Porous Inorganic and Hybrid Systems for Drug Delivery: Future Promise in Combatting Drug Resistance and Translation to Botanical Applications

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ABSTRACT: Background: Porous micro- and nanoparticles have the capacity to encapsulate a large quantity of therapeutics, making them promising delivery vehicles for a variety of applications. This review aims to highlight the capacity of inorganic and hybrid (inorganic/organic) particles for drug delivery with an additional emphasis on combatting drug resistant cancer. We go one step further and discuss delivery applications beyond medicinal delivery, as there is generally a translation from medicinal delivery to botanic delivery after a short lag time.

Methods: We undertook a search of relevant peer-reviewed. The quality of the relevant papers was appraised using standard tools. The characteristics of the papers are described herein, and the relevant material and therapeutic properties are discussed.

Results: We discuss 4 classes of porous particles in terms of drug delivery and theranostics. We specifically focus on silica, calcium carbonate, metal-phenolic network, and metal-organic framework particles. Other relevant biomedically relevant applications are discussed and we highlight outstanding therapeutic results in the relevant literature.

Conclusion: The findings of this review confirm the importance of studying and utilizing porous particles for therapeutic delivery. Moreover, we show that the properties of porous particles that make them promising for medicinal drug delivery also make them promising candidates for agro-industrial applications.

Introduction

Porous nano- and microparticles hold promise for a wide variety of applications ranging from sensing to therapeutic delivery.¹ The delivery of functional cargo is facilitated by the pores of the particles, as the free pore volume gives a larger surface area to load the cargo onto in comparison to non-porous particles, and the tortuous paths of the pores allow for some degree of control over release. Additional functionalization steps, such as capping, can also allow for triggered controlled release based on a variety of stimuli.² To this end, a wide variety of porous particles have been developed for therapeutic delivery using benign and/or biogenic synthesis materials.³ The use of benign materials means that only the cargo itself will elicit a response in the target organism, which allows for much easier dosing regimens.³ Porous particles offer additional benefits over the administration of free cargo, as the cargo is concentrated in the particles and can therefore be used in smaller quantities to elicit a similar effect, not to mention the reduction in side effects that can be achieved through the targeting of loaded particles.⁴ Moreover, the high surface area of porous particles also allows for the loading of multiple therapeutics, thereby providing a strategy to circumvent drug resistance in tumors.⁵ We highlight the specific promise of porous particles for combatting drug resistant cancer towards the end of this review. However, porous particles have broadly failed to translate into clinical application in drug delivery for humans, primarily due to issues balancing stealth and targeting in humans.⁶⁻⁸ A promising area outside of therapeutic delivery to humans is the delivery of therapeutics to plants using porous particles, which we highlight briefly at the end of this review.⁹⁻¹⁰ Overall, it is expected that porous particles will continue to be used for therapeutic delivery in medicine and other industries with developments in codelivery facilitating the treatment of drug resistant diseases.

Porous particles

Porosity can be imbued into most materials through bottom-up or top-down approaches.¹¹⁻¹² Top-down approaches usually require etching, making it generally more useful for large microscopic and macroscopic materials.¹³ Alternatively, bottom-up approaches allow for the generation of pores during material formation, which is generally the only possibility for generating porous nanoparticles.¹⁴ Two particularly important classes of porous nanomaterials are inorganic and hybrid nanomaterials. The most common types of inorganic particles are silica (SiO_2)¹⁵ and calcium carbonate (CaCO_3) particles,¹⁶ where the pores can form spontaneously during material synthesis or can be engineered through templating approaches. These two materials are biocompatible, and have facile and low-cost synthesis routes, making them ideal candidates for drug delivery. Hybrid materials, composed of both inorganic and organic materials, have more complex biocompatibilities as a wide variety of metals are toxic to humans and therefore cannot be incorporated into drug delivery vehicles. Still, trace and essential minerals can be used safely, and two major classes of hybrid materials, namely metal-phenolic networks (MPNs)¹⁷⁻¹⁸ and metal-organic frameworks (MOFs),¹⁹ have shown some promise for drug delivery. Overall, inorganic and hybrid porous particles are two classes of materials useful for loading a wide range of therapeutics and are therefore of interest for a variety of therapeutic applications including combatting drug resistant tumors, and agro-industrial delivery applications (**Figure 1**).

Figure 1. Schematic demonstrating that porous particles (inorganic or hybrid) can be loaded with a wide variety of therapeutics and functional molecules to target specific applications.

INORGANIC POROUS PARTICLES

Controlled release of therapeutics from SiO₂

Multifunctional mesoporous silica nanoparticles (MSNs) have been widely used as carriers for drug delivery,²⁰⁻²¹ as they have well-defined and controllable diameter (tens nm to micro-size), morphology (spherical and non-spherical shapes), porosity (2-30 nm), and surface functionalization. Additionally, MSNs have a high surface area and can therefore load large quantities of therapeutics.²²⁻²³ The size and morphology of the MSNs influence their biodistribution and transmembrane transport,²⁴ while porosity allows for the loading of cargo with different molecular weights,²⁵ and surface modification can allow for reduced fouling and targeting. Polyethylene glycol (PEG) is the most widely used method to avoid non-specific protein adsorption and clearance by the mononuclear phagocyte system (MPS) for drug delivery vehicles. PEGylated MSNs have longer blood circulation time and lower capture by the spleen and liver compared to bare MSNs.²⁶ In contrast, targeting moieties including either small molecules (e.g., folic acid, RGD motifs, mannose) or biomacromolecules (e.g., antibody,

galactose, hyaluronic acid) have been used to modify MSN surfaces to increase the specific binding for targeted drug delivery.²⁷ To improve the efficacy of drug delivery, MSNs are usually modified with multiple moieties to achieve different functionalities simultaneously. For example, drug-loaded MSNs have been coated with a single lipid bilayer to prevent non-specific drug release, followed by PEGylation to reduce nonspecific biological interactions with cells and tissues. Peptides were then used as targeting ligands to target distinct cells (e.g., cancer cells). Modification with pH-responsive peptides can disrupt endosomes during internalization to allow for drug delivery into the cytosol.²⁸ In this subsection, we will mainly focus on the engineering of MSNs for triggered drug release.

