b*-(PDMAEMA-*co*-PBMA-*co*-poly(propylacrylic acid)). The nanoparticle could bind to biofilms through the electrostatic interaction between positively charged PDMAEMA and the negatively charged biofilm and tooth surface. This nanoparticle was able to load 22 wt % of Farnesol, which represents a more than 400-fold improvement compared to the poorly soluble free Farnesol. pH-responsive release of Farnesol was achieved in a rapid manner: 75% after 12 h at pH 4.5. This high loading, rapid release, and superior binding affinity yielded strong antibiofilm activity.[860] Liu et al. developed a mixed-shell polymeric micelle that consisted of PEG-*b*-PCL and PAE-*b*-PCL. These micelles displayed pH- and lipase-responsive release of encapsulated triclosan. Micelles containing only a PEG shell displayed stealth properties, enhanced circulation time, and significant biofilm penetration. At pH 5, PAE became positively charged, which allowed electrostatic targeting of the negatively charged *S. aureus*. This resulted in biofilm accumulation at pH 5 that did not occur in nanoparticles lacking PAE. Subsequently, lipase secreted by bacteria degraded the micelles, releasing triclosan at the vicinity of the bacteria to yield strong antibacterial effects.[861] Similarly, Xi et al. fabricated a dual corona polymersome that was composed of PCL-*b*-poly(Lysine-*co*-Phenylalanine) and PEG-*b*-PCL. Poly(Lysine-*co*-Phenylalanine) represented a cationic antibacterial polypeptide that could bind, and damage negatively charged bacterial membranes. Fluorescence microscopy images and CLSM images of *S. aureus* biofilm confirmed the penetration and disruption of the biofilm by these dual corona vesicles.[862]

To improve biofilm penetration, hybrid particles containing magnetic nanoparticles such as superparamagnetic iron oxide nanoparticles (SPIONs) have been investigated. Geilich et al.

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Chem. Rev. 2024, 124, 5505−5616

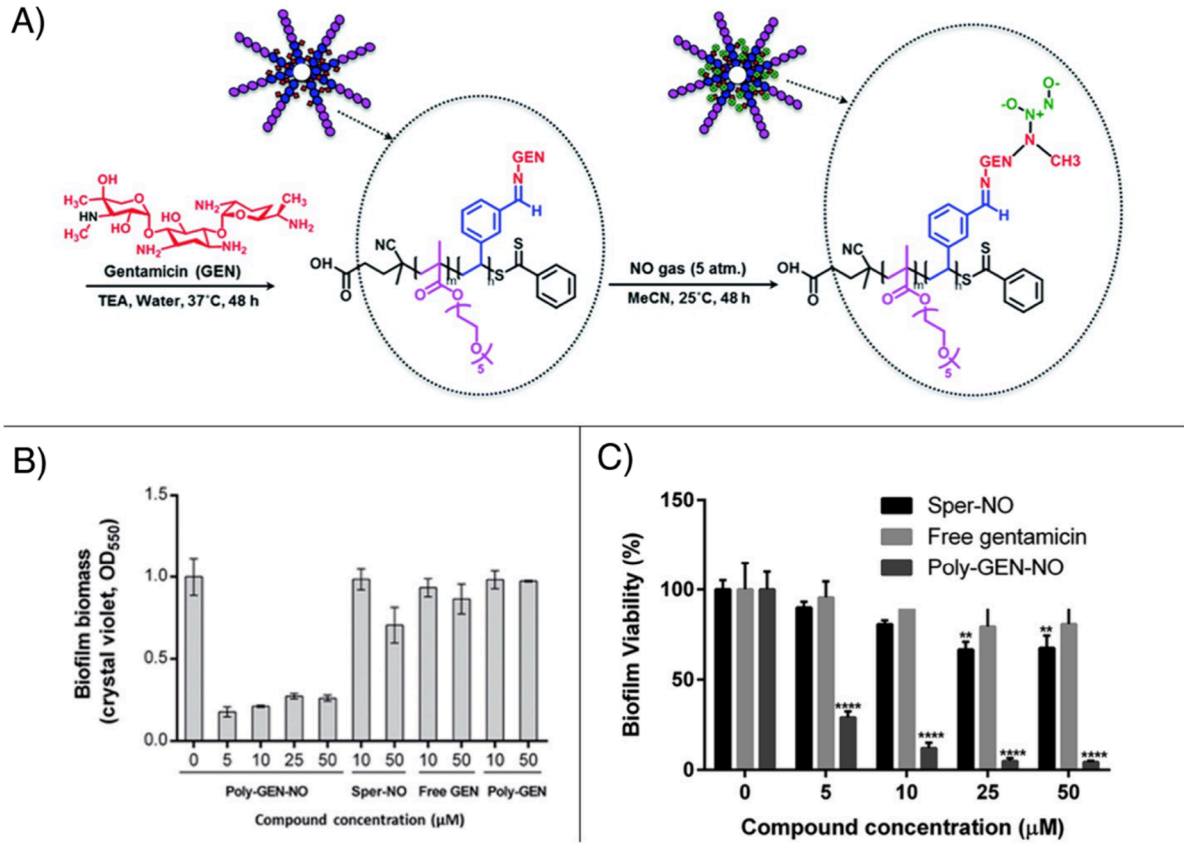

Figure 61. Synergistic polymeric nanoparticles designed to eliminate biofilms through the release of the antibiotic gentamicin and the production of bactericidal nitric oxide (A). The nanoparticles (Poly-Gen-NO) displayed outstanding antibiofilm properties including biofilm mass reduction (B) and elimination of biofilm viability (C). Reproduced with permission from ref. 865. Copyright 2016, Royal Society of Chemistry.

encapsulated SPIONs into a methicillin-loaded polymersome formed from mPEG-*b*-PDLLA. The iron oxide-encapsulating polymersomes displayed strong penetration against *S. epidermidis* biofilms only when they were exposed to a magnetic field. Complete eradication of the biofilm was observed for iron oxide encapsulated nanoparticles with methicillin. Moreover, the polymersomes did not exhibit off-target toxicity when a range of magnetic fields were applied.[863]

Recently, Yu et al. designed a host−guest system for the co-delivery of melittin, an antimicrobial peptide, and the antibiotic ofloxacin. The host (H) was a large-pore mesoporous silica nanoparticle (MSN) modified by PEI and capped by *β*-cyclodextrin, while the magnetic-responsive guest (G) was an adamantane coated MSN capped by Cucurbituril. Melittin was loaded with cyclodextrin, while ofloxacin was loaded with cucurbituril. Guest and host co-assembled into a host−guest supramolecular cluster through the interaction between *β*-cyclodextrin on G and adamantane on the host. Electrostatic interactions, an applied magnetic field, or the presence of heat was able to release loaded cargo from this host−guest nanoparticle, eradicating >97% of the biofilm and 100% of the bacteria *P. aeruginosa*. This host−guest nanoparticle represents a design with extremely strong *in vivo* antibacterial activity.[864]

Nitric oxide (NO) is an important signaling molecule in the biofilm lifecycle. Several NO generating nanoparticles have been scrutinized as potential drug-delivery designs. Nguyen et al. conjugated gentamicin to a PEG-vinylbenzaldehyde copolymer through a hydrolysable Schiff base linker. NO was then reacted with a secondary amine on gentamicin to form the nanoparticle. These nanoparticles demonstrated superior bactericidal efficacy and anti-biofilm activity compared to either an NO donor or gentamicin alone. 90% of the bacteria in the biofilm was eliminated after treatment of 10 μM nanoparticles in 1 h compared to only 7% and 5% by using gentamicin or an NO donor alone (Figure 61).[865] Shen et al. developed an NO releasing nanoparticle composed of PEG-*b*-PCouNO, which was responsive to visible light. The monomer CouNO contained an *N*-nitrosoamine-based NO donor and a coumarin chromophore. Upon visible light irradiation, NO was released and observed via an increase in coumarin fluorescence. Thus, this nanoparticle was dual functional, releasing and monitoring the release of NO concurrently. *In vitro* experiments against *P. aeruginosa* biofilm using this design demonstrated a 3.5-fold reduction of bacteria after light irradiation.[866]

Photothermal therapy and photodynamic therapy utilize photosensitizers, which can generate heat and ROS under irradiation, terminating bacteria and biofilms. Chen et al. utilized photodynamic therapy for treatment of endophthalmitis. Nanoparticles comprising a pH-responsive poly(acrylic acid) coated ZIF-8 were functionalized with polydopamine and Ag nanoparticles, and further modified with vancomycin and aminated PEG. Vancomycin on the surface of the particles facilitated bacteria targeting, and bactericidal activity was generated by both Ag nanoparticles and ROS produced by laser irradiation. This synergistic effect resulted both in the eradication of a biofilm and a 2-fold reduction in bacteria in an endophthalmitis model.[867]

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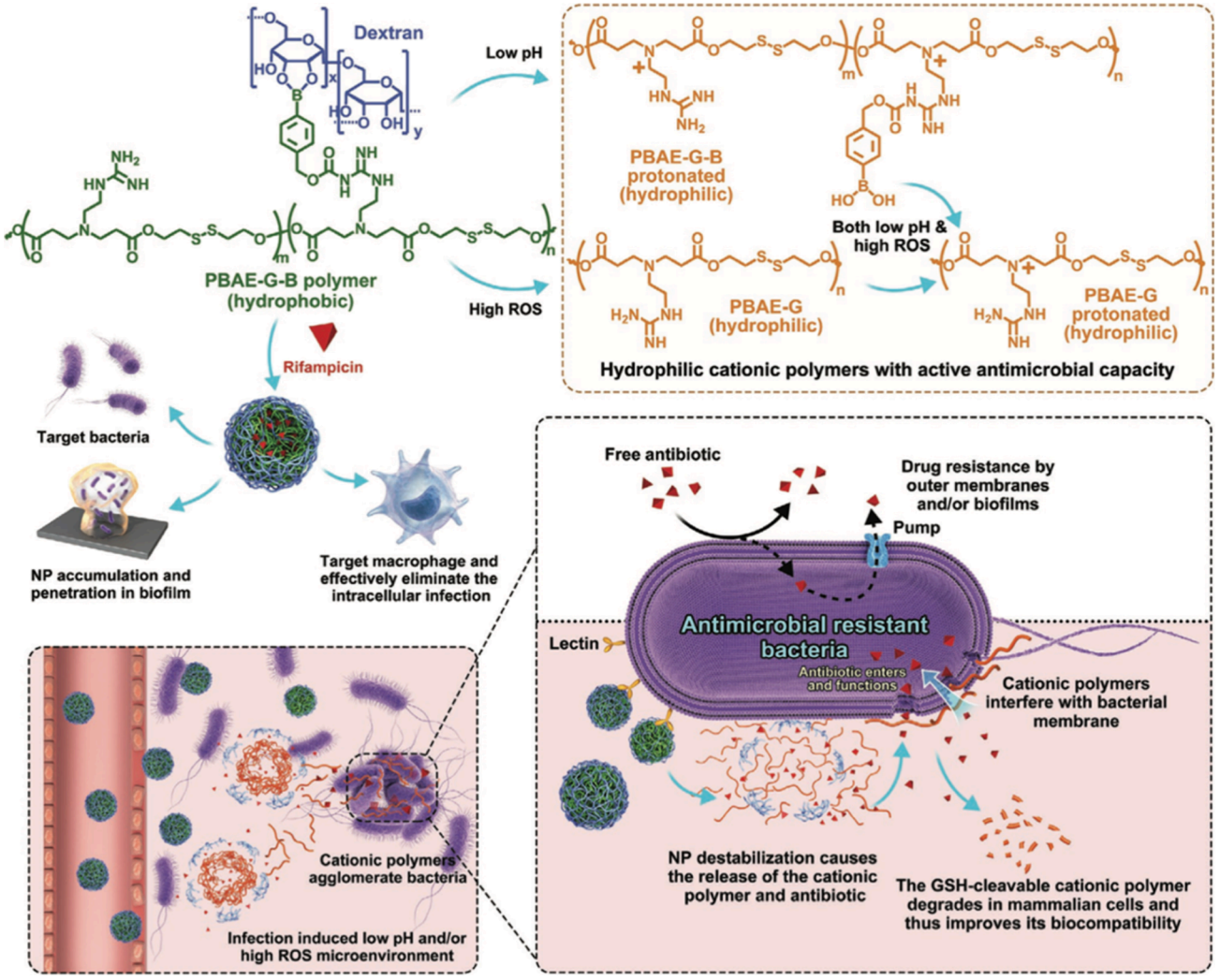

Figure 62. A dual-responsive nanoparticle that encapsulates the antibiotic rifampicin and preferentially targets antibiotic resistant bacteria. At the bacterial infection site, the nanoparticle's pH- and redox-responsive behavior released both rifampicin and toxic cationic polymer fragments. This nanoparticle eliminated rifampicin-resistant bacteria 40 times more efficiently than the unencapsulated drug. Reproduced with permission from ref. 874. Copyright 2021, Wiley-VCH.

