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Ultrasonic Encapsulation – A Review

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Highlights

- Ultrasonic preparation of encapsulated functional materials is reviewed.
- Mechanisms responsible for expression of functional properties are described.
- Promising applications for ultrasonically synthesized materials are identified.

Keywords: ultrasound, encapsulation, functional foods, bioproducts, emulsions, sonoprocessing, responsive polymers

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Abstract

Encapsulation of materials in particles dispersed in water has many applications in nutritional foods, imaging, energy production and therapeutic/diagnostic medicine. Ultrasonic technology has been proven effective at creating encapsulating particles and droplets with specific physical and functional properties. Examples include highly stable emulsions, functional polymeric particles with environmental sensitivity, and microspheres for encapsulating drugs for targeted delivery. This article provides an overview of the primary mechanisms arising from ultrasonics responsible for the formation of these materials, highlighting examples that show promise particularly in the development of food and bioproducts.

1. Introduction

Ultrasonics is a versatile technology with proven effectiveness to create a range of catalytic and functional materials that have applications across a multitude of fields including food [1], imaging [2], energy production [3] and therapeutic/diagnostic medicine [4]. The primary mechanism responsible for the creation of these materials is known as acoustic cavitation, which is the formation and collapse of bubbles influenced by ultrasound [5]. Ultrasound's versatility is owed in part to its broad active frequency region that can be tuned and applied specifically to control the intensity and number of cavitation events. These can be used to control aspects of materials such as particle size, surface roughness and structure.

Ultrasound can be used to promote the internalization of materials through a process known as encapsulation. The motivation for encapsulation is to protect, prolong or stabilize the internalised material from environmental deterioration and enables pharmaceuticals and/or nutrients to be delivered with enhanced efficacy in biological systems. These delivery systems take a number of different forms. A simple example found in foods is an emulsion [6]. The dispersion of an oil within water enables effective loading of oil soluble nutrients into aqueous food media, and is a useful strategy for preparing functional food products. Another example is the use of environmentally sensitive polymers to create core-shell structures that can be used to entrap materials such as drugs [7]. These polymer delivery agents respond to changes in pH, temperature or other external stimuli such that they release entrapped drug material only under specific conditions, thereby prolonging drug efficacy. These polymers can be synthetic or natural, such as proteins. Microspheres and microcapsules made from proteins have the advantage of being bio-compatible and bio-degradable, and have been extensively studied for pharmaceutical applications [8].

Whilst there are a number of reviews [4, 6, 7] covering the formation of different types of encapsulated materials, there has yet to be a review that brings together these different systems with details on how to effectively create them using ultrasonics. This review will provide a guide towards the application of ultrasound to promote encapsulation of materials, focusing on examples of relevance to the food, biomaterial and pharmaceutical industries.

2. Theory of applied ultrasound

This section provides an overview of the principles of ultrasound. A focus is made on the key physical and chemical effects of ultrasound in aqueous systems to provide background for the

subsequent discussion on the application of ultrasound-promoted encapsulation in aqueous systems.

2.1 Characteristics of ultrasound

Ultrasound is generally defined as sound at frequencies above 16 kHz. It is (generally) not audible when transmitted through the air. When sustained through a liquid medium (e.g. water), the ultrasonic pressure oscillations may cause in-phase expansion and contraction of the dissolved gas bubbles i.e. the bubble expands during the negative pressure cycle and contracts during the positive pressure cycle. This bubble oscillation is accompanied by diffusion of gas/vapour in and out of the bubble during the expansion and contraction respectively. The diffusion of gas in and out of the bubble is not equal [9] and under certain conditions, i.e. oscillation driven above a certain threshold pressure, the diffusion process can result in net accumulation of mass within the bubble over time. This results in net bubble growth and is known as rectified diffusion, a process unique to bubbles oscillating within a sound field. In a field containing multiple bubbles, the interaction of bubbles by collisions combining to form a larger bubble can also result in what is known as coalescence, and is another source of net bubble growth in an acoustic sound field [10].

Both rectified diffusion and coalescence cause bubble growth. Bubbles within a sound field will grow