Controlled cargo release from MSNs can be tuned by external stimuli (e.g., UV-vis light, IR light, magnetic field, temperature, specific molecules) or internal stimuli (e.g., pH, enzymes, reducing agent),²⁷ and three strategies have been developed to fabricate these stimuli-responsive MSNs. (**Figure 2**). Magnetic Fe₃O₄ particles can be conjugated to MSNs via a disulfide linkage (**Figure 2a**). Cell-produced antioxidants (e.g., dihydrolipoic acid) or intracellular reducing agents (e.g., GSH) can cleave the disulfide bonds to open the MSN pores in the presence of an external magnetic field, which results in release of the loaded cargo.²⁹ Similar designs have been used to fabricate redox-responsive MSNs by using collagen as capping molecule instead of Fe₃O₄ particles.³⁰ When oligonucleotides are used as capping molecules for the fabrication of bio-gated delivery systems, the cargo release occurs in the presence of the complementary oligonucleotide or in the presence of deoxyribonucleases, or after heating (**Figure 2b**).³¹⁻³⁵ Another alternative chemical reaction for controlling release with capping materials is host-guest reorganization between α -cyclodextrin (α -CD) and anilinoalkane groups based on hydrogen-bonding.³⁶ Specifically, anilinoalkane groups were covalently bonded onto MSNs with a free anilino group on the end of the linker. Complexation between α -CD rings and anilino groups at neutral pH capped the pores and encapsulated the cargo inside the MSNs, and when the pH decreased (e.g., in endosome or lysosome), the nitrogen atoms were protonated, which decreased the binding affinity and allowed the α -CD rings to escape and thereby release the cargo. Besides α -CD, amine modified β -cyclodextrin (β -CD) has also been used to cap MSN pores for drug encapsulation via bridging β -CD and MSNs with a disulfide bond.³⁷ Reducing agents (e.g., GSH) in intracellular compartments can cleave the disulfide bonds to remove the β -CD rings, and thereby open the MSN pores and release the cargo. In addition, poly(ethylene glycol) modified with adamantane (and folate) can be functionalized onto MSNs via host-guest reorganization to reduce non-specific interaction and increase specific targeting with certain cancer cells. The high drug-delivery efficacy of these multifunctional MSNs is attributed to the synergetic effects of folate-mediated targeting and stimuli-triggered drug release.

Figure 2. Controlled release can be designed by different strategies including (a,b) pore gating, (c,d) surface coating, and (e,f) internal pore modification. Figure reproduced with permission from Ref 27. Copyright American Chemical Society 2014.

Responsive surface coatings are an alternative method to control the drug encapsulation and release from MSNs. For example, a temperature-responsive polymer, poly(*N*-isopropylacrylamide) (PNIPAM), has been coated on MSNs for the tuning of uptake and release of model drugs above the lower critical solution temperature (LCST) and below the LCST, respectively (**Figure 2c**).³⁸ Surface polymerization of disulfide cross-linked coatings on MSNs has been designed as a reductively sheddable layer for controlled drug delivery (**Figure 2d**).³⁹⁻⁴⁰ To generate enzyme-responsive coatings, de la Torre et al. used a derivative of the T22 peptide (i.e., polyphemusin II peptide) to functionalize MSN surfaces.⁴¹ Upon the internalization of peptide-coated MSNs, endosomal proteolytic enzymes could cleave the peptide coating and release the loaded drugs. Additionally, the peptide can also target CXCR4-expressing lymphoma cells, and therefore, the combination of specific targeting and enzyme-responsiveness of the peptide coating can improve the drug delivery efficacy. Recently, pH-responsive coating on MSNs have been engineered via the supramolecular assembly of tannic acid (TA) and Cu^{II} ions based on coordination interactions.⁴² Specifically, a photoacid generator (i.e., 2-nitrophenyl acetate) and rhodamine B were pre-loaded into MSNs, followed by TA/ Cu^{II} coatings, which have been proved to be a pH-responsive coatings for intracellular drug delivery.⁴³ Upon exposure to UV light, photolysis of the photoacid generator resulted in release of acid, which enables the disassembly of the TA/ Cu^{II} coatings and the release of rhodamine B. Alternatively, cargo can be

directly attached to the pores and surface of the silica nanocarriers. Both coordinative and covalent bonds can be cleaved by various stimuli such as competitively binding molecules or reducing agents to activate cargo release.^{30, 44} Zink and co-workers have presented different nanocarriers with on-demand controllable release mechanisms, including nanoimpellers consisting of azobenzene groups that have UV-light-activated release of a cell membrane-impermeable dye.⁴⁵

Due to the large surface area and pore volume of MSNs, controlled cargo release can be achieved via responsive conjugation of the cargo molecules in the MSN pores. Griebenow and coworkers reported the encapsulation of a model enzyme, carbonic anhydrase, in MSNs via a reduction-sensitive disulfide bond.⁴⁶ For pH-triggered release, cargo can be loaded in MSNs through coordination bonding, which is stable at neutral pH while unstable at low pH inducing DOX release.⁴⁷⁻⁴⁸ Except for using MSNs as carriers, MSNs have been also used as templates for the fabrication of polymer replica particles with tunable size, shape, composition, stiffness, degradability, and surface functionality for improving drug delivery efficacy.^{1, 49-50} For example, the mechanical tunability of MSN-templated particles can mimic red blood cells, which is promising for intravenous drug delivery.⁵¹⁻⁵⁴

CaCO₃ particles as therapeutics and therapeutic carriers

Calcium carbonate (CaCO₃) is one of the most common inorganic materials and is used in broad fields due to its availability, low cost, safety and biocompatibility.³ It is one of the most abundant mineral in nature and is the main component of the shells of marine organisms.⁵⁵ Although calcium is essentially required for various biological processes such as intracellular cell signaling, blood clotting, nerve function, and so on, less than 1% of total body calcium is necessary for critical metabolic functions and the other 99% is stored in bones and teeth.⁵⁶ Besides the biocompatibility, the porosity of most carbonates also means that a wide variety of therapeutics can be loaded into CaCO₃ particles.⁵⁷ In itself, CaCO₃ is a therapeutic and is used as an antacid to relieve heartburn, acid indigestion, and upset stomach. Due to its solubility in acidic environments, intravenously administered CaCO₃ particles can modulate local tumor environments to inhibit tumor growth⁵⁸ or can be orally administered and dissolve in the stomach acid before being absorbed into the blood stream as Ca²⁺.⁵⁹ Moreover, as particle template porous CaCO₃ particles can be dissolved to yield freestanding porous therapeutic structures.^{2, 60} Due to these beneficial properties, CaCO₃ particles hold promise for a variety of therapeutic applications.