7.3.3. Antimicrobial Resistance. Antimicrobial resistance (AMR) is the ability of microbes to survive and spread despite the presence of antimicrobial therapies. The Organization for Economic Co-operation and Development estimates that AMR will result in over 2 million fatalities in Europe, North America, and Australia alone in the next 30 years, and cost upwards of US$3.5 billion per year.[868] The mechanisms of AMR are diverse, and include drug efflux (mechanisms to pump drugs out of active region), poor therapeutic uptake, and microbe-induced drug modification or inactivation.[869] Therefore, discovering new ways to treat drug-resistant bacteria, or prevent the onset of AMR, represents a vital global health challenge over the coming century. Combining two separate therapies into one delivery system is a plausible solution to AMR, given the probability that bacteria develop resistance to both therapies concurrently is extremely low. Focusing on methods that disrupt bacterial membranes is another strategy worthy of investigation, given bacteria cannot easily alter their membrane composition.

NO-generated nanoparticles have been utilized to combat AMR. Liu et al. co-delivered NO and methicillin in a chitosan-graft-PAMAM polymer vector to treat MRSA. Conjugation of PAMAM to chitosan reduced toxicity while maintaining a high degree of loaded NO. The initial burst release of NO had strong antimicrobial and membrane disrupting performance, reducing the biofilm by 67% and MRSA by 80%. Furthermore, *in vivo* studies showed that the nanoparticles eliminated most of the MRSA in an infected skin model, due to the synergistic effect of released methicillin.[870]

Photothermal therapy triggered by NIR has strong bactericidal properties due to membrane disruption and protein/enzyme denaturation. Several nanoparticles have been studied to treat resistant bacteria on skin. Xiao et al. employed a zeolite-based imidazolyl skeleton (ZIF-8) coated with the photothermally active polydopamine and loaded with vancomycin to design a synergistic hybrid nanoparticle. SEM images illustrated the destruction of bacterial membranes when treated with this design. *In vivo* experiments against vancomycin-resistant *E. coli* showed a significantly superior healing effect upon nanoparticle treatment with NIR light.[871]

Strain selective delivery is advantageous, as it minimizes the dosages necessary to achieve similar therapeutic outcomes. Li et al. synthesized two polymers that self-assembled into polymersomes and were selectively responsive to penicillin G

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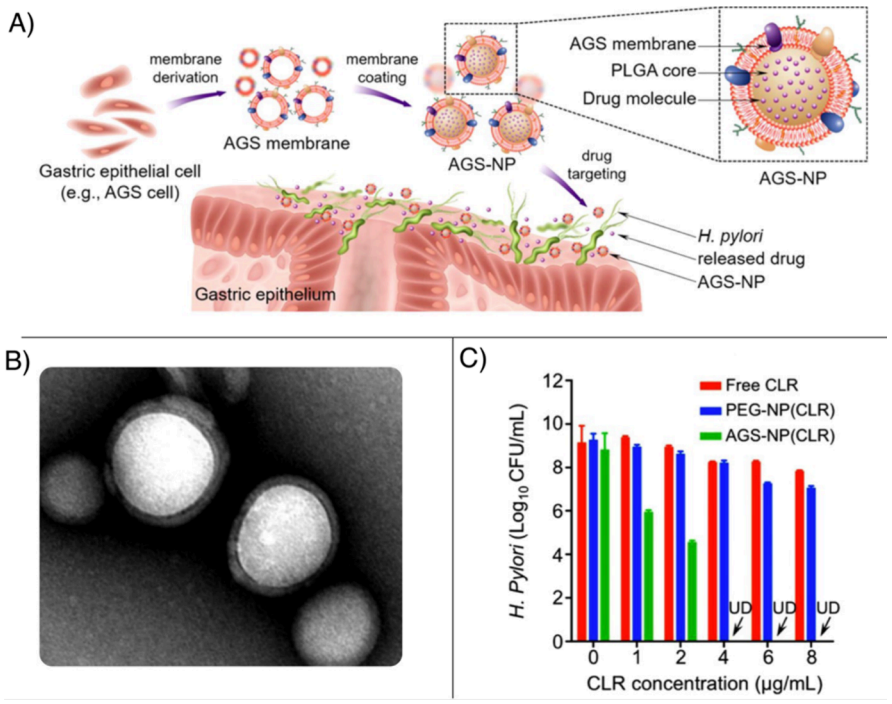

Figure 63. (A) A schematic representation of the preparation of gastricepithelial cell membrane-functionalized PLGA nanoparticles (AGS-NP) that preferentially targets *H. pylori* bacteria and release of antibiotic payload resulting in enhanced antibacterial efficacy. (B) TEM image of AGS-NP. (C) *In vitro* bactericidal activity of free clarithromycin (CLR), CLR-loaded PEGylated nanoparticle (PEG-NP (CLR)), CLR-loaded AGS-NP (AGS-NP (CLR)) ; the AGS-NP - loaded with the antibiotic CLR, was able to eliminate *H. Pylori* far more efficiently than either the free drug or PEGylated nanoparticle (PEG-NP), due to radically enhanced bacterial targeting. Reproduced with permission from ref. 881. Copyright 2018, Wiley-VCH.

amidase and β-lactamase (Bla) through self-immolative cleavage. Both polymersomes encapsulated antimicrobial agents that were released via selective enzymatic degradation. The vancomycin-loaded Bla-responsive polymersomes exhibited MRSA strain-selective release and *in vivo* healing capabilities.[872]

Nucleic acids have also been explored as therapeutic cargo that can inhibit certain genes related to AMR. For example, Sun et al. synthesized a tetrahedral framework of nucleic acids for the delivery of ampicillin to methicillin-resistant MRSA. This nucleic acid scaffold reduced *murA* and *murZ*, genes related to the production of bacterial membranes, thus promoting membrane fusion and damage and yielding strong antimicrobial activity against MRSA.[873]

Cationic polymers are also capable of causing membrane disruption, and designs that combine these polymers with antibiotics have been scrutinized. Ye et al. designed a pH and ROS-responsive nanoparticle consisting of poly(β-amino ester) (PBAE)-guanidine-phenylboronic acid and dextran (Figure 62). Dextran served both to bind to planktonic bacteria and to improve uptake by cells. At the infection site, these nanoparticles dissembled due to the low pH and high level of ROS, releasing both rifampicin and the cationic guanidine polymer, which is a membrane-perturbing moiety. This nanoparticle was observed to bind and kill rifampicin resistant *P. aeruginosa* with a 40-fold increase in efficiency compared to free rifampicin.[874] A tetracycline encapsulated PLA-*b*-PEG-*b*-PEI nanoparticle was examined as a drug-delivery vehicle against tetracycline-resistant *E. coli*. The nanoparticle not only exhibited a much lower tetracycline minimum inhibitory concentration, but also enhanced biofilm penetration and macrophage uptake. The improved activity was attributed to the positively charged PEI on the surface of the nanoparticle, which was able to electrostatically bind to the negatively charged bacterial membrane. *In vivo* tests showed that the antimicrobial properties of the nanoparticle were over twice as efficient as its non-charged counterpart.[875] Landis et al. synthesized a redox and enzyme-responsive nanoparticle comprising poly(oxanorborneneimide), guanidine, maleimide, tetraethylene glycol monomethyl ether, and a dithiol-disulfide cross-linker. Carvacrol oil was loaded into these particles, and was released in the presence of GSH and porcine liver esterase. *In vitro* results showed that the particles had broad-spectrum activity against both Gram-positive and Gram-negative biofilms. Moreover, where *E. coli* rapidly develops resistance in only a few passages (treatment cycles), nanoparticle treatment yielded no *E. coli* resistance even after 20 passages.[876]

7.3.4. *Helicobacter pylori* Infections. *Helicobacter pylori* is a type of Gram-negative bacteria that is responsible for one of the most prevalent infections worldwide. This bacteria causes diseases such as peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma, gastric adenocarcinoma, and gastric cancer.[877] To treat an *H. pylori* infection, drug-delivery systems must overcome the harsh gastric environment (pH ~ 1), penetrate mucosal membranes and biofilms, and perform targeted drug release at specific bacterial sites.

Jing et al. synthesized a polyion complex using negatively charged sodium tripolyphosphate and positively charged ureido-conjugated chitosan to encapsulate amoxicillin. This nanoparticle could withstand pH levels of ~1 and exhibited pH-responsiveness at neutral pH levels (~7) for a sustained, targeted release of amoxicillin at pH 6 and 7. Furthermore, the ureido group was found to target the urea transport protein on

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

H. pylori, resulting in an 87% reduction of bacterial growth in 24 h *in vitro*.[878] Similarly, Cong et al. modified a carboxymethyl chitosan-based micelle with this ureido functionality. Their micelle was stable in gastric fluid and was able to release clarithromycin gradually, yielding a 92% elimination of bacteria in only 30 minutes.[879] Arif et al. functionalized a chitosan-based nanoparticle with a thiol moiety via cysteine conjugation. These particles were stable at pH ∼ 1 but became unstable at neutral pH, releasing amoxycillin, while the added thiol group improved bacterial mucosal adherence. Compared to an unthiolated control, these nanoparticles were twice as efficient at inhibiting bacterial growth (77% inhibition at 24 h).[880]

Other *H. pylori* targeting strategies include using natural cell membranes or biosurfactants. Angsantikul et al. coated a clarithromycin-loaded PLGA nanoparticle with the plasma membranes from a gastric epithelial cell.[881] Such membranes preferentially bind to *H. pylori*, and the resultant nanoparticles had a 10-fold higher bacterial binding capacity than their PEGylated counterparts. These membrane-functionalized nanoparticles also demonstrated improved bacterial reduction *in vivo* (Figure 63). Li et al. synthesized clarithromycin-loaded chitosan nanoparticles. This nanoparticle was coated with rhamnolipids and DSPE-PEG 2000 that bestowed prolonged blood circulation and improved the mucus penetration capability. Rhamnolipids are biosurfactants produced by *P. aeruginosa* and are capable of biofilm disruption. The rhamnolipid-functionalized nanoparticles reduced biofilm mass by 89% and eliminated more than 97% of *H. pylori* within the biofilm. This design was twice as efficient as non-PEGylated nanoparticles with the same composition. *In vivo*, the biosurfactant-functionalized nanoparticles exhibited a biofilm reduction efficiency of 90%.[882]

Magnetic polymer nanoparticles have also received attention for *H. pylori* treatment due to their mucus penetration capability. Yang et al. modified a superparamagnetic iron oxide nanoparticle (SPION) with chitosan and poly(acrylic acid) to form a hybrid nanoparticle loaded with amoxicillin. This particle was both pH-responsive and had improved mucoadhesive properties, while the presence of SPIONs facilitated mucus penetration under an applied magnetic field. When a magnetic field was applied for only 30 minutes, the hybrid nanoparticles eliminated 60% *H. pylori*, in contrast to only 20% when treated with free amoxicillin.[883]

7.3.5. Pulmonary Infections. Lungs are exposed to many external pathogens that can cause a wide range of diseases. One of the most historically relevant diseases is tuberculosis (*Mycobacterium tuberculosis*), which is still one of the leading causes of death worldwide.[884] Pulmonary bacterial infections are also associated with pneumonia, sepsis,[885] and cystic fibrosis.[886] Biofilms and mucosal membranes generally reduce the efficacy of conventional treatment by preventing antibiotics from reaching target sites within the lungs. For this reason, polymeric nanoparticle-based drug-delivery systems have been the subject of recent investigations, due to their high therapeutic efficacy and sophisticated targeting capability.

pH-responsive nanoparticles are at the forefront of this research, given that the pH at pulmonary infectious sites is between 5 and 6.5, which is lower than the general physiological environment. Chai et al. encapsulated the drug polymyxin B into a polyion complex nanoparticle consisting of DMMA-modified chitoligosaccharide. Polymyxin is an excellent pulmonary antibiotic for Gram-negative bacteria; however, it also causes nephrotoxicity and neurotoxicity. The encapsulation of this drug in a polyion complex resulted in a design almost three times less toxic to mice than the drug in its free form. Furthermore, the nanoparticles disassembled at low pH (pH 5.5), facilitating targeted drug release and yielding a higher bactericidal efficiency compared to a non-pH-responsive nanoparticle in an infected lung model.[887] Similarly, Gao et al. fabricated a PAMAM azithromycin (AZM) conjugate (PAMAM-AZM) loaded into a DMMA-modified PEG-*b*-Polylysine (Plys) nanoparticle (Figure 64).[888] At pH 6.0,

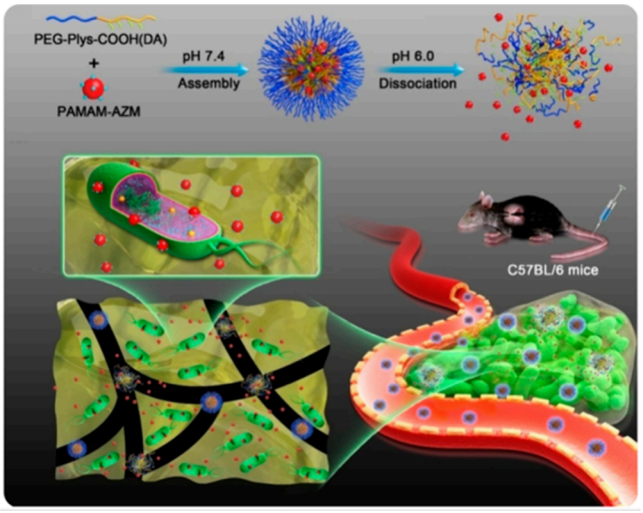

Figure 64. A pH-responsive nanoparticle comprising an antibiotic drug−polymer conjugate for the enhanced treatment of chronic lung infections. The endogenous pH-induced release yielded smaller drug−polymer conjugate cationic nanoparticles that yielded strong biofilm penetration and bacteria elimination, as well as reduced inflammation. DA refers to DMMA. Reproduced with permission from ref. 888. Copyright 2020, American Chemical Society.