Taking calcium supplements can reduce the risk of osteoporosis, but the supplements are not readily absorbed in the gastrointestinal tract. Powderizing CaCO₃ can be a solution and this has been done by a bottom-up approach such as the precipitation reaction occurring by mixing Ca²⁺ and CO₃²⁻ ions or a top-down approach such as the pulverization of cockle shell.⁶¹ Rangari and co-workers loaded the model drug, 5-fluorouracil into eggshell-derived CaCO₃ nanoparticles,⁶² and prepared tablets consisting of the CaCO₃ nanoparticles (more than 80 wt%) and binders. New Zealand White Rabbits were used as an animal model for digestion and radiographs were taken after ingesting the tablets. The radiograph images revealed that the tablet remained in the stomach of the rabbit for up to 3 h suggesting a sustained degradation of the tablet. CaCO₃ particles can also enhance the oral bioavailability of hydrophobic drugs with low-solubility.⁶³

Orally administered CaCO_3 nanoparticles rapidly interact with biological fluids containing proteins, enzymes, electrolytes, and other biomolecules, which eventually form a layer around the particles called a corona. Kim and co-workers investigated the interaction of CaCO_3 nanoparticles with biological liquids⁵⁶ and showed that immunoglobulins, apolipoproteins, thrombin, and fibrinogens play important roles in protein corona formation on CaCO_3 nanoparticles. They also suggest that the CaCO_3 primarily present as particulate forms in gastrointestinal fluids but enter circulatory system by being dissolved as Ca^{2+} (about 4%) and partially transformed into CaHPO_4 *in vivo*.

Figure 3. A wide variety of therapeutics can be loaded into CaCO_3 particles. Figure reproduced with permission from Ref 57. Copyright Wiley 2015.

Volodkin and co-workers prepared porous CaCO_3 microparticles and used them as templates for the layer-by-layer⁶⁴⁻⁶⁵ (LbL) assembly of polyelectrolyte capsules and particles.^{2, 60} The porous CaCO_3 microparticles had a surface area of $8.8 \text{ m}^2 \text{ g}^{-1}$ and an average pore size of 35 nm based on the BET analysis. The polyelectrolyte adsorbed not only on the surface of the particles but also within the pores due to diffusion mechanisms. By dissolving the CaCO_3 particles using ethylenediaminetetraacetic acid (EDTA) solution, replica polyelectrolyte particles and capsules could be obtained. Furthermore, the porous CaCO_3 particles could act as not only a sacrificial template but also a reservoir of cargos, representing an efficient encapsulation method for LbL capsules. Richardson et al. expanded this approach by loading a wide variety of cargo onto CaCO_3 particles including MOFs, proteins, DNA, nanoparticles, and small molecule drugs (**Figure 3**).⁵⁷ Svenskaya and co-workers loaded a photosensitizer, photosens (a mixture of sulfonated aluminum phthalocyanines) into porous CaCO_3 particles for anticancer drug delivery.⁶⁶ Biomolecules can also be loaded, and Wang and co-workers prepared CaCO_3

particles modified with two functional peptides for efficient gene delivery.⁶⁷ One is the KALA peptide,⁶⁸ which can destabilize lipid membranes and facilitate cellular uptake.⁶⁷ The other one is the arginine-rich peptide, protamine, which has membrane translocating and nuclear-localizing activities. As compared with unmodified CaCO₃/DNA nanoparticles and mono-functionalized Protamine/CaCO₃/DNA and KALA/CaCO₃/DNA nanoparticles, dual-functionalized KALA/Protamine/CaCO₃/DNA nanoparticles exhibited significantly improved gene delivery efficiency due to the enhanced cellular uptake and nuclear localization. Moreover, after removing the CaCO₃ core, and when functionalized with targeting molecules, drug loaded capsules could successfully target specific regions of the vasculature (plaques) in vivo.⁶⁹

HYBRID MATERIALS

MPNs as responsive and theranostic carriers

Modifying the surface of an object results in an entirely new subset of properties and possible chemical interactions without necessarily changing the object underneath. Recently a new type of porous surface modifying material, metal-phenolic networks (MPNs), has been reported in the literature. Recent reviews and research broadly on MPNs can be referenced for a more thorough look at the composition and uses outside of drug delivery.^{17-18, 43, 70} Briefly, MPNs are constructed from two major compounds: metal ions and polyphenol phytochemicals. When these two precursors are mixed with substrates (e.g., microparticles), a MPN layer (~10 nm)⁷¹ builds up on the substrate due to the formation of coordination bonds and phenol-substrate interactions.^{17, 72} The galloyl or catechol groups within the polyphenol compounds provide sites for metal ions to cross-link, resulting in a stable yet flexible matrix around the template substrates.^{43, 73} Using this metal-polyphenol crosslinking and the natural affinity of polyphenols for various surfaces, a wide variety of functional materials (microcapsules,⁴³ replica particles,⁷⁴ nanoparticles,⁷⁵⁻⁷⁶ superstructures,⁷⁷ synthetic spores,⁷⁸⁻⁷⁹ etc.) have been engineered for a wide spectrum of biological applications.¹⁸ Furthermore, there is great interest in exploring the applications of MPNs and MPN-based materials in biomedical and biological applications due to their high safety and biocompatibility.⁸⁰ Various polyphenols such as tannic acid (TA), epigallocatechin gallate (EGCG), and gallic acid (GC) have already received FDA labeling of Generally Recognized as Safe (GRAS).⁸¹ The maximum intake of polyphenols that humans can process is 13.6g/60 kg a day,¹⁸ however this value can vary depending on the different polyphenol species. Polyphenols were traditionally used in leather industry due to their ability to form multiple interactions with collagen fibers,⁸² which leads to the enhancement of the thermal and antibacterial properties of animal skin.⁸³ There is also an understanding amongst many scientists that polyphenols confer various health benefits (antioxidant, antibacterial, antiviral, etc.),⁸¹ although not all health claims have substantiated evidence yet.

One of the strongest potentials for MPN-based materials is their application in drug delivery. This is based on the formation of MPNs by metal-phenolic coordination. When the pH decreases, the coordination network can be disassembled, which leads to an increase in the MPN film porosity. MPNs demonstrate great versatility in being able to assemble around particulate templates using a diverse tool-box of coordinating compounds and this versatility opens the door for drug delivery systems with tailorable intricate physicochemical properties.^{43, 84} For example, the coordination of different metal ions in the MPNs leads to different disassembly times, which

could be ideal for the engineering of advanced drug delivery systems based on the microenvironment in pathological sites. Guo et al. showed that there was a six-fold time difference in disassembling Cu^{II}-TA capsules (25% at 1 h) and Al^{III}-TA capsules (25% at 6 h) at pH 5.⁴³ Al^{III}-TA has an agreeable profile for dissolution at external tumor sites (pH gradient of 5.7-6.8), and endosomal and lysosomal compartments (pH 5.0-6.0).⁸⁵ Synthetic polyphenols can also replace natural building blocks (e.g., TA) in MPN networks.⁸⁶ This was achieved through functionalizing or conjugating catechols to different polymers, e.g., polyethylene (PEG)-catechol, and hyaluronic acid (HA)-catechol. Researchers are now also furthering the chemistry for forming synthetic galloyl polymers, which should also have impacts on future applications of MPN-based materials as the synthesis procedures become more accessible.⁸⁷⁻⁸⁸ This modular assembly of different functional catechol-based polymers provides a robust and tailorable platform for the engineering of advanced drug delivery systems. Encapsulation of chemotherapeutic agents, such as doxorubicin (DOX) in PEG-based MPN capsules, then adds therapeutic properties necessary for drug delivery.⁸⁵ MPNs can also modulate the protein corona, and the presence of a protein corona on HA following injection into human serum had a favorable effect on CD44 receptor binding, demonstrating increased targeting specificity.⁸⁹ While proteins normally adsorb on foreign particles within the bloodstream and reduce targeting precision, the opposite effect was found in that system as the protein corona only decreased non-specific binding. The nanoscale length-scale that is engineered into MPN materials adds an additional advantage for drug delivery. Dai et al. reported the engineering of MPN-integrated Pt prodrug nanoparticles (PtP NPs).⁷⁵ PtP NPs can be constructed from two types of synthetic polyphenol building blocks and PEG-catechol and Pt prodrug-galloyl hybrids were assembled through the coordination with Fe³⁺ in the microenvironment of nanoscale emulsions, which resulted in ≈ 100 nm diameter nanoparticles. In this study, PtP NPs were shown to have long circulation times (elimination half-life of ≈ 18 h), and the PtP NPs demonstrated four times better inhibition of tumor growth in mice than either free prodrug or cisplatin (**Figure 4**). This study demonstrated the wide tunability and extraordinary utility of MPN in drug delivery in vivo. Using the nucleation of drug molecules in water, Fe^{III}-TA coating can be also applied using paclitaxel (PTX)⁹⁰ or DOX⁹¹ cluster as templates to form nanostructured drug delivery systems.

Figure 4. a) Tumor growth inhibition of luciferase-expressing PC3 cells treated with different groups at the same Pt dose. Data presented as mean $\pm$ SD ($n = 7$ for PBS and $n = 8$ for other groups). b) In vivo bioluminescence images of mice bearing luciferase PC3 cell xenograft tumors post 10 d treatment with different groups. c) Resected luciferase-expressing PC3 tumors from experimental groups at the 21st day. d) Time-dependent in vivo fluorescence imaging of Ce6-labeled PtP NPs intravenously injected into mice with luciferase-expressing PC3 xenograft tumors; the blue dashed circle is the location of the tumor. e) Fluorescence intensity of the tumor region. Data are presented as mean $\pm$ SD ($n = 2$). Photomicrographs illustrate f) 4'-6-diamidino-2-phenylindole (DAPI) stained nuclei, g) RECA + endothelial cells, and h) Ce6-labeled PtP NPs in the tumor, and i) the merged image. Figure reproduced with permission from Ref 74. Copyright Wiley 2017.

The metal ions used in forming MPNs can be exchanged with boronic acid. The engineering of boronate-phenolic networks (BPNs) led to multiple stimuli responsive properties potentially useful for the development of more complexes, multifaceted drug delivery systems. Boronate covalent chemistry allows phenylboronate acid to crosslink with the galloyl groups of TA in a manner akin to the MPNs discussed above.⁹² However, the dynamic covalent bonds can be disengaged by competing cis-diols in addition to the disassembly of phenolic networks that occurs at acidic pH. This ability to disassemble in the presence of cis-diols does not compromise the integrity of the system, with the film thickness and monodispersity remaining unchanged

from those seen in MPNs. BPN hydrolysis was found to occur faster in low pH than in MPN studies, however BPN capsules proved fairly stable in blood plasma. In vivo stability tests showed that the local injection of BPN capsules at tumor sites, which naturally accumulate a variety of carbohydrates, did not lead to the disassembly of the BPN capsules (**Figure 5**). This result indicated that they had remained stable in biological environments even in the presence of some cis-diol-containing molecules. This BPN-based delivery system has multiple response mechanisms and the potential for use in closed-loop insulin delivery, expanding the possibilities associated with MPN-based drug delivery.

Figure 5. Stability studies of the BPN capsules. a) Capsules incubated in HBP with and without treatment with 100×10^{-3} M mannitol: DIC images of capsules in HBP solution with or without 100×10^{-3} M mannitol at different times. Scale bars are 2 μ m. b) The remaining capsule populations before and after 12 h incubation in HBP with and without 100×10^{-3} M mannitol. $**P < 0.01$ (Student's t-test). c) Tumor formation and injection of ^{64}Cu /BPN capsules into the tumor. d) PET/CT image of mice 5 and 12 h after capsule injection (maximum intensity projection). e) Standard uptake values located at the tumor site at 5 and 12 h post-injection. NS, not significant. Data are means $\pm$ SD, $n = 3$ in (b), and $n = 2$ in (e). Figure reproduced with permission from Ref 91. Copyright Wiley 2014.

The aforementioned metal ion modularity imparts extreme variability to many other, therapeutic, properties of MPNs with changing the dissociation kinetics in acidic environments. Radioactive Cu^{II} has PET imaging visibility, while Fe^{III} and Gd^{III} have MRI visibility. Fluorescent MPN capsules are also within the realm of possibilities;⁸⁴ for example, designated co-ligands such as 2-thenoyltrifluoroacetone (TTA) and acetylacetone (AA) intensify the fluorescence of Eu^{III} -TA and Tb^{III} -TA networks allowing for red and green networks, respectively. Hybrid metal ion coordination in MPNs has great potential to integrate diverse qualities of different metal ions. Examples of the multimodal functionality in these composite matrices include $(\text{Cu}^{\text{II}}\text{-Eu}^{\text{III}}\text{-TTA})$ -

TA with combined fluorescent and PET/CT imaging capabilities, and multicolor (Eu^{III}-TTA/Tb^{III}-AA)-TA fluorescent networks. Metals also often have inherent catalytic properties, and the incorporation of Fe³⁺ ions on the p53 plasmid-loaded particles was designed to eradicate cancer cells via ferroptosis/apoptosis hybrid pathway.⁹³ This apoptosis pathway harnessed the oxidative stress regulation ability of p53 and the Fenton reaction induced from Fe^{III}-TA complexes. A recent study by Guo et al. focused on the catalytic effects of Fe^{III}-based MPNs for breaking down H₂O₂ into O₂ for ultrasound imaging purposes. A quantifiable difference was seen between the mean recorded grey scale intensity for mice with GPx1 knocked out (a gene incorporated in the removal of H₂O₂) versus without (i.e., accumulates more H₂O₂). The theranostic benefits stemming from metal ion versatility highlights another important utility of MPN networks.