DMMA was cleaved, causing nanoparticle disassembly and releasing the PAMAM-AZM conjugate. PAMAM-AZM, due to its small size and positive charge, exhibited a 3-fold increase in biofilm penetration compared to an unresponsive nanoparticle control. Furthermore, the nanoparticle eliminated bacteria three times more efficiently than free AZM. *In vivo* tests using a chronic lung infection model exhibited strong nanoparticle accumulation and bacterial elimination of over 99.5%.

Antimicrobial peptides (AMPs) have been investigated for the treatment of pulmonary bacterial infections in lieu of antibiotics. Casciaro et al. encapsulated an AMP—a frog skin-derived esculentin-1a (Esc(1-21)) and its diastereoisomer Esc(1-21)-1c—into a nanoparticle based on PVA and PLGA. These 250 nm particles displayed improved mucus and biofilm penetration, while *in vivo* tests showed a 17-fold increase in anti-bacterial performance, which was attributed to the protection of AMPs from lung proteases by the nanoparticle.[889]

Antibiotics can also be used as targeting moieties to deliver nanoparticles to bacterial targets, as they have specific interactions with bacteria that can be utilized. Chen et al. designed a pH and lipase-responsive, ciprofloxacin encapsulating nanoparticle, whereby PEG-*b*-PCL was conjugated with vancomycin via a pH-cleavable hydrazone bond. Vancomycin was able to target the D-Ala-D-Ala group on the bacterial membrane, while pH levels below 6 caused the disruption and disassembly of the nanoparticles, releasing ciprofloxacin. The

https://doi.org/10.1021/acs.chemrev.3c00705
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particles could be further degraded by lipase secreted by *P. aeruginosa* to promote release. This nanoparticle design exhibited a significant reduction of bacteria in lungs compared to free vancomycin and ciprofloxacin.[890] Zhang et al. synthesized a nanoparticle composed of biotinylated PEG-*b*-PAE-*b*-PEG grafted with the antibody ICAM-1, which can act as a targeting moiety. The nanoparticles showed pH and enzyme-responsive release through swelling and degradation, with increased targeting efficiency. *In vivo* tests showed that the co-delivery of ciprofloxacin and the anti-inflammatory agent (2-[amino-carbonyl]amino-5-(4-fluorophenyl)-3-thiophene-carboxamide) by antibody coated nanoparticles significantly reduced the bacterial burden in lung and reduced inflammation, resulting in an improved survival rate of 90%.[891]

P. aeruginosa is another bacteria that can cause pulmonary infections such as pneumonia, septicemia, and endocarditis. Wan et al. synthesized D-α-tocopheryl PEG-succinate (TGPS)-coated PLGA nanoparticles. These nanoparticles were found to have a faster mucus penetration compared to PLGA nanoparticles alone. Against *P. aeruginosa* biofilms, the encapsulation of azithromycin in these TGPS particles increased the drug's therapeutic efficacy almost 3-fold compared to free azithromycin.[892] Deacon et al. loaded tobramycin via ionic cross-linking into an alginate/chitosan nanoparticle functionalized with DNase. DNase was able to cleave DNA in the mucus reducing its viscoelasticity and thus improving the nanoparticle's mucus penetration and bactericidal performance against *P. aeruginosa*.[893] Baelo et al. prepared nanoparticles based on PLL and PLGA that were further functionalized by DNase. Cationic PLL stabilized the nanoparticles and protected the encapsulated antibiotic ciprofloxacin, resulting in a slower drug release profile. DNase degraded extracellular DNA within the biofilm matrix, improving the penetration of the nanoparticles. Ultimately, this nanoparticle eradicated over 99.8% of a biofilm.[894]

For the purpose of highly efficient antimicrobial therapy, polymeric nanoparticles possess several key advantages compared to traditional antibiotics. First, therapeutic cargo is protected when encapsulated in nanoparticles. This is crucial in order to deliver fragile macromolecular therapeutics such as peptides, proteins, and nucleic acids. Second, polymeric nanoparticles allow for the delivery of higher concentrations of antimicrobial drugs as well as the codelivery of multiple therapies, significantly increasing therapeutic efficacy. Third, the sophistication and versatility of polymeric nanoparticles allow for efficient navigation of a wide variety of hostile bodily environments, as well as targeted delivery via stimuli-responsiveness. In the case of biofilms, which seriously inhibit—or even eliminate entirely—the efficacy of traditional antimicrobial drugs, robust stimuli-responsive polymeric nanoparticles offer a promising new method for highly efficient biofilm penetration.

However, there remain significant challenges that prevent the full proliferation of polymeric nanoparticles as an antimicrobial drug-delivery vehicle. Currently, there exists a lack of adequate comparison studies between nanoparticles and traditional antimicrobial strategies, and the majority of designs are confined to targeting specific bacteria strains, rather than being generally effective over a wide range of species. Moreover, studies probing the efficiency of any polymeric nanoparticle design should employ a traditional antimicrobial therapy as a control, to fully understand the efficacy of any new design. The efficiency of antimicrobial polymeric nanoparticle designs would no doubt be improved by a more complete understanding of the mechanisms by which these particles interact with bacterial cells and other biological barriers preventing direct drug delivery, although this shortcoming is certainly not limited to antimicrobial nanoparticles. Despite these challenges, polymeric nanoparticles, due to their sophistication, ability to encapsulate a diverse set of therapeutics, stimuli-responsiveness, and overall versatility, represent one of the foremost strategies to enhance the efficiency of antimicrobial drug delivery, and are expected to become more vital as the efficacy of traditional antibiotic treatment becomes less effective over time.

7.4. Other Diseases

7.4.1. Cardiovascular Diseases. Cardiovascular diseases (CVDs) are among the leading causes of death worldwide. They encompass a group of disorders that impact the heart and blood vessels, with the most prevalent conditions including atherosclerosis, myocardial infarctions, strokes, deep vein thrombosis, pulmonary embolisms, and coronary heart diseases.[895,896] The limitations associated with conventional CVD treatment methods have generated enthusiasm for more sophisticated therapeutic and diagnostic platforms, of which polymeric nanoparticles are some of the most promising. Nanoparticles to treat CVDs are generally designed based on their intended clinical application, which can include therapeutic delivery to the heart or the vasculature, delivery of imaging agents for diagnostics and theranostics, or even the creation of nanoengineered biomaterials.[896]

Atherosclerosis—the thickening or hardening of arteries—is the principal cause of many cardiovascular diseases. The most prevalent methods for treating atherosclerosis involve the delivery of statins, which are a group of therapeutic agents widely recognized to reduce blood cholesterol levels and hence manage atherosclerotic cardiovascular diseases.[897] Polymeric nanoparticles exhibit enormous potential in achieving site-specific delivery of statins, thereby enhancing their oral bioavailability and promoting target specific interaction, while minimizing undesired side effects.[898−900] Oxidative stress is a key contributor to the development of atherosclerosis, specifically due to the excessive production of ROS.[901] Moreover, monocytes and macrophages play a key role in the initiation and progression of atherosclerosis. Therefore, polymeric nanoparticles that are responsive to changes in the redox environment offer the ability to enhance atherosclerosis treatment via site-specific drug delivery. Zhang and co-workers designed an ROS-responsive, simvastatin-loaded biodegradable micelle composed of an HA-coated PEG-*b*-poly(tyrosine-ethyl oxalyl).[902] This micelle was designed to achieve site-specific delivery of simvastatin to reduce atherosclerotic plaque, resulting in remarkable therapeutic effects. The hydrophobic poly(tyrosine-ethyl oxalyl) block was able to react with overexpressed H_2O_2 present in the plaque area, reducing the ROS concentration and releasing simvastatin to exert its anti-inflammatory action. In addition, *in vivo* studies demonstrated that the HA-coated micelles effectively reduced the plaque content compared to the non-targeted micelles, simultaneously inhibiting macrophages by targeting CD44 receptors and decreasing the level of ROS to treat atherosclerosis. Moreover, polymeric nanoparticles loaded with other anti-inflammatory drugs that respond to the oxidative microenvironment of atherosclerotic plaques have also been developed, yielding site-specific drug delivery.[903] Wu et al. reported andrographolide-

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Chem. Rev. 2024, 124, 5505−5616

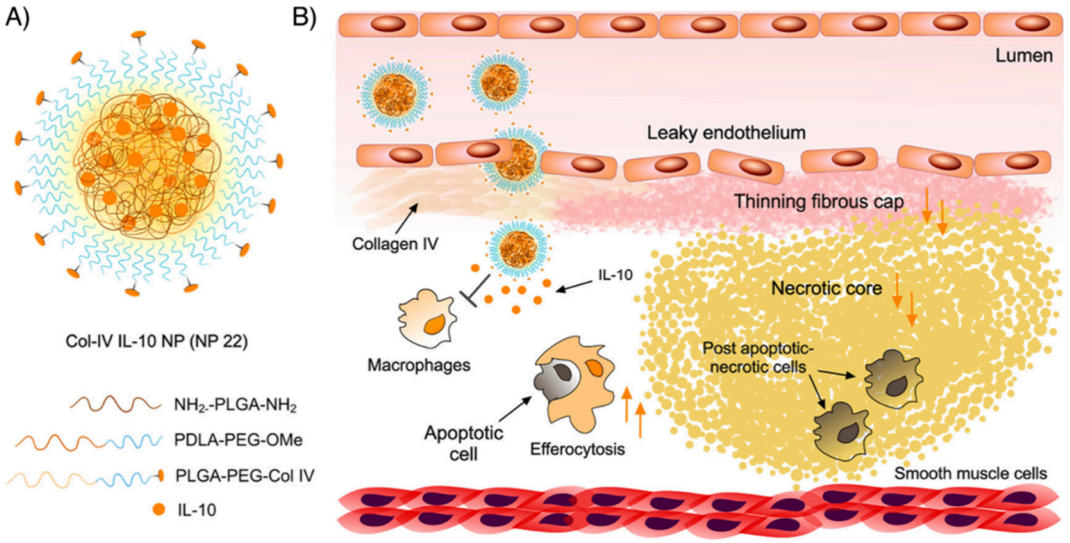

Figure 65. (A) A schematic illustration of a targeted anti-inflammatory nanoparticle (Col-IV IL-10 NP (NP22)) formulated via self-assembly of a blend of NH_2-PLGA-NH_2, PDLA-*b*-PEG-OMe, PLGA-*b*-PEG-Col IV, and IL-10. (B) The targeted nanoparticles were able to enter the atherosclerotic plaque via leaky endothelial junctions and bind to the exposed collagen IV (Col IV). The IL-10 payload was released within the plaque in a controlled manner, resulting in increased efferocytosis, an improvement in the fibrous cap size, and a decrease in necrotic core size. Reproduced with permission from ref. 911. Copyright 2016, American Chemical Society.

loaded micelles based on the block copolymer, poly(ethylene glycol)-*b*-poly(propylene sulfide) (PEG-*b*-PPS).[904] In this context, the thioether functionality of PPS undergoes oxidation when exposed to ROS, resulting in a transition to a hydrophilic state, and prompting particle disassembly within an oxidative environment. This disassembly facilitated drug release and enabled a synchronized therapeutic effect to alleviate both inflammation and oxidative stress.

Cardiovascular diseases can also stem from excessive inflammation, prompting significant interest in anti-inflammatory therapies that resolve inflammation.[905,906] Typically, this resolution is facilitated by proresolving lipids (e.g., lipoxins, resolvins, protectins, and maresins) and protein mediators (e.g., interleukin-10 (IL-10), transforming growth factor-β (TGFβ), and annexin A1). These therapeutic agents inhibit the accumulation of inflammatory cells while facilitating their removal. They also serve to eliminate pathogens, cellular remnants, and inflammatory cytokines, aiding in the restoration of damaged tissues.[907,908] Polymer nanoparticles capable of delivering these resolution-enhancing agents offer the ability to enhance their therapeutic efficacy by achieving systemic circulation, site-specific delivery, and controlled release. For example, Farokhzad and co-workers designed biodegradable PLGA-*b*-PEG nanoparticles coated with collagen IV ligands, which effectively addressed the unfavorable characteristics of advanced atherosclerotic lesions by delivering the anti-inflammatory peptide Ac2-26—an annexin A1/lipocortin 1-mimetic peptide.[909,910] In a subsequent study, a similar type of Col IV-targeted PEG-*b*-PLGA nanoparticle was engineered to enable the controlled release of the anti-inflammatory cytokine IL-10 to atherosclerotic plaques specifically.[911] These nanoparticles were able to suppress the mRNA expression levels of the proinflammatory cytokine TNF-α (Tnfa) in RAW 264.7 macrophages, thus confirming the efficiency of IL-10 controlled release. As a result, inflammation in a self-limited peritonitis model was significantly reduced compared to the native IL-10. Moreover, the nanoparticles were capable of effectively preventing the development of vulnerable (rupture prone) plaques by reducing plaque thickness and decreasing necrotic cores after 4 weeks of weekly injections in mice with existing atherosclerosis (Figure 65).