More recently, polyphenols have also been utilized to convert complex structures (e.g., nanoparticles, nanowires, and cells) into fundamental building blocks for superstructures.⁷⁷ Superstructuring has been previously reported through surface functionalization with polyelectrolytes, DNA, antibodies, etc, however the facile assembly and disassembly of MPNs offers a simple route to prepare various superstructures through the hierarchical assembly of a diverse range of polyphenol-functionalized building blocks, (i.e., nanoparticles, nanorods, nanosheets, bacterial cells, mammalian cells, etc.) onto larger structuring templates (polymeric particles or cells). By careful choice of building blocks, hybrid systems capable of self-reporting and tracking their own drug release could be realized. NaYF₄:Yb/Er nanoparticles coupled with DOX-loaded SiO₂ nanoparticles created a system which allowed monitoring of drug release quantities through fluorescence intensity changes.⁹⁴ Thus, not only can MPNs be harnessed for drug delivery and theranostic applications, but they also can be used to convert functional materials into building blocks for the generation of more complex systems of diverse and adaptable superstructures for advanced drug delivery and diagnostics.

MOFs for the delivery of gasotransmitters, synthetic drugs, and biomolecules

Constructed from metal ions/clusters bridged by organic linkers, metal-organic frameworks (MOFs) represent an emerging class of porous crystalline materials with high surface areas and tunable pore microenvironments.⁹⁵ In the last two decades, MOFs have been exploited and have shown unprecedented promise in gas storage/separation, chemical sensing, catalysis, proton conductivity, and biotechnology.⁹⁶⁻⁹⁷ Importantly, MOFs can be constructed from biofriendly building units under physiological conditions with fine tuning of particle size, morphology and surface chemistry, making MOFs an ideal candidate for controlled therapeutic delivery applications.⁹⁸⁻¹⁰³

Gasotransmitters, including NO, CO, and H₂S, are important biological signaling molecules.¹⁰⁴ For instance, NO induces vasodilation within the vasculature, inhibits platelet aggregation, prevents neutrophil/platelet adhesion to endothelial cells, inhibits smooth muscle cell proliferation and migration, regulates programmed cell death (apoptosis) and maintains endothelial cell barrier function. NO also acts as a neurotransmitter and acts as an antimicrobial agent.¹⁰⁵ Delivery of gasotransmitters from a storage material is therefore attractive for many in vitro and in vivo anti-bacterial, anti-thrombotic and wound healing applications.¹⁰⁶ Recent studies employing MOFs have point out new avenues for controlled delivery of

gasotransmitters.¹⁰⁷ Morris and coworkers studied the NO storage and delivery using Ni, Co and Cu-containing MOFs (M-CPO-27 (M = Ni/Co) and HKUST-1, respectively) for vasodilatory effect in porcine coronary artery.¹⁰⁸ However, the presence of toxic metals and the stability issue of the choice of MOFs could prevent their real-world drug delivery applications. Instead of loading gasotransmitter gas molecules in MOF pores, Diring et al. developed an alternative strategy to functionalize NO chemically to the MOFs.¹⁰⁹ 2-nitroimidazole and 5-methyl-4-nitroimidazole were used as ligands to synthesis photoactive MOFs NOF-1 and NOF-2, respectively. Nitroaromatic compounds were known to undergo photoinduced nitro-to-nitrite rearrangement and subsequent bond cleavage to release NO radicals.¹¹⁰ In their work, the as-synthesized MOFs were embedded in a biocompatible matrix for cell attachment and proliferation. Upon activation by a localized two-photon laser, the nitro-containing ligand within the MOFs released NO radicals locally. Through the movement of the focal point of the laser, precise control of the NO delivery was achieved. The biological relevance of the exogenous NO produced by this strategy is evident by an intracellular change in cellular calcium concentration, mediated by nitric oxide-responsive plasma membrane channel proteins. In a more recent study, Diring et al. functionalized CO into a Zr-based UiO-67-type framework (UiO-67-bpy) via post-synthetic metalation of MnBr(bpy)(CO)₃ to the MOF ligand.¹¹¹ CO release from the framework was achieved upon exposure to a visible light source at 460 nm. Similar to their previous work, a fluorescent probe was used to detect the cell response to the released CO. This technique demonstrated an easy-to-localize platform for the therapeutic release of CO.

Controlled delivery of small molecular drugs using MOFs is one of the primary focus currently being exploited, largely owing to the exceptional surface area of MOFs (generally in the range ~1000-8000 m² g⁻¹) that can afford unprecedented loading of drugs. For example, up to 1.4 g of ibuprofen per gram of MIL-101(Cr), have been achieved (**Figure 6**).¹¹² In addition, slow drug release up to 21 days from MOFs was also demonstrated, showing prospects of using MOFs for sustained release applications. Similar to porous silica and zeolites, the loading and release of drugs is generally governed by passive diffusion as a result of the concentration gradient between inside and outside of MOFs. Therefore, extra particle engineering strategies are necessary for using MOF particles beyond simply diffusion controlled drug release.

Figure 6. (Left): Kinetics of delivery of Ibuprofen from several porous MOFs carriers (SBF, 37 °C); (Top right): Pore openings of the MIL-53 solid: water (left), ibuprofen (center) and open form (right); (Bottom right): Schematic view of the larger cage (left) and the smaller cage (right) of MIL-100. Metal octahedra, oxygen and carbon atoms are in orange, red, and black,

respectively. Figure reproduced with permission from Ref ¹¹². Copyright American Chemical Society 2011.

Tan et al. decorated nanosized UMCM-1-NH₂ MOF particle surface with pyridinium pendants through post-synthetic modification.¹¹³ After loading the MOFs with drugs, the particles were capped by anionic pillarenes (carboxylatopillar[5]arene, CP5) through host-guest interaction between CP5 and pyridinium pendants. The CP5 capping prevented passive drug release at neutral pH, however, at acidic pH, this molecular cap was removed due to the protonation of the pillarenes and their dissociation from the framework surface, leading to triggered drug release. Other than pH, temperature was also exploited as a trigger to control the delivery of drugs from MOFs. Nagata et al. decorated a temperature-responsive polymer poly(N-isopropylacrylamide) (PNIPAM) to UiO-66-HN₂ particles (**Figure 7**).¹¹⁴ PNIPAM has a T_c of 31 °C, therefore, at lower temperature (e.g. 25 °C), the particles exhibited rapid release of guest molecules, while the release was suppressed at higher temperatures (e.g. 40 °C).

Figure 7. (a) Schematic image of controlled release of guest molecules from PNIPAM coated MOFs using temperature. Figure reproduced from Ref ¹¹⁴. Copyright Royal Society of Chemistry 2015.

External triggers were also explored as potential strategies to synthesis stimuli-responsive MOF particles. Furukawa and coworkers designed a near-infrared (NIR) light-responsive MOF composites for controlled delivery of anthracene.¹¹⁵ In that work, gold nanorods were first coated by a layer of alumina, followed coordination replication to convert alumina into MOFs [Al(OH)(1,4-ndc)]_n in the presence of organic linkers, yielding MOF particles containing a gold nanorod core. Upon NIR irradiation, the photothermal effect of gold nanorods caused the MOF particles rapidly to heat up, leading to the release of guest molecules. In a similar work, polypyrrole nanoparticles were used as the photothermal source and loaded into MIL-100 frameworks.¹¹⁶ Doxorubicin was loaded in the MOF shell. With NIR irradiation, temperature increase in the polypyrrole core led the drug payload to be released, causing controlled cell apoptosis. However, one of the major limitations of using NIR technique was the penetration depth in biological tissues. As an alternative strategy, magnetic stimulus-responsive systems were developed. Most MOF-based nanocarriers for this approach are usually composed of core-shell structure, e.g. iron oxide was often used as a magnetic core within a MOF shell. Importantly, the excellent magnetic properties from the core also enable biomedical imaging applications, e.g. MRI. For example, Fu and coworkers synthesised composite nanoparticles composed of Fe₃O₄ core and UiO-66 shell.¹¹⁷ The superparamagnetic Fe₃O₄ nanoparticles

enabled quick targeting by using an external magnetic field and demonstrated excellent MRI constructing ability. Simultaneously, the UiO-66 shell enabled the loading of anticancer drug, allowing theranostic applications to be realized. In another work, Sahu and coworkers designed Fe₃O₄-IRMOF-3 core-shell nanoparticles for theranostic applications.¹¹⁸⁻¹¹⁹ The nanoparticle composite was further functionalized with targeting molecules and loaded with anticancer drug. This work demonstrated that the combination of controlled drug delivery, MRI, and cell imaging in the multifunctional porous nanoplatform.

Biomacromolecules such as enzymes and DNA are an important class of therapeutic molecules receiving tremendous amount of attention. For example, gene and protein therapies have demonstrated their potential as the next generation therapeutic agents beyond synthetic drugs.¹²⁰⁻¹²² However, the use of MOFs as delivery vehicles for biomacromolecules are rare, although small biomolecules such as siRNA has been extensively studied in the literature.¹²³ Owing to the pore size restriction of most MOFs, bulky biomacromolecules were initially functionalized to the external surface of MOF particles.¹²⁴⁻¹²⁷ However, exposing fragile biomolecules directly to the biological environment may have detrimental effects to the biomolecules, ultimately leading to the loss of therapeutic effects. To address this issue, two general strategies have been developed to encapsulate biomolecules inside MOFs: 1) expanding the MOF pore sizes, and 2) introducing biomolecules during MOF synthesis. Up to date, several MOFs have been developed with pore sizes in the mesoporous size range for hosting biomacromolecules including proteins and enzymes.^{98, 128-130} However, they are limited by the choice of specific MOFs and the fact that MOF synthesis is generally complex.

Figure 8. Schematic highlighting the ability of MOFs to be mineralized around biomolecules for the encapsulation of intact proteins, enzymes, and nucleic acids. Figure reproduced with permission from Ref ¹⁰⁰. Copyright Nature Publishing 2015.

Recently, in situ formation of biomolecules/MOF composites were reported, showing new avenues of MOFs as delivery vehicles of biomacromolecules (**Figure 8**).^{100, 131} Following the successful encapsulation of proteins in situ, Liang and coworkers were the first to demonstrate the controlled delivery of proteins and DNA from MOFs.¹⁰⁰ In that work, various proteins and DNA were introduced into aqueous MOF growth solution. Due to the affinity of metal ions and organic ligands to the biomacromolecules, the MOF precursors were attracted around the biomolecules, leading to the rapid crystallization of a MOF coating around the biomolecules. This process eliminates the consideration of framework pore sizes by encapsulating biomolecules during MOF formation. Various proteins, enzymes and DNA were successfully encapsulated in ZIF-8, a pH sensitive MOF. At neutral pH, ZIF-8 is stable, whereas at pH 6, the protonation of 2-methylimidazole ligand lead to the framework disassembly, causing the release of biomolecules. Although non-therapeutic proteins and DNA were used in this proof-of-concept study, functional biomolecules such as polysaccharides, siRNA and therapeutic proteins is envisaged to be studied in the future.¹³² Very recently, Liang and Richardson, and coworkers demonstrated that protein patterns, whole living cells, and even multicellular organisms can be integrated with MOFs,^{19, 133-136} showing new prospects in cell therapy and cell manipulation.

Vaccines based on protein antigens have been developed recently with improved safety and effectiveness.¹³⁷ Although rare, MOFs have been used as vaccine delivery vehicles. For example, Zhang et al. studied ZIF-8 for vaccine delivery in vitro and in vivo using ovalbumin as a model antigen.¹³⁸ Ovalbumin was loaded in ZIF-8 during in situ MOF crystallization, followed by postsynthetic modification of the particle surface with unmethylated cytosine-phosphate-guanine oligodeoxynucleotides (CpG ODNs) to improve the biocompatibility and immunogenicity. The vaccine nanopartitcles elicited potent immune memory response, and both in vitro and in vivo experiments showed that the vaccines could induce strong humoral and cellular immunity. More recently, Sharad et al. demonstrated that MOFs can be loaded with CRISPR/Cas9 for efficient intracellular delivery of gene editing nanoparticles.¹³⁹ These studies highlight the potential of MOFs as efficient delivery vehicles for biomolecules.

Porous particles for treating drug resistant tumors via therapeutic co-delivery

Despite the wide promise of porous nanoparticles for therapeutic applications in humans, they have failed to be translated successfully into the clinic for a variety of medical reasons.⁶⁻⁸ This translational gap is present in part due to the much more advanced human immune system, and due to issues with using xenograft animal models that might not accurately reflect the tumor state in humans. Still, a particularly promising therapeutic application of nanoparticles is in combatting drug resistant tumors,¹⁴⁰⁻¹⁴¹ especially as the pores of porous nanoparticles allow for a variety of cargo to be simultaneously loaded.¹⁴² Of the particles covered in this review, MSNs are by far the most commonly used for combatting drug resistant tumors,¹⁴³ with various approaches highlighting the promise of porous particles for co-delivery and niche applications in drug resistant tumor treatment. For example, doxorubicin and siRNA can be co-loaded into MSNs¹⁴⁴ to combat drug resistant cells. Other approaches have focused on controlling the release profile of anticancer drugs rather than co-delivery. The pore size of MSNs can be changed, which modifies the release profile of the encapsulated drugs (doxorubicin). Although the exact mechanism for combatting drug resistance in cancer cells is not fully elucidated, larger pores allowed for the highest toxicity in drug resistant cancer cells.¹⁴⁵ Another approach utilized the

pH sensitivity of micelles encapsulated in MSNs to allow for gradual, pH-responsive release of doxorubicin after cell uptake, which allowed for improved cytotoxicity in drug resistant cancer cells.¹⁴⁶ Still another approach for combatting drug resistant tumors with MSNs has been realized by targeting the nanoparticles directly to the nucleus using a TAT-derived peptide in order to prevent the anticancer drug from being pumped out of the cytoplasm.¹⁴⁷