Biomimetic polymeric nanoparticles coated with biological cell membranes represent a drug-delivery vector with unique advantages including high biocompatibility, prolonged circulation half-life, and disease-specific targeting.[912] Wang et al. developed rapamycin-loaded PLGA nanoparticles camouflaged with RBCs, aiming to reduce clearance by the mononuclear phagocytic system and yield more efficient atherosclerosis treatment.[913] These nanoparticles exhibited sustained drug-release kinetics, effective inhibition of macrophage proliferation *in vitro*, and a long blood circulation time *in vivo*. Additionally, the nanoparticles were able to diffuse through vascular walls and accumulate within pathological lesions more efficiently. This phenomenon is more pronounced in atherosclerotic lesions due to the presence of a leaky endothelium in inflamed environments and leaky micro vessels within atherosclerotic plaques. The biomimetic nature of these nanoparticles enhanced their accumulation within established atherosclerotic plaques in a mouse model, while also reducing macrophage-mediated phagocytosis, thereby facilitating targeted drug release. Thus, the RBC membrane cloaked nanoparticles demonstrated strong therapeutic efficacy against atherosclerosis progression, reducing the plaque area ratio from 20.1% to 6.2%, in contrast to control nanoparticles without RBC coating, which only decreased to 14.8%. In another study, Liang et al. developed biomimetic RBC-cloaked PLGA-based nanoparticles for the controlled delivery of probucol, a compound with anti-inflammatory, antioxidative and hypolipidemic effects.[914] These nanoparticles exhibited sustained drug release kinetics, good biocompatibility and anti-inflammatory effects *in vitro*, and led to delayed blood circulation *in vivo*, significantly delaying the progression of atherosclerosis.

Heart failure and myocardial infarction are critical cardiovascular events that frequently result in mortality. For

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

instance, during a single episode of myocardial infarction, the heart may lose up to ~25% of its cardiomyocytes (cells responsible for heart contraction). As a result, the regeneration of new cardiomyocytes is crucial to the proper functioning of the heart. However, the rate of cardiomyocyte proliferation in adults is relatively poor, rendering the heart incapable of regenerating its lost cells. As a consequence, the heart initiates a self-healing mechanism termed ventricular remodeling, involving the formation of fibrotic scar tissue. This process gradually induces a weakening of heart muscles, resulting in a progressive decline in muscle strength that ultimately leads to congestive heart failure and death.[893,915] Thus, there is a strong incentive for drug-delivery vehicles, including polymeric nanoparticles, to more efficiently deliver cardioprotective drugs directly into the infarcted myocardium and cardiovascular system for the diagnosis, treatment and ultimate prevention of heart failure.[916−918] Oxygen therapy via sustained delivery of oxygen following myocardial infarction can effectively rescue cardiac cells and restore cardiac function.[919] Recently, Guan et al. engineered an oxygen-releasing core−shell polymeric nanoparticle to address the current limitations of oxygen delivery in treating myocardial infarctions.[920] The oxygen-releasing nanoparticles were fabricated with a degradable polymer, poly(*N*-isopropylacrylamide-*co*-hydroxyethyl methacrylate-*co*-acrylate-oligolactide-*co*-*N*-acryloxysuccinimide) as the shell, and a polyvinylpyrrolidone/H_2O_2 complex as the core. The nanoparticle was functionalized with a layer of catalase immobilized on the shell. Furthermore, the nanoparticle's surface was cloaked with a platelet membrane to decrease the non-specific clearance by the immune system, and conjugated with the peptide CSTSMLKAC to improve accumulation in the cardiac ischemia site. Upon degradation of the shell, H_2O_2 is converted to H_2O and O_2 by catalase, allowing the nanoparticles to achieve a 4-week continuous release of oxygen, which is notably longer than the 2 weeks associated with typical oxygen-releasing systems. Despite some limitations, this system is a promising strategy to alleviate cardiac hypoxia by delivering oxygen, subsequently enhancing the survival of cardiomyocytes through ATP generation, stimulating angiogenesis (the formation of new blood vessels), and reducing cardiac fibrosis without inducing substantial inflammation.

7.4.2. Neurological Disorders. Neurological disorders encompass a wide range of diseases that affect the central nervous system, which primarily comprises the brain and the spinal cord. Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, motor neuron diseases, traumatic brain injury, stroke, and brain cancers are some common neurological disorders that impact millions of people worldwide. The blood−brain barrier (BBB) plays a huge role in pathogenicity of neurological disorders while also preventing the efficient delivery of therapeutics to the nervous system. Thus, novel and efficient drug-delivery vectors are essential to combat these conditions due to the severe limitations of the current and widely available methods.[19,921]

Polymeric nanoparticles, given their versatility, tunability and sophisticated design capability, have the potential to address the complex and multi-factorial limitations of current treatments, which include penetrating the BBB and controlling the delivery of drugs at the site of action.[19,921−924] Kataoka and co-workers developed a BBB crossing polymeric micelle that targeted highly expressed glucose transporter-1 (GLUT1) molecules on brain capillary endothelial cells[925] These polymeric micelles were formulated through the self-assembly of negatively charged glucose-modified PEG-*b*-PAsp and positively charged CH_3O-PEG-*b*-poly([5-aminopentyl]-α,β-asparatamide) (PEG-*b*-P(Asp-AP)) ionomers. The surface of polymeric micelles was decorated with glucose to optimize the GLUT1-mediated transport across the brain capillary endothelial cells (BCECs) layer.[20] The glucose density on the surface of nanoparticles was successfully regulated to improve their distribution within the brain. They also highlighted that the delivery of nanoparticles through the BBB and their accumulation in the brain can be efficiently manipulated by controlling blood glucose levels through external stimulation. In a subsequent study, glucose-decorated polyion complexes were developed to enhance the efficient brain accumulation of antisense oligonucleotides (ASO). These nucleotides are therapeutics used for the treatment of disorders associated with the central nervous system, such as Alzheimer's disease, Huntington's disease, and Amyotrophic lateral sclerosis.[926] A polyion complex micelle was prepared through the self-assembly of PEG-*b*-PLL modified with a block copolymer composed of 3-mercaptopropyl amidine and 2-thiolaneimine. The antisense nucleotides were encapsulated within the micellar core through electrostatic interactions (Figure 66).

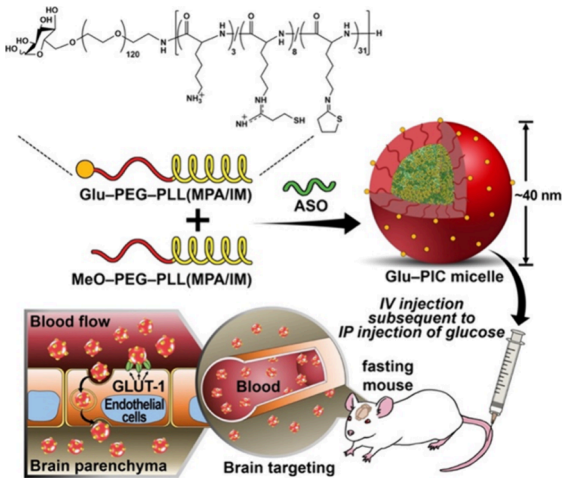

Figure 66. A schematic representation for the preparation of ASO-loaded glycosylated-polyion complex (GLU-PIC) micelles via self-assembly of mixture of MeO-PEG-*b*-PLL(MPA/IM) and glycosylated PEG-*b*-PLL(MPA/IM) (GLU-PEG-*b*-PLL(MPA/IM). The rapid increase in blood glucose level was achieved by injecting the glucose solution into overnight-fasting mice to trigger GLUT1 translocation, and GLU-PIC micelles were then intravenously administered to enhance the brain accumulation via GLUT1-mediated transcytosis. The rapid increase in blood glucose level can boost the BBB crossing of the micellar nanoparticles while improving ASO delivery to the brain. Reproduced with permission from ref. 926. Copyright 2020, Wiley-VCH.

This polymeric nanoparticle, decorated with multiple glucose molecules, achieved enhanced brain accumulation owing to multi-valent binding with GLUT1 transporter molecules on the plasma membrane of BCECs, in response to an increase in blood glucose level after a fasting period. As a result, the nanoparticles exhibited significant knockdown of a target non-coding RNA (MALT1) in the major regions of the brain, such as the cerebral cortex, hippocampus, midbrain, and hypothalamus, thus demonstrating that the ASO was successfully delivered to the appropriate area of the brain. These studies

https://doi.org/10.1021/acs.chemrev.3c00705
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indicate that a sophisticated polymeric nanoparticle design is able to traverse the BBB through the inclusion of functional groups and targeting ligands. For more information on BBB, the reader is directed to the following reviews.[19,922,927]

Alzheimer's disease (AD) is a neurodegenerative disorder that can be clinically diagnosed by the symptoms of memory loss as well as related cognitive impairment such as poor judgment and decision making. It is characterized by the formation of extracellular senile plaques and intracellular neurofibrillary tangles, mainly composed of amyloid-β (Aβ) peptide and hyperphosphorylated tau protein, respectively, although this remains an active area of study.[922] Among the different therapeutic strategies to treat AD, the clearance of Aβ peptide from the brain is one of the most widely researched.[928] It should be noted that the buildup of Aβ proteins in the brain as a direct cause of AD, particularly in their oligomeric form, has come under recent scrutiny.[929] Brambilla et al. developed an anti-Aβ_{1-42} monoclonal antibody decorated PEGylated poly[hexadecyl cyanoacrylate-*co*-methoxypoly(ethylene glycol) cyanoacrylate] (P(HDCA-*co*-MePEGCA)) nanoparticle. This particle was capable of effectively binding with Aβ peptide present in both blood and serum.[930] In a subsequent study, Carradori et al. demonstrated that this system could be further enhanced to reduce brain Aβ peptide levels by binding to circulating Aβ peptides in the blood stream and facilitating their elimination through classical nanoparticle clearance pathways.[931] *In vivo* studies reported that these anti-Aβ_{1-42}-functionalized nanoparticles decrease the Aβ peptide and its oligomer levels in the brain by ∼20%, resulting in a substantial increase in plasma Aβ levels and the complete recovery of memory loss in an AD-like mouse model.

Research has centered on functionalizing the surface of polymeric nanoparticles with specific ligands such as surfactants, antibodies, and peptides to effectively target BBB receptors and promote transport to the nervous system. Meng et al. developed Huperzine A (HupA)-loaded PLGA nanoparticles with surface modification of lactoferrin-conjugated *N*-trimethylated chitosan (TMC) for the efficient intranasal delivery of HupA to the brain for AD treatment.[932] These targeted nanoparticles exhibited significantly higher mucin adsorption (∼87%) compared to the non-targeted PLGA nanoparticles (∼32%), verifying their excellent mucosal adsorption efficiency. *In vivo* studies demonstrated that these targeted nanoparticles were highly distributed in the brain over a prolonged period through the active targeting of lactoferrin and the mucoadhesion of TMC, compared to non-targeted nanoparticles. Moreover, the concentration of HupA was significantly higher in various regions of brain, compared to the non-targeted nanoparticles, demonstrating that lactoferrin and TMC modification facilitated the enhanced access of HupA to the brain. In another study, Liu et al. reported a multifunctional polymeric nanoparticle for AD treatment, aiming to improve the co-delivery of a therapeutic gene and a peptide drug across the BBB.[933] The nanoparticles were based on PEGylated dendrigraft PLL, and consisted of: 1) RVG29, a brain-targeting peptide known for its ability to bind to the specific n-acetylcholine receptors found in both the BBB and brain parenchyma cells; 2) Plasmid DNA encoding BACE1-AS shRNA, intended for delivery into the brain to facilitate the down-regulation of BACE1, a molecule closely associated with the formation of Aβ plaques; and 3) D-peptide, an inhibitor composed entirely of D-amino acids, which has proven effective in disrupting the formation of *Tau* fibrils in the progression of AD. Similarly sophisticated polymeric nanoparticle designs for AD treatment have been recently reviewed.[922,928,934]