Similar to MSNs, CaCO_3 particles have been used to combat drug resistant cancers. For example, by loading two anticancer therapeutics (doxorubicin and paclitaxel) could be co-loaded into CaCO_3 particles stabilized with alginate.¹⁴⁸ The co-loaded particles showed ~30% superior cytotoxicity in comparison to free doxorubicin against drug resistant cells in vitro. Instead of co-delivering anticancer drugs, another approach is to co-deliver an anticancer drug (doxorubicin) with a drug resistance inhibitor (tarquidar), which can lead to improved cytotoxicity against drug resistant cancer cells in vitro.¹⁴⁹ Instead of co-delivering two small molecule therapeutics, P53 plasmids could be co-loaded with doxorubicin for effective in vitro killing of drug resistant cancer cells.¹⁴² The pores in CaCO_3 particles mean that more than two drugs can be loaded into a single particle, and Hai and coworkers demonstrated the versatility of porous particles by loading a variety of therapeutics. Gold nanorods for photothermal heating and light-triggered drug release were loaded in combination with doxorubicin, 17-AAG (anticancer therapeutic), afatinib (anticancer therapeutic), and anti-HER-2 antibodies (**Figure 9**).⁵ This combination allowed for controlled cytotoxicity against a variety of drug resistant cancer in vitro.

Figure 9. Schematic highlighting the versatility of CaCO_3 particles in loading multiple anticancer therapeutics. Figure reproduced with from Ref 5. Copyright Wiley 2016.

As MOFs have only started being used for drug delivery in the past decade, there are relatively few accounts of their use in combatting drug resistant tumors. Still, multiple approaches to combatting drug resistance have been realized, including co-delivery of drugs, delivery of protected siRNA, and photodynamic therapy.^{123, 150-151} For example, Chen et al. loaded the surface of Fe-based MOFs (MIL-101(Fe)) with Ru or Se nanoparticles and siRNA (**Figure 10**).¹⁵⁰ The nanoparticles and siRNA can interact with the metal sites in the MOF, and this coordination protects the siRNA from degradation. Two strands of siRNA targeted towards silencing genes responsible for multidrug resistance, VEGF and P-gp, were simultaneously loaded onto the MOFs, while the Se/Ru nanoparticles acted as anti-cancer agents. Drug resistant xenograft mouse models showed a reduction in tumor size after administration of the MOFs co-loaded with Se/Ru nanoparticles and siRNA, demonstrating the use of MOFs in combating drug resistant tumors. Other co-delivery strategies have also been realized using cisplatin and siRNA

for ovarian cancer.¹²³ Lin and coworkers utilized 3 different siRNAs and combined them with MOFs and cisplatin to overcome drug resistance in vitro. Lin and coworkers also used porphyrin-based MOFs used for photodynamic therapy to kill cancer cells resistant to cisplatin and radiation therapy.¹⁵¹ Radical oxygen species ($^1\text{O}_2$) were generated using visible light, and tumors in xenograft mice models showed severe reduction and even complete disappearance after multiple treatments with the MOFs followed by irradiation.

Figure 10. Mechanism of the reversal of drug resistance and induced apoptosis by the disruption of microtubules in MCF-7/T (Taxol-Resistance) cancer cells using MOFs. Figure reproduced with permission from Ref ¹⁵⁰. Copyright American Chemical Society 2017.

Although promising in many applications, MPNs have not been around long enough for use in combatting drug resistant tumors. It is foreseeable that a variety of approaches to combatting drug resistance would be possible with MPNs due to their versatile nature and incorporation of various functional building blocks, but only time will tell. Overall, porous particles are excellent candidates for applications in killing drug resistant tumors due to their high loading efficiency and ability to simultaneously load multiple therapeutics of different classes (e.g., small molecule, nucleic acid, nanoparticle, and antibody). Development should continue in this space as more porous particle systems move from in vitro to in vivo.

Porous systems for controlled release in agro-industrial applications: Biomass modification, protection and growth control.

Many of the challenges faced in medicinal drug delivery are mirrored in other fields. For example, the controlled release of active compounds has not been restricted to medicine as it has been an important technological upgrade to traditional agriculture practices resulting in new and improved bioengineered plants as well as enhanced delivery of fertilizers and biocides. It has been commonly observed that findings from drug delivery are translated, with some time delay, to agro-industrial applications. Specifically, delivery systems have been designed with two types of release kinetics: to accelerate the release of otherwise poorly soluble compounds (useful for short and quick remediation, such as for fungicide or foliar nutrients release), or alternatively to retard the release of soluble compounds (useful for long-term slow release of micronutrients, e.g. for fertilization). Delivery systems can be designed to carry small molecules through the plants cell walls in order to promote targeted-specific delivery and for *in vivo* labeling or imaging.¹⁵²

For agricultural applications, the interactions between the carrier material and the surrounding environment have to be taken into consideration including the effect of weather fluctuations that generally can be difficult to assess. Because of their relative chemical and biological inertness, porous inorganic supports are especially attractive for applications in the delivery of biocides (pesticides and herbicides), fertilizers, nucleotides, proteins, and other molecules of interest for agro-industrial applications (**Figure 11**).¹⁵³ Recent efforts have discussed the utilization of mesoporous silica, biogenic silica, and layered double hydroxides for such purposes. In parallel, calcium carbonate is currently used commercially for the controlled release of fertilizers;¹⁵⁴ however, the contribution of the porosity has not been thoroughly evaluated. The use of halloysite, porous tubular micro-scaled aluminum silicate, has generally been limited to the protection of bio-based materials.¹⁵⁵⁻¹⁵⁶ Greenhouse plant production, e.g. hydroponics, have smaller volumes of production, but a higher degree of control over external variables and considerably higher yields. Therefore, they could greatly benefit from more advanced porous delivery systems as a mean of providing both nutrients and biocides on demand. The nano- and micro-porous nature of these particles is associated with their high specific surface area, and is responsible for the increased density of binding sites between the active cargo and the porous particle, where the pores are often manipulated to promote controlled and responsive delivery.¹⁵³