Parkinson's disease is a neurodegenerative disorder associated with the progressive loss of dopaminergic neurons, mainly in the substantia nigra pars compacta, leading to a decreased level of dopamine in the striatum—a region of the brain related to movement and reward. Recently, polymeric nanoparticles have been developed to deliver exogenous dopamine and levodopa (L-DOPA) into the brain.[935] Entrapment of dopamine within polymeric nanoparticles can replace the reduced amounts of the endogenous dopamine in a sustained and controlled manner. Pahuja et al. successfully developed dopamine-loaded PLGA nanoparticles to enhance dopamine delivery to the brain.[936] Fluorescent microscopy demonstrated that these nanoparticles were capable of crossing the BBB and capillary endothelium in the striatum and substantia nigra in a rat model. Systemic intravenous administration of these nanoparticles delivered a considerable level of dopamine (∼45 ng/mL within 6 h) compared to the basal plasma dopamine level in the rats (<0.5 ng/mL). Plasma half-life of dopamine was increased from 1.22 h to 2.53 h in comparison to bulk dopamine administration. Furthermore, it was reported that neurobehavioral abnormalities, such as locomotor activity, were significantly reversed due to nanoparticle-mediated dopamine delivery, suggesting that dopamine was successfully delivered. In another study, dopamine was loaded within polymeric nanoparticles comprising albumin and PLGA.[937] Albumin was employed to enhance the BBB crossing via endogenous albumin pathways involving gp60 receptor-mediated transcytosis. The therapeutic efficacy of these nanoparticles was tested in a rat model (20 mg per animal), resulting in a significant improvement in motor coordination and balance compared to a non-lesioned animal model, indicating the successful delivery of dopamine. Moreover, Vong et al. developed a polymeric nanoparticle to enhance the delivery and therapeutic efficacy of L-DOPA in a mouse model.[938] L-DOPA is a dopamine precursor that can easily cross the BBB compared to dopamine. However, L-DOPA demonstrates significantly poor pharmacokinetic properties compared to dopamine, with a short half-life and undesirable side effects due to frequent administration and higher doses. To overcome these limitations, the nanoparticles were prepared via the self-assembly of an L-DOPA-conjugated amphiphilic block copolymer, PEG-*b*-poly(*O*,*O*′-diacetyl-L-DOPA). It was postulated that the peptide bonds in the polymer backbone could be hydrolyzed by physiological enzymes such as protease and esterase to slowly liberate L-DOPA into the bloodstream. Improved pharmacokinetic profiles were observed in mice when treated with these nanoparticles compared to free L-DOPA. Specifically, the plasma level of L-DOPA was maintained up to 12 h after nanoparticle administration, compared to only 0.5 h after the injection of free L-DOPA. Moreover, the nanoparticles did not induce any dyskinesia symptoms, a complex and undesirable side effect that limits the clinical use of free L-DOPA.

Overall, the application of polymeric nanoparticles for cardiovascular diseases and neurological diseases is still in its early stages of development. Thus, further research is necessary to advance the design of polymeric nanoparticles for clinical applications. Mainly, the anatomical differences between human and small animal models have substantially hindered the clinical translation of current research.[927,935] However, the sophisticated design capabilities of polymeric nanoparticles

https://doi.org/10.1021/acs.chemrev.3c00705
Chem. Rev. 2024, 124, 5505−5616

offer possible solutions to challenging delivery barriers of these particular diseases that are not available to other drug-delivery vectors.

7.5. Theranostics

Theranostic nanoparticles integrate therapy and diagnostics into a single nanoscale platform, with the aim of providing patients with more precise and personalized healthcare.[939] Polymeric nanoparticles exhibit unique advantages as efficient theranostic systems. First, polymeric nanoparticles possess strong biocompatibility, allowing them to interact with biological tissues in the body with minimal clearance by the immune system. Second, polymeric nanoparticles offer tunability, enabling precise designs tailored to various diseases and therapeutic requirements. This section will delve into the application of polymeric nanoparticles in the field of theranostics over the past decade, with a particular emphasis on magnetic resonance imaging (MRI), phototherapy, radionuclide imaging techniques such as positron emission tomography and single photon emission computed tomography.

7.5.1. MRI. *7.5.1.1. ^{19}F MRI.* MRI is a widely employed radiological method for tissue analysis, offering exceptional spatial resolution without the associated risks of ionizing radiation. In MRI, an appropriate resonant frequency magnetic field is applied, inducing the excitation of specific atoms within the tissues. These excited atoms emit a radiofrequency signal upon returning to their equilibrium state, which is then captured and translated into an image. Fluorine MRI, a heteronuclear MRI imaging technique, was first reported in 1970 and has developed into a promising imaging technique for cancer diagnosis.[940] As an MRI probe, the fluorine (F) atom has several advantages: the ^{19}F isotope is naturally abundant, very sensitive, and has an advantageous signal-to-noise ratio. Moreover, fluorine in the human body is mainly stored in solid form throughout bones and teeth, resulting in very little background noise for the fluorine probe.[941]

Given these advantages, versatile fluorine-containing exogenous tracers have been constructed and used in the diagnosis and treatment of disease. Normally, MRI signal intensity is proportional to the concentration of fluorine content, spin-spin relaxation time (T_2), and inversely proportional to spin-lattice relaxation time (T_1). Therefore, researchers have tried to increase the fluorine concentration in contrast agents. However, due to the aggregation of fluorine atoms, the heteronuclear dipole interaction is enhanced when the fluorine content is increased, resulting in a decrease in T_2, which leads to MRI signal reduction. In biological systems, fluorine atoms also aggregate due to hydrophobicity, which further reduces MRI signal intensity.[942] In order to develop fluorine-containing contrast agents suitable for biological systems, fluorinated polymeric nanoparticles have garnered increasing attention in recent years.

Fluorine aggregation, which represents a challenge to strong signal intensity, can be drastically minimized by linking hydrophilic polymer chains to fluorinated polymer chains. This both increases the actual amount of fluorine, and reduces fluorine aggregation through the formation of flexible, more hydrophilic polymer chains. In 2014, Thurecht and co-workers pioneered hyperbranched fluorine-functionalized polymeric nanoparticles by using RAFT polymerization.[943] These polymers use trifluoroethyl monomers to generate ^{19}F MRI signals, and PEG to enhance the hydrophilicity and biocompatibility of the nanoparticles. Furthermore, the hyperbranched backbone facilitated subsequent modification with fluorophores and targeting ligands. This adaptibility is crucial in theranostic applications, where targeting specific tissues or pathologies is a necessary diagnostic tool. ^{19}F MRI signal expression was observed in tumors after injecting mice with the fluorine-functionalized nanoparticles. To further increase the fluorine content in fluorinated polymers, Whittaker and co-workers employed perfluoropolyether as the contrast agent.[944] A RAFT agent was functionalized with approximately 40 equivalents of fluorine atoms allowing for the synthesis of hydrophilic, fluorine-functionalized (30 wt %) PEG polymers. This notable increase in fluorine content directly correlates with enhanced MRI signal intensity, demonstrating the importance of fluorine density in imaging efficiency. In a subsequent study, hyperbranched polymer nanoparticles composed of trifluoroethyl acrylate were functionalized with perfluoropolyether for superior *in vivo* imaging of breast cancer (Figure 67).[945] The hyperbranched particles had a high fluorine content, and were linked to a peptide aptamer for breast cancer targeting. These nanoparticles yielded superior tumor accumulation and excellent *in vivo* ^{19}F MRI sensitivity.

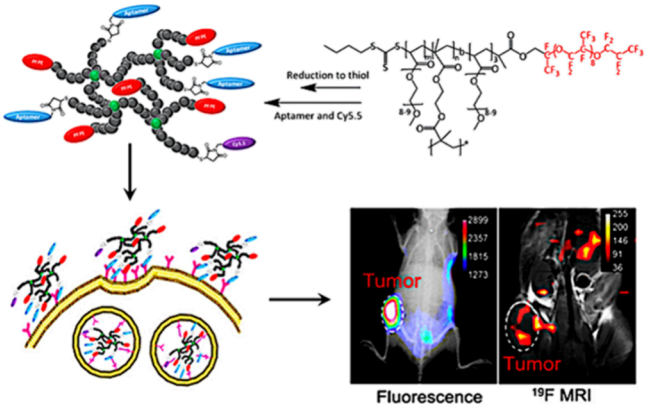

Figure 67. Hyperbranched polymer nanoparticles for ^{19}F MRI. The nanoparticles were functionalized with perfluoropolyether for increased fluorine content as well as a tumor targeting aptamer, yielding sensitive *in vivo* ^{19}F MRI capability. Reproduced with permission from ref. 945. Copyright 2018, American Chemical Society.

Thayumanavan and co-workers designed a fluorine functionalized nanogel to improve the T_2 relaxation time and ^{19}F MRI signal intensity.[946] First, they synthesized amphiphilic polymers containing fluorinated monomers that subsequently self-assembled into micelles. Then, the nanogel was cross-linked to preserve and strengthen its structure. Finally, the polymer in the core was decomposed to reduce the core density. These fluorinated nanogels displayed increased T_2 relaxation times and elevated MRI signal intensity. This increase in the T_2 relaxation time and signal intensity is a notable achievement, as it directly translates to improved imaging quality and diagnostic accuracy in MRI. The elevated signal intensity also suggests potential for lower doses of the contrast agent to be used, which could reduce potential side effects.

In order to further enhance the potential of ^{19}F MRI for the diagnosis and treatment of diseases, researchers have also prepared stimuli-responsive polymeric nanoparticles. Thurecht and co-workers designed a system that can be used to detect

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Chem. Rev. 2024, 124, 5505−5616

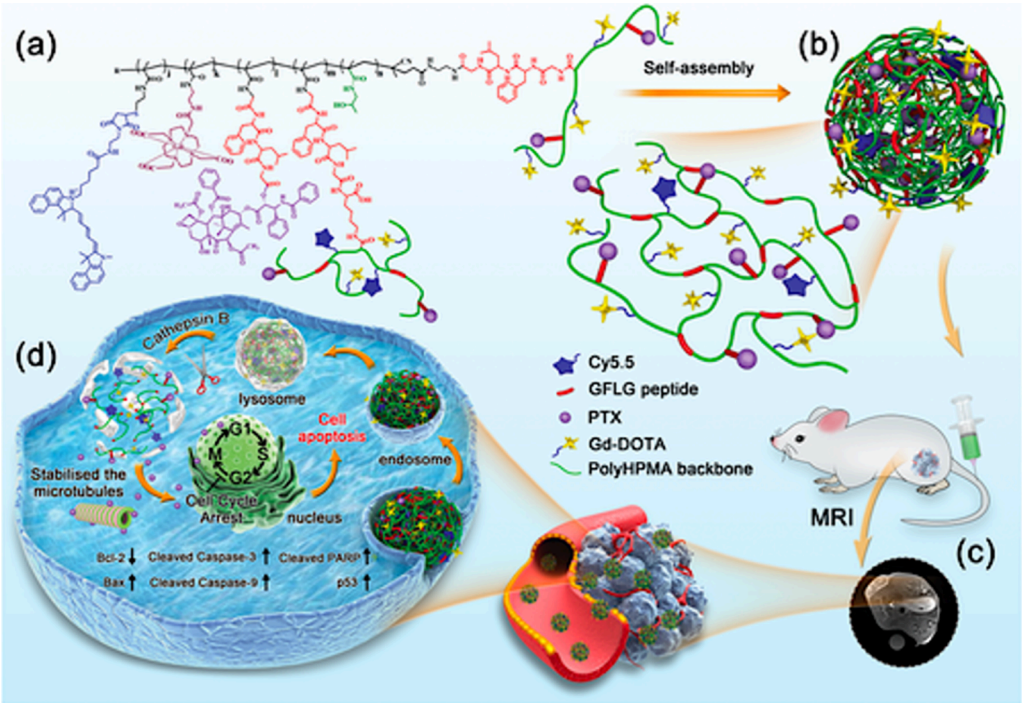

Figure 68. A schematic illustration of enzyme-responsive biodegradable theranostic nanoparticles via self-assembly of branched PHPMA, containing Gd(III)-complexed DOTA side chains (GD-DOTA). Enzyme responsiveness was introduced through the peptide GFLG. After tumor cell uptake, the nanoparticles are capable of acting as MRI contrast agents. Reproduced with permission from ref. 953. Copyright 2020, Wiley-VCH.

drug release.[947] DOX, docetaxel, and CPT were attached to a polymer backbone via dynamic covalent bonds. Relaxation measurements by ^{19}F NMR showed that the addition of the hydrophobic drugs reduced the mobility of the fluorinated fragments, thus decreasing the T_2 relaxation time and hence reducing image intensity. However, upon drug release this quenching effect disappears, and the ^{19}F MRI intensity was significantly enhanced. This dynamic response to drug release is crucial for real-time monitoring of drug delivery and efficacy, offering potential for optimizing therapeutic regimens. Based on this same principle, Gao and co-workers designed multichromatic pH-activatable ^{19}F nanoparticles through a combination of pH-responsive polymers and fluorinated monomers.[948] Upon a pH drop, the polymers transitioned from hydrophobic to hydrophilic, leading to nanoparticle disassembly and generating strong ^{19}F MRI signals. This probe had a sensitive response (ON/OFF ∼ 0.25 pH) and allowed for highly specific endogenous pH measurements. Meanwhile, Tang et al. designed a ^{19}F MRI multi-responsive nanoparticle with cascade signal activation/amplification.[949] This system was composed of an amphiphilic polymer with hydrophilic groups, trifluorotoluene groups, and disulfide bonds for conjugation. These trifluorotoluene groups and the NIR-absorbing dye indocyanine green led to the formation of nanoparticles due to $\pi-\pi$ stacking, which is a type of supramolecular interaction. Initially, the ^{19}F MRI signal generated by the fluorine-functionalized nanoparticle was almost zero. However, after exposure to a reducing environment, the cleavage of disulfide bonds led to the disassembly of the nanoparticles, which activated the ^{19}F MRI signal. Under infrared irradiation, the dye molecules absorbed light energy to generate heat. This photothermal effect provides a mechanism for the destruction of tumors, and enhances ^{19}F MRI signal by further dispersing the nanoparticles into smaller soluble sections. This multi-faceted approach, combining therapeutic and diagnostic capabilities, exemplifies the potential of polymeric nanoparticles in revolutionizing cancer treatment and imaging.

7.5.1.2. MRI with Paramagnetic Metal. With the exception of fluorine atoms, the most common MRI method is based on hydrogen atoms. MRI uses a magnetic field to excite hydrogen atoms in tissue at an appropriate resonance frequency. These excited hydrogen atoms emit a radiofrequency signal when they return to equilibrium, which is then translated into an image. However, it is sometimes necessary to use MRI contrast agents that contain substances that are paramagnetic or superparamagnetic. These agents, by interacting with an external magnetic field, alter the relaxation times of atoms in the tissue to enhance the visibility of internal structures.[950] For example, contrast agents can make blood vessels, tumors, or specific organs appear more clearly in an image. Commonly used contrast agents for MRI include gadolinium (Gd) and superparamagnetic iron oxide (SPIO).

Currently, commercial gadolinium(III) ion complexes, including megluminian gatoterate (Gd-DOTA; Dotarem) and dimegluminian gadopentetatu (Gd-DTPA; Magnevist), have been developed for widespread use as MRI contrast agents.[951] Meanwhile, researchers have successfully combined these materials with polymer nanoparticles to create MRI-compatible nanoparticles. One straightforward approach involves modifying the nanoparticle surface using chelator derivatives (e.g., DOTA-NHS) through click chemistry. This surface modification technique is critical as it enables the stable attachment of Gd chelates to the nanoparticles, ensuring their efficacy as contrast agents while potentially reducing systemic toxicity. Gd chelates have been added to the surface of

https://doi.org/10.1021/acs.chemrev.3c00705
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polymeric nanoparticles through the complexation of Gd(III).[587,952] Another approach is to synthesize macromolecules containing Gd(III) ion complexes, which then self-assemble into nanoparticles. Cai et al. synthesized a branched polymer, PHPMA, containing DOTA side chains via RAFT, and subsequently formed Gd-containing macromolecules through complexation with Gd(III) (Figure 68).[953] They further assembled these macromolecules into nanoparticles through nanoprecipitation. Kim et al. synthesized PEG-*b*-poly(histidine) amphiphilic block copolymers containing DTPA end groups with DTPA at the hydrophobic end.[954] These amphiphilic copolymers self-assembled into pH-responsive micelles upon complexation with Gd(III). The Gd(III) complexes were located in the hydrophobic core, resulting in a reduced T_1 relaxation rate. However, upon the protonation of poly(histidine)'s imidazole groups, the micelles disassembled, leading to an increase in the T_1 relaxation rate. This dynamic response to pH enhances the utility of these nanoparticles, potentially allowing for more precise imaging of specific pathological sites.

Enhancing the MRI signal intensity of Gd(III) ion complexes with polymeric nanoparticles has been the subject of more recent research. Compared with commercially available small-molecule Gd(III) ion complexes, macromolecule-complexed gadolinium chelates have the advantage of high relaxation rates and long retention times in the bloodstream.[955] Li et al. used RAFT polymerization to synthesize linear, hyperbranched, and star-shaped macromolecular ligands and complexed them with Gd(III) to obtain macromolecular gadolinium contrast agents with higher relaxation rates.[956] The diversity in the shapes of these macromolecules (linear, hyperbranched, and star-shaped) potentially impacts their pharmacokinetics and biodistribution, which is a critical aspect of their functionality as contrast agents. Hydrogels and polymersomes have also been employed to enhance MRI signal, as they can load high amounts of gadolinium very efficiently.[957,958] These polymeric nanoparticles have also been shown to effectively reduce cytotoxicity. This improved safety profile could potentially expand the applicability of MRI contrast agents to a broader patient population.

Another widely studied MRI contrast agent are SPIONs, which have a magnetic core composed of iron oxide. Researchers have developed various methods for synthesizing SPIONs and functionalizing them through both covalent and non-covalent approaches.[959] Huang et al. synthesized SPIONs from a solution of $Fe(acac)_3$ using the thermal decomposition method.[960] Subsequently, folic acid was conjugated to the surface to enhance the targeting capability of these SPIONs. Malekzadeh et al. modified Fe_3O_4 nanoparticles with dendritic polymeric citric acid and PEG, successfully preparing MRI contrast agents for drug loading.[961] Liao et al. used a layer-by-layer assembly approach to combine folic acid-coated SPIONs with cyanine dye and paclitaxel, creating magnetic targeted therapy nanoparticles.[962]

Meanwhile, researchers have also attempted to assemble SPIONs into micelles, vesicles, or core−shell nanoparticles for theranostic applications.[963] Yang et al. developed novel magneto-vesicles with accumulated SPIONs in the polymer membrane, where the SPION content increased with the membrane thickness. This design not only achieved enhanced MRI contrast but also demonstrated the potential for dose control in drug-delivery systems.[964] Liu et al. prepared contrast agents with a high relaxation rate by *in situ* generation within vesicles.[965] Zhu et al. encapsulated SPIONs and drug molecules within degradable PLGA shells.[966] This nanoparticle disassembled under mildly acidic conditions, resulting in a concurrent release of both the SPIONs and the encapsulated drug, enabling *in vivo* therapy and drug monitoring. Additionally, SPIONs themselves possess therapeutic effects, which can be achieved through inducing cell apoptosis[967] or hyperthermia therapy.[968,969] The dual functionality of SPIONs as both therapeutic agents and contrast enhancers underscores their potential as versatile tools in the realm of cancer therapy and imaging.

7.5.2. Phototherapy. In recent years, phototherapy has developed into an important tool in the theranostic treatment of tumors. Phototherapy can be divided into photodynamic therapy (PDT) and photothermal therapy (PTT).[970] PDT and PTT differ from other methods of drug delivery in that their corresponding nanoparticles contain photosensitizers that can generate heat (PTT) or reactive oxygen species (PDT) when irradiated with certain wavelengths of light. This generated heat can then eliminate cells within a specific area. Photosensitizers can be used in a variety of optical imaging techniques, such as fluorescence imaging and photoacoustic imaging. In fluorescence imaging, photosensitizers absorb specific wavelengths of light and emit fluorescent photons, enabling visualization of molecules, cells, and tissues within biological samples. In photoacoustic imaging, the light-absorbing properties of photosensitizers induce localized heating, resulting in the generation of acoustic signals that are used to create deep-tissue images. This combination of diagnostics and simultaneous *in situ* therapy has attracted great interest among researchers looking to design sophisticated drug-delivery vehicles. Polymers are one of a myriad of photosensitizers, but their strong biocompatibility and synthetic diversity have made them an attractive choice for designing therapeutic vectors. This section will highlight designs whereby the polymer component is acting as the primary phototherapy functionality. It is also possible to include small molecules within a polymer nanoparticle to conduct PDT and PTT, as previously highlighted.

In order to design phototherapeutic nanoparticles, researchers have employed different strategies to enhance the efficacy of the optical reagents used. For example, semiconductor polymer nanoparticles (SPNs) have attracted increasing interest in biomedicine due to their optical activity and low cytotoxicity. Lyu et al. developed an intraparticle molecular orbital engineering approach to enhance PTT effects and acoustic signals.[971] In this work, SPNs were synthesized by nanoprecipitation, where molecular orbital alignment between semiconductor polymers and fullerenes allowed for photoinduced electron transfer. Specifically, the fluorescence of the semiconductor polymer was completely quenched, meaning that the vast majority of energy was released as heat. The photoacoustic signal and photothermal temperature were increased by a factor of 2.6 and 1.3, respectively, compared to the system without fullerene. This study provides a strategy to construct intramolecular photoinduced electron transfer by incorporating a quencher, which enhances non-radiative heat generation.

Guo et al. utilized planar electron acceptors (A) and electron donors (D) to construct conjugated polymer, which self-assembled via nanoprecipitation into nanoparticles.[972] This rigid D-A structure effectively introduces intramolecular charge

https://doi.org/10.1021/acs.chemrev.3c00705
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transfer (ICT), which increases infrared absorption. The higher D-A intensity resulted in a stronger ICT, which yielded faster photothermal heating and a stronger photoacoustic signal. Similarly, Liu et al. also designed photothermal nanoparticles that utilized a planar D-A conjugate structure.[973] This conjugate was functionalized with long alkyl chains to suppress intermolecular interactions, as well as triphenylamine, which acted as a molecular rotor. The overall design facilitated an excited-state electron transfer process known as twisted intramolecular charge transfer (TICT), which significantly enhanced the photothermal and photoacoustic properties of the nanoparticles. The surface of these photothermal nanoparticles was modified with a polymeric cationic shell, which enhanced nanoparticle uptake in tumors, resulting in strong anti-tumor efficacy.

In seeking to design more efficient photothermal nanoparticles, research has focused on increasing the wavelength of light needed to stimulate heat generation, improving the overall efficiency of photothermal conversion, and developing phototherapeutic nanoparticles with multiple modalities. NIR light can be divided into two different "windows", the first between 650 and 950 nm (NIR-I) and the second between 1000 and 1700 nm (NIR-II). Most photothermal nanoparticles absorb in NIR-I, while few utilize NIR-II. In photoacoustic imaging, the background signal from the NIR-II interval is greatly diminished, and thus research has sought to design more nanoparticles that absorb light in this range. Jiang et al. developed a new semiconductor polymer nanoparticle that allows photoacoustic imaging in both the NIR-I and NIR-II regions.[974] Their polymer adopts an alternating D-A structure in the form of D-A1-D-A2, where A1, A2 refer to two different electron acceptors, and A2 has a stronger electron absorption capability. The introduction of the A2 monomer with a stronger electron absorption capability is a key factor in achieving absorption in the NIR-II region, and demonstrates the importance of molecular design in tuning optical properties. These semiconductor polymers were subsequently encapsulated into nanoparticles via amphiphilic self-assembly. The resulting nanoparticle had an absorption of 1253 nm, well within NIR-II, due to the electron-absorbing A2 monomer. The control without the A2 monomer showed no absorption in the NIR-II region. Subsequent photoacoustic measurements showed that the signal generated using the NIR-II light source had a lower background noise, a higher signal-to-noise ratio, and a deeper detection capability. Guo et al. designed photothermally active nanoparticles based on polymers with a D-A structure, as well as a tumor-targeting peptide conjugated to the particle surface.[975] These nanoparticles had a photothermal conversion efficiency of 30% under 1064 nm irradiation. Such a long wavelength allowed superior penetration of a mouse skull, and the nanoparticle displayed strong anti-tumor efficacy. This research details an effective paradigm for the treatment of brain tumors through the use of phototherapeutic nanoparticles.

Enhancing photothermal conversion efficiency is the subject of significant research. Zhang et al. reported the concept of a light trapping unit to enhance the photothermal conversion efficiency of polymers.[976] Their design was based on electron D-A conjugated semiconducting polymers functionalized with light trapping units on their side chains. These functionalized semiconducting polymers formed nanoparticles via self-assembly, and the particles exhibited a 62.3% photothermal conversion efficiency while achieving complete tumor regression. Tang and co-workers synthesized a novel aggregation-induced emission (AIE)-active luminogen (AIEgen) (Figure 69).[977] This AIEgen maintained a D-A structure

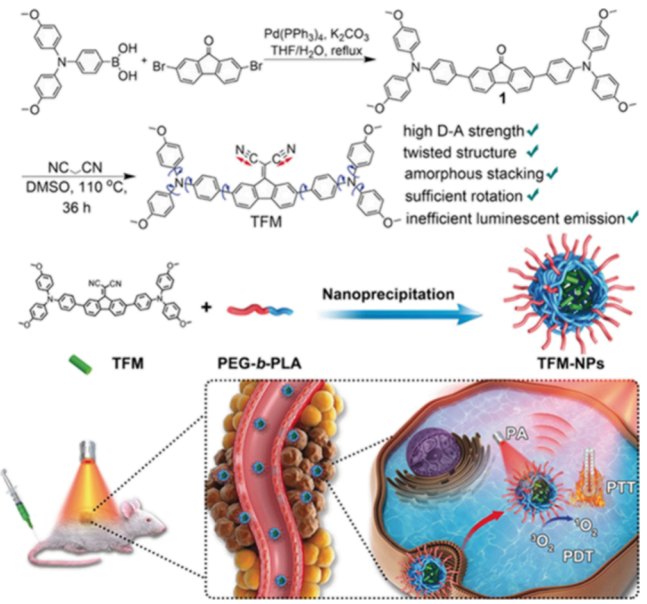

Figure 69. A luminescent nanoparticle based on aggregated-induced emission (AIE). These nanoparticles had a high photothermal conversion due to the twisting capability of the loaded fluorophore, and the nanoparticle was able to produce ROS, yielding strong anti-tumor performance. Reproduced with permission from ref. 977. Copyright 2019, Wiley-VCH.

but comprised a rotor-like, twisted structure. This twisted structure allowed for efficient intramolecular motion, which enhanced thermal energy generation. After co-incubation with amphiphilic polymers, stable nanoparticles were obtained via nanoprecipitation. The particles had a photothermal conversion efficiency of 51.2%. Additionally, the small singlet-triplet energy gap in these nanoparticles facilitated efficient ROS production, making them dual-functional for both photothermal therapy and ROS-based tumor treatment. It is also important to note that the excitation wavelengths used in the two examples above were around 635 nm. This wavelength falls within the NIR-I window, which, while offering less tissue penetration than NIR-II, still provides significant advantages in terms of reduced photodamage and increased safety for clinical applications.