Synthetic porous silica particles, especially MSNs, have been widely investigated for biocide delivery.¹⁵⁷⁻¹⁶⁰ In this case, the physicochemical characteristics of the mesoporous silica particles, i.e. pore size and surface area, are closely correlated to the biocide adsorption capacity and subsequent release rate.¹⁵⁸ In general, the preparation of silica delivery systems requires the cargo loading of pre-synthesized nano/micro particles using incubation in an appropriate solvent. Furthermore, more sophisticated synthetic silica-based biocide delivery systems have also been prepared to improve responsiveness¹⁰ and biocompatibility.¹¹ Redox responsiveness of such biocide delivery systems can be achieved by grafting short-chain decanethiol onto mesoporous silica as “gatekeepers” (see MSN section for more details on controlling cargo release from silica).¹⁶¹ In another study, silica capsules containing insecticide were used to achieve higher biocidal efficiency for termite control.¹⁶² Biocompatibility of the silica carrier is necessary in this applications so that foraging worker termites could carry the insecticide loaded silica over long distances to further spread it inside of the colony. To prepare this biocide delivery system, the insecticide was dissolved in an oil phase that was emulsified via sonication in the presence of a peptide surfactant, followed by addition of tetraethyl orthosilicate (TEOS) for silica shell formation. By controlling the amount of silica precursor and its condensation time, it was

possible to obtain shells with different thickness (8 to 44 nm), promoting tunable biocide release.¹⁶²

Figure 11. a) Schematic representation of important constraints to plant's growth in an agro industrial context. Namely, climatic conditions (UV, temperature and soil acidity), the presence of biological hazards (bacteria, insects, fungi or weed) and lack of nutrients. b) representation of the controlled release profiles of a compound of interest that would alleviate the hazards highlighted in a). c) Schematic representation of the delivery of RNA/DNA to plants via mesoporous particles. Adapted with permission from Refs ^{152-153, 163}. Copyright Cell Press 2016 and Elsevier 2017.

The utilization of mesoporous silica has also attracted attention as a vehicle for the bioengineering of plants.¹⁶⁴⁻¹⁶⁶ Bioengineering is one of the most interesting applications of mesoporous particles in agriculture-related fields, but is currently limited by the costly and sophisticated steps required for their preparation.¹⁶⁷ The possibility to control pore size and particle size through bottom-up routes can overcome barriers related to the uptake of particles by plants, which is limited by the morphology and composition of plant cell walls and tissue.¹⁶⁸⁻¹⁶⁹ The size of the endocytic vesicles, which are responsible for transportation of molecules into the plant cells, vary considerable between plants from 0.2 to 3 μm . Thus, the delivery system needs

to be designed according to the targeted plant tissue. A parallel can be drawn with human drug delivery where the kidney filtration is around ca. 5 nm and the lung fenestration lies at around 200 nm leading to an optimal size range for particles between 5 nm and 200 nm.¹⁵² Also, the surface chemistry of the particles (carriers) plays a fundamental role in plant cell endocytosis as it does in mammalian cells.¹⁶⁴ For instance, the topography of a plants' surface varies significantly which can result in everything from iridescent colors to superhydrophobicity to adhesive properties.¹⁷⁰ Using a controlled surface chemistry, delivery systems can be designed to induce plant defense mechanisms in response to biotic (insects, bacteria, fungi) or abiotic (such as UV or acidity of rain) stress,¹⁵² as well being used for genetic modification.¹⁷¹⁻¹⁷³

For agro-industrial applications, one of the most promising inorganic architecture is bio-based (biogenic) silica as a support for the controlled release of biocides and fertilizers. Porous biogenic silica particles can be obtained from biorefinery platforms of Si-accumulating plants such as horsetail¹⁷² and rice husk.¹⁷⁴ Their fractal-like architectures results in specific surface areas of up to 400 m² g⁻¹. Whereas it is an important consideration for controlled release in animals, the very large polydispersity of biogenic silica has no negative consequences for agricultural applications, and allows for the preparation of simple and cheap delivery systems without any associated synthesis hazards. Some good examples of biogenic porous delivery systems are the preparation of a biopesticide delivery system via poly carboxylic acid mediated cross-linking between silica and neem bark extract,¹⁷⁵ cellulose and silica nanocomposites for tebuconazole release,¹⁷⁶ and straw ash (biochar and biogenic silica) to control chlorpyrifos loss by leaching and volatilization.¹⁷⁷ Other combinations between polysaccharides and inorganic particles have been applied for controlled release, such as the combination of starch and alginate with kaolin and bentonite to form porous beads to entrap and release biocides.¹⁷⁸

Layered doubled hydroxides (LDH) are also a porous system of interest to improve the delivery of nutrients to plants. Their ionic exchange characteristics can be useful for the remediation of soils and ground water.¹⁷⁹ For instance, LDH can be used for selective phosphate removal or for the controlled release of fertilizers.¹⁶³ Furthermore, as the layered double hydroxides are nanoparticles composed of sheets of adjustable sizes, they can also be used as carriers for the delivery of biomolecules into plant cells.¹⁸⁰ The immobilization of biomolecules of interest in-between the platelets is a way to transport them through cell walls with minimal damage, without loss of efficiency, and without unspecific reaction to non-targeted tissues.¹⁸¹ Both LDH and halloysites have also been used to control the release of an herbicide, showing similar release profiles and efficiency.¹⁵⁶

Overall, the pharmaceutical developments of the last decades are a significant source of inspiration for agro-industrial delivery applications. Nevertheless, the biology of plants varies from that of humans and the conditions for delivery are affected by significantly different parameters. The principal differences lie in the unique surface chemistry of plants. The human body has a strong immune system it will interact and process readily most of the delivery systems it ends up in contact with, whereas plants' surface can have limited wettability and topology, which minimize the endocytosis of surface adsorbed particles. Additionally, whereas long term toxicity is a common concern both for delivery in plants and humans; pollution, climatic conditions, local fauna and flora wellbeing, and soil types are concerns unique to plant delivery.

Outlook

Porous particles have demonstrated versatility in a wide range of therapeutic applications including human and agricultural drug delivery. The general focus when designing porous particles for therapeutic delivery has been on safe and biocompatible particles, however it is likely that future developments will harness inherent properties of the particles as therapeutics in themselves. This could be done by doping in additional metals during inorganic particle synthesis, or through utilizing therapeutic organic ligands for hybrid porous particles. The current target of tackling drug resistant cancers has many parallels to targeting drug resistant bacteria, fungi, or agricultural pests. Therefore, we believe the design principles surrounding drug delivery with porous particles will be incorporated into a wide variety of delivery fields and may even show potential in disparate fields like catalysis and energy. Conversely, the porous materials mentioned above are often used for catalysis and energy applications, and breakthroughs in these fields could help guide developments in drug delivery. For example, metal containing porous particles (MOFs and MPNs) can perform unique catalysis and redox reactions and scavenge radicals through the incorporation of biofriendly metal ions into the particles.¹⁸²⁻¹⁸⁵ Conducting metal-based catalytic reactions inside of the body and inside tumors may offer a unique way forward in fighting cancer and combatting multidrug resistant tumors.

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