Seeking to further enhance photothermal efficiency, Li et al. designed a D-A-D conjugated small molecule in which the sulfur atoms were replaced by heavier selenium atoms.[978] As the atoms were replaced, the molecular energy gap decreased, and the absorption peak shifted from NIR-I to NIR-II. After assembling these small molecules into nanoparticles with amphiphilic block copolymers, they achieved a 77% photothermal conversion efficiency under 1064 nm light excitation. Furthermore, these particles exhibited excellent photoacoustic properties, deep tissue penetration, and high PTT efficiency. The same group also designed oligomeric materials with high photothermal conversion efficiency through an A-D-A structure containing one strong electron donor, and two strong electron acceptors.[979] This strong A-D-A structure leads to a narrow energy gap and facilitates light trapping, and the resulting intramolecular charge transfer also leads to

https://doi.org/10.1021/acs.chemrev.3c00705
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fluorescence quenching. On the other hand, the flexible D-A linkage is able to undergo intramolecular rotation, which promotes nonradiative decay. This material was loaded into nanoparticles, which subsequently exhibited a photothermal conversion efficiency of 82% under the irradiation of 808 nm light. These nanoparticles were tested *in vivo* and were able to completely eliminate a tumor, demonstrating their potential as powerful agents for cancer therapy with minimal invasiveness and high specificity.

Multimodal treatment systems represent the most complex form of photothermal nanoparticles, but have garnered significant interest due to their potentially high clinical efficiency. Li et al. synthesized a semiconducting polymer functionalized with cell membranes of activated fibroblasts.[980] These nanoparticles not only targeted cancer-associated fibroblasts, but also exhibited NIR fluorescence, photoacoustic, photothermal, and photodynamic properties. This multi-modal functionality allows for a comprehensive therapeutic approach, combining diagnosis, imaging, and treatment in one system. In addition, Tang and co-workers synthesized multi-functional, stimuli-switchable nanoparticles that employed a light-controlled molecule dithienylethene (DTE).[981] Under external UV/vis light irradiation, the DTE molecule can reversibly switch its structure between an open-ring isomer and a closed-ring isomer, which each have different energy levels. When DTE is in the ring-closed form, it can act as a quencher and ultimately generate a photoacoustic signal. When the DTE is in its ring-opened form, fluorescence is produced along with ROS. These switchable nanoparticles were injected into mice preoperatively, and tumors were imaged through photoacoustic imaging (ring-closed form). For residual tumors post-surgery, the incision site can be irradiated for 5 min at 610 nm, which converts DTE to its ring-opened form, allowing for the tumor to be fluorescently imaged. This approach highlights the potential for personalized, on-demand therapy, adapting to the changing needs of the patient during the course of treatment. These nanoparticles are also photothermally active, providing a mechanism for tumor suppression.

7.5.3. Radionuclide Imaging and Positron Emission Tomography. Radionuclides are unstable isotopes that emit radiation primarily through radioactive decay, including alpha (α) particles, charged beta particles (positrons, β+; electrons, $\beta-$), gamma (γ) rays, or electron (e) radiation.[982] Researchers combine these radionuclides with biologically relevant molecules to develop radiopharmaceuticals, which are then applied to visualize organs or identify infected tissues.[983] Depending on the specific decay processes of radionuclides, two primary nuclear imaging modalities have been developed: single-photon emission computed tomography (SPECT) and positron emission tomography (PET). SPECT is designed for gamma-emitting radionuclides, while PET is specifically used for positron-emitting radionuclides.[984] SPECT and PET offer high sensitivity and the ability to penetrate deep tissues, with detection limits ranging from a billionth to a trillionth of a molar.[985]

Furthermore, in clinical settings, SPECT and PET can be integrated with anatomic imaging methods, such as computed X-ray tomography (CT), to develop hybrid systems like SPECT/CT and PET/CT. These combinations are instrumental in generating three-dimensional images, enabling precise localization.[986,987] Consequently, SPECT and PET are not only valuable in monitoring drug metabolism but also play a crucial role in the diagnosis and staging of cancer.[988] A variety of radionuclides are utilized in clinical applications. For SPECT, these include technetium-99m (half-life = 6 h), indium-111 (half-life = 67.2 h), and iodine-123 (half-life = 13.2 h). In contrast, PET employs radionuclides such as fluorine-18 (half-life = 110 min), gallium-68 (half-life = 1.13 h), zirconium-89 (half-life = 78.41 h), and copper-64 (half-life = 12 h).[989] Generally, nonmetallic radionuclides are bonded covalently to organic molecules, whereas metal radionuclides are attached to their parent compounds using chelating agents.[990]

In one study, Zhou et al. developed a polymersome capable of SPECT/CT imaging and efficient anti-tumor drug delivery.[991] This polymersome was formed via the self-assembly of the polymer PCL-*b*-PGlu-stat-(L-glutamic acid-alendronic acid), which incorporates alendronic acid units in its chain. These acid units can chelate the radionuclide ^{99m}Tc, enabling SPECT visualization of the polymersomes. *In vivo* tests, which included loading the polymersomes with DOX, demonstrated the ability to track drug distribution dynamically via SPECT/CT imaging and facilitate real-time diagnostics. Similarly, Yang et al. synthesized iodine-125 (^{125}I)-labeled ICG-decorated polymer PEG-poly(L-tyrosine-^{125}I)-(indocyanine green), which self-assembled into micelles.[992] Upon NIR irradiation, these micelles, accumulating in tumor tissues, enabled simultaneous fluorescence/photoacoustic/SPECT imaging for precise tumor localization. Furthermore, they could be used for PTT to treat the tumor.

To further enhance the signal strength in SPECT imaging, Zhong's group developed polymersomes with exceptionally high iodine content.[993] First, they utilized iodine-functionalized trimethylene carbonate as a monomer to synthesize PEG-*b*-poly(iodine trimethylene carbonate) via ring-opening polymerization. Remarkably, this polymer contains an ultra-high iodine content of 60.4 wt%. Then, after being labeled with iodine-125, this polymer self-assembled into polymersomes that were characterized by iso-osmolality, low viscosity, and non-toxicity. These properties are important to ensure biocompatibility and patient safety during imaging and therapy. In a subsequent study, iodine-131 was used for labeling, whereby released beta radiation exhibited significant toxicity toward 4T1 cells, thus yielding strong performance as a therapeutic agent in radiopharmaceutical therapy for tumors.[994,995]

PET is a widely employed nuclear medical imaging technique that offers high spatial resolution and sensitivity. PET imaging has found extensive application in molecular imaging, for disease diagnosis and treatment response monitoring. In PET, radioactive isotopes are administered into the body and their emitted radiation is captured by a camera to generate images. Researchers have integrated radioactive nuclides with polymeric materials, designing nanoparticles applicable to a variety of biomedical contexts. Fletcher et al. utilized a hyperbranched polymer based on PEG to load zirconium-89 (^{89}Zr), enabling quantitative ^{89}Zr-PET imaging.[996] This approach demonstrates the potential for highly precise and targeted imaging, facilitating better disease monitoring and management. Ediriweera et al. employed a hyperbranched polymer that conjugated copper-64 (^{64}Cu) for real-time detection and quantification of drug release.[997] Chen et al. designed a radioactive nanoscale metal−organic framework (MOF). In this design, ^{89}Zr-UiO-66 was surface-engineered with pyrene-modified polyethylene glycol (Py-PEG) for enhanced tumor targeting and drug delivery. This

https://doi.org/10.1021/acs.chemrev.3c00705
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MOF exhibited excellent radiochemical stability and material integrity, allowing for the efficient loading of DOX. By incorporating the F3 peptide as a targeting ligand, specific and significantly improved tumor targeting was achieved *in vivo*, along with no notable *in vivo* toxicity. This research highlights the potential of radioactive nanoscale PEGylated metal-organic frameworks to improve biocompatibility and serve as the basis for diverse applications in cancer diagnosis and therapy (Figure 70).[998]

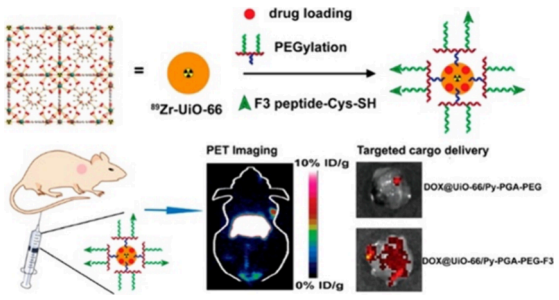

Figure 70. Schematic synthesis route of MOF-polymer conjugates (^{89}Zr-UiO-66/Py-PGA-PEG-F3) and the PET imaging. Intrinsically radioactive MOF (^{89}Zr-UiO-66) was produced through the incorporation of positron-emitting isotope zirconium-89 (^{89}Zr), and further modified with Py-PEG and conjugated with an F3 peptide ligand. DOX was loaded onto MOF to serve as a both therapeutic cargo and a flurosecence visualizer. Reproduced with permission from ref. 998. Copyright 2019, Americal Chemical Society.

Theranostics yields a more detailed understanding of the characteristics of a particular therapeutic target site, and thus allows for rapid and efficacious disease treatment. Polymeric nanoparticles can generally enhance the performance of theranostic materials, either by incorporating a greater amount of diagnostic functionality, or by more efficiently targeting disease sites. The versatility of polymeric nanoparticles in encapsulating various diagnostic or therapeutic agents, combined with their ability to target specific sites, makes them promising candidates for the development of advanced theranostic systems. Phototherapy for cancer treatment, which combines the diagnostic capabilities of photo-active compounds with their anti-tumor photothermal efficacy, is a particularly attractive concept. However, research into polymeric nanoparticles for theranostics is still in its infancy, with the focus currently on fundamental studies, rather than widely applicable systems. This emerging field holds great promise, but further research and ultimately clinical trials are necessary to fully realize the potential of polymeric nanoparticles in theranostic applications. To date, there are no theranostic polymeric nanoparticles designs that have received clinical approval, underscoring the need for continued innovation and rigorous evaluation in this area.

8. CONCLUSIONS AND PERSPECTIVE

Drug delivery is one of the most important and extensively investigated challenges in medical research. An optimized drug-delivery system has the potential to radically enhance therapeutic efficacy, minimize potentially toxic off-target effects, and even open-up new strategies to treat previously untreatable diseases. Furthermore, as therapeutics begin to shift generally from small-molecule drugs to larger biomacromolecules such as peptides, proteins, monoclonal antibodies, and nucleic acids, the need for drug-delivery vehicles will become even more pronounced. Among the myriad of currently relevant drug-delivery vectors, polymeric nanoparticles, in our view, sit at the forefront. Polymeric nanoparticles are unique in that their functional complexity allows for well-tailored, responsive, and highly targeted designs (Figure 71). Such a level of complexity is simply not available

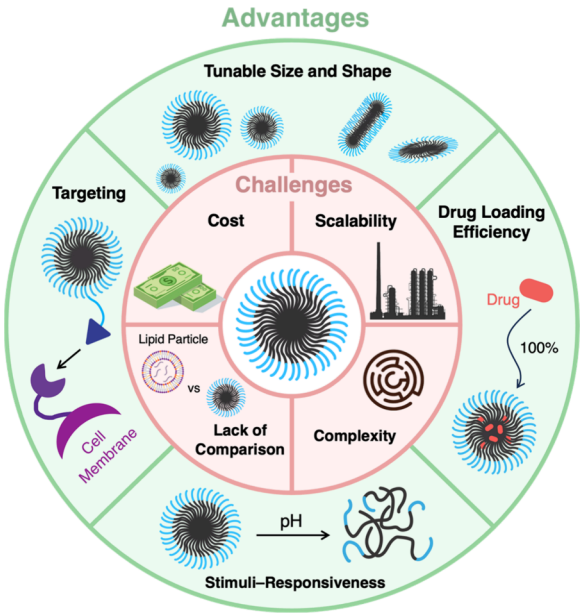

Figure 71. Polymeric nanoparticles offer enormous advantages as drug-delivery vehicles compared to other vectors, including tunable size and shape, highly specific targeting, stimuli-responsiveness and efficient drug loading—to name a few. There are, however, a number of challenges preventing their smooth clinical transition, including their inherent complexity, high cost, scalability issues, and a lack of clear comparisons with other drug-delivery technology, such as lipid particles.

for other drug-delivery designs. The enormous drug-delivery potential of polymeric nanoparticles is dictated by five primary features.

First, polymeric nanoparticles can be tailored to very specific sizes (1−1000 nm), with a high degree of monodispersity around their average diameter. Such a monodisperse sample of particles is important, given that size plays a vital role in modulating interactions with various biological environments.

Second, polymeric nanoparticles can be designed with exotic architectures such as rods, worms, disks, and many others. The impact that particle architecture has on drug delivery is still an active research area, but evidence suggests that drug delivery can be enhanced significantly by specific alterations to nanoparticle shape.

Third, polymeric nanoparticles can be designed to respond to specific endogenous stimuli, chief among which are pH, redox environment, enzymatic environment, and temperature. Stimuli-responsiveness is a powerful feature of any delivery vehicle, as it allows for the release of a drug exclusively at the target site, which increases therapeutic efficacy while minimizing potential off-target effects. The complexity and tunability of polymer functionality, upon which these nanoparticles are based, allows for very well-tailored stimuli-responsiveness, which can discriminate between very slight changes in biological environments. There continues to be new

https://doi.org/10.1021/acs.chemrev.3c00705
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techniques developed that improve the specificity of stimuli-responsive capabilities to control cargo release, while minimizing off-target effects. Recent advances of note are self-immolative systems and the design of multi-stage-responsive systems.

Fourth, polymeric nanoparticles can be functionalized with biological adducts of various sizes, such as targeting ligands and receptors. This allows the nanoparticle to potentially co-opt the body's own mechanisms to enhance its targeting capabilities and hence improve its drug-delivery efficacy.

Fifth, polymeric nanoparticles can be loaded with a great variety of therapeutic cargos at very high loading efficiencies. These therapeutics include both hydrophobic and hydrophilic drugs, as well as large biomacromolecules such as proteins and nucleic acids. Such diverse cargo opens the door to new kinds of treatment that at present are inefficient or unachievable. Furthermore, these therapeutics can be loaded either passively, or by chemical conjugation to the nanoparticle, which may better protect the cargo and minimize off-target effects.

As well as these five principal features, polymeric nanoparticles have other advantages too, including increased thermodynamic stability, self-immolating capability, which provides a further mechanism to reduce toxicity, and the fact that polymer nanoparticles themselves can act as adjuvants. Some of the most powerful and efficacious drug-delivery designs are polymeric nanoparticles that combine aspects of all the aforementioned advantages. In short, polymeric nanoparticles, due to their tunability, versatility and functionality, represent a drug-delivery vehicle with great drug loading capacity and therapeutic efficacy.

Surveying the clinical history of particle-based drug delivery, one can loosely identify three generations of nanoparticle. Lipid nanoparticles comprise the first generation. After 20 years, these particles are now achieving widespread clinical success, as demonstrated by the fact that the therapeutic cargo (mRNA) across multiple COVID-19 vaccines is delivered by lipid nanoparticles. These kinds of nanoparticles are not covered here, but are described in great detail elsewhere. Polymeric nanoparticles that employ an amphiphilic block copolymer that self-assembles into micelles represent the second generation. These somewhat basic designs are widely used in clinical trials, with the first anti-cancer products beginning to permeate the market. The third generation of nanoparticles are more functionally diverse, being "smart" polymeric nanoparticles that can respond to stimuli or target specific endogenous sites, resulting in high levels of pre-clinical therapeutic efficacy. Both the second and third generations of nanoparticles are covered in depth in this review. As the second generation progresses through late-stage clinical trials and into commercial relevance, research is shifting toward optimizing the design and scalability of these more sophisticated third generation nanoparticles.

Given their strong preclinical performance, why are polymeric nanoparticles, particularly the highly sophisticated designs, not more relevant in clinical trials and the wider pharmaceutical industry? The fact that polymeric nanoparticles can be imbued with exotic functionality and architecture implies that their synthesis and formulation is also complex. Hence, there are a number of challenges involved with commercially viable production. Scalability and cost are the two primary concerns. For example, nanoprecipitation is one of the most important particle synthesis procedures, but occurs under highly dilute conditions with very low solids content, and thus cannot easily be scaled-up. Furthermore, to synthesize nanoparticles with an enhanced targeting or stimuli-responsive capability, more expensive monomers/ligands are required. Such an expense entails higher production costs that can only be offset by outsized clinical benefits. Finally, many of the conventional synthesis techniques for polymeric nanoparticles yield batch-to-batch variability when upscaled, which is undesirable for commercial production. As a result of these challenges, almost all the highly efficacious and sophisticated nanoparticle designs are synthesized on small scales in university laboratories. It is no coincidence that the polymeric nanoparticles that have advanced to late-stage clinical trials and into wider commercial application, are the simplest designs—block copolymer micelles.

As well as commercial production challenges, adequate characterization methods and intracellular assays that can probe the behavior of polymeric nanoparticles throughout the body's varied and complex environments are lacking. This lack of characterization is challenging for all drug-delivery vehicles, but for polymeric nanoparticles, which are specifically designed to utilize the variability inherent in biological environments, such an absence is an acute problem. In addition to characterization issues, many of the quality control tests associated with polymeric nanoparticles are at present unfamiliar to large pharmaceutical companies. It is also noted that polymeric nanoparticles, which have displayed high drug-delivery performance under *in vitro* conditions, seem to lose this efficacy in animal models and clinical trials. This phenomenon is also not unique to polymeric nanoparticles, and its exact causes are unknown. Some of the causes likely involve batch-to-batch inconsistency, the inherent heterogeneity across different patients and cell-lines, differences between *in vitro* and *in vivo* conditions, and the fact that slight changes in particle shape and composition are observed to alter nanoparticle performance.

In addition to characterization methods, our understanding of the body's complex biological environments is also deficient. Nanoparticles are subjected to biological roadblocks as soon as they are injected, and must overcome several different endogenous environments to reach their target sites, which are normally intracellular. The body's varying environment is well understood in a general sense; however, a truly robust and specific understanding of each roadblock remains elusive. It is likely that polymeric nanoparticles, which are finely tuned to take advantage of varying biological environments, are significantly impacted by this lack of knowledge. Some have suggested reframing the design of polymeric nanoparticles around specific endogenous pathways or diseases, rather than a composition-driven "bottom up" approach.[999] In practice, this means dedicating more resources to understanding specific biological hurdles or diseases, and how they interact with nanoparticles.

Finally, the field of polymeric nanoparticles for drug delivery would benefit substantially from research that compares the efficiencies of different polymeric nanoparticle designs and evaluates the performance of polymeric nanoparticles with other drug-delivery vectors, such as lipid nanoparticles or cell penetrating peptides. Currently, the vast majority of scientific literature regarding polymeric nanoparticles are novel designs that only report powerful delivery capability, either through enhanced drug loading, intracellular targeting, or stimuli-responsiveness. Such research is vital, but there remains a lack of agreement over which designs are best optimized in terms of

https://doi.org/10.1021/acs.chemrev.3c00705
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production and cost for more widespread clinical and commercial application. Comparison studies between different nanoparticle designs would help remedy this problem. As well as such comparison studies, standardized testing methods for polymeric nanoparticles across different labs and commercial environments would also go a long way to furthering their clinical potential.

Polymeric nanoparticles are slowly graduating from foundational research to clinical trials, and block copolymer micelles represent the first wave of widely available polymeric drug-delivery vehicles. Despite the challenges that so far have impeded the progression of polymeric nanoparticles as commercial products, the benefits of these nanoparticles, whose sophisticated design allows for radically enhanced targeting, drug loading, and stimuli-responsiveness, is potentially enormous. Polymeric nanoparticles will have a profound influence as drug-delivery vehicles for increasingly sophisticated therapy over the course of this century.

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Author Contributions

This review was written through the contribution of all authors. **Maximilian Beach** and **Umeka Nayanathara** have contributed equally to the writing of this review and are co-first authors. CRediT: **Yanting Gao** writing-original draft, writing-review & editing; **Changhe Zhang** writing original draft; **Yijun Xiong** writing-original draft, writing-review & editing; **Yufu Wang** writing-original draft, writing-review & editing; **Georgina K. Such** funding acquisition, writing-original draft, writing-review & editing.

Notes

The authors declare no competing financial interest.

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ACKNOWLEDGMENTS

This work was supported by the Australian Research Council (DP210103174). Umeka Nayanathara also acknowledges Dr. Albert Shimmins Postgraduate Writing-Up Award for the funding support.

ABBREVIATIONS

ABC	Accelerated blood clearance
AMP	Antimicrobial peptide
AMR	Antimicrobial resistance
APC	Antigen presenting cell
APN	Aminopeptidase N
ATRP	Atom transfer radical polymerization
BBB	Blood−brain barrier

https://doi.org/10.1021/acs.chemrev.3c00705
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CMC	Critical micelle concentration
CVD	Cardiovascular disease
DC	Dendritic cell
DLS	Dynamic light scattering
DOX	Doxorubicin
DTT	Dithiothreitol
DTX	Docetaxel
DMMA	2,3-Dimethyl maleic anhydride
EGFR	Epidermal growth factor receptor
ECM	Extracellular matrix
EPR	Enhanced permeability and retention
FRET	Forster resonant energy transfer
GI	Gastrointestine
GOD	Glucose oxidase
GSH	Glutathione
HA	Hyaluronic acid
HBPs	Hyper branched polymers
IC_{50}	Half maximal inhibitory concentration
LCST	Lowest critical state temperature
MHC	Major histocompatibility complex
MMP	Matrix metalloproteinase
mRNA	Messenger RNA
MRSA	Methicillin-resistant *S. aureus*
MSN	Mesoporous silica nanoparticles
MTO	Mitoxantrone
MW	Molecular weight
NIR	Near-infrared
NP	Nanoparticle
PAA	Poly(amino acid)
PAAm	Poly(acrylamide)
PAE	Poly(amino ester)
PAMAM	Poly(amido amine)
PAN	Poly(acrylonitrile)
PAsp	Poly(L-aspartic acid)
PBMA	Poly(butyl methacrylate)
PBS	Phosphate buffer saline
PCL	Poly(ε-caprolactone)
PDEAEMA	Poly(2-(diethylamino)ethyl methacrylate
PDMAEMA	Poly(2-(dimethylamino)ethyl methacrylate
PDPAEMA	Poly(2-(diisopropylamino)ethyl methacrylate
PDLLA	Poly(D,L-lactide)
PDMA	Poly(*N*,*N*-dimethyl acrylamide)
PDMS	Poly(dimethyl siloxane)
PEG	Poly(ethylene glycol), aka PEO
mPEG	Methoxy poly(ethylene glycol)
PEGMA	Poly(ethylene glycol) methacrylate
PEI	Polyethyleneimine
PEO	Poly(ethylene oxide), aka PEG
PEtG	Poly(ethyl glyoxylate)
PGAm	Poly(glycoxylamide)
PGA	Poly(glycolic acid)
PGlu	Poly(glutamic acid)
PHEA	Poly(hydroxyethyl acrylate)
PHEMA	Poly(hydroxyethyl methacrylate)
PHPMA	Poly(*N*-(2-hydroxypropyl) methacrylamide)
PIC	Polyion complex
PISA	Polymerization-induced self-assembly
PLA	Poly(lactic acid)
PLGA	Poly(lactic-*co*-glycolic acid)
PLL	Poly(L-lysine)
PMMA	Poly(methyl methacrylate)
PMOx	Poly(2-methyl-2-oxazoline)
PNIPAm	Poly(*N*-isopropyl acrylamide)
POEGMA	Poly(oligo (ethylene glycol) methyl methacrylate)
POx	Polyoxazoline
PPE	Poly(phosphate ester)
PPN	Poly(phosphonate)
PPG	Poly(propylene glycol)
PNAM	Poly(*N*-acryloyl morpholine)
PRINT	Particle replication in non-wetting templates
PS	Polystyrene
PSar	Polysarcosine
PDT	Photodynamic therapy
PTT	Photothermal therapy
PTX	Paclitaxel
PVA	Poly(vinyl acetate)
PVP	Poly(vinylpyrrolidone)
QD	Quantum dot
QM	Quinone methide
QSPRs	Quantitative structure property relationships
RDRP	Reversible deactivation radical polymerization
RAFT	Reversible addition-fragmentation chain transfer (polymerization)
RBCs	Red blood cells
RES	Reticuloendothelial system
RGD	Arginylglycylaspartic acid
ROP	Ring-opening polymerization
ROMP	Ring-opening metathesis polymerization
ROS	Reactive oxygen species
SEM	Scanning electron microscopy
SPIONs	Superparamagnetic iron oxide nanoparticles
TEM	Transmission electron microscopy
sgRNA	Single guide RNA
siRNA	Small interfering RNA
SIL	Self-immolative linker/linkage
SIP	Self-immolative polymer
SNAPPs	Structurally nanoengineered antimicrobial peptide polymers
SPIONs	Superparamagnetic iron oxide nanoparticles
TEM	Transmission electron microscopy
STING	Stimulator of interferon genes
UCST	Upper critical state temperature
H_2O_2	Hydrogen peroxide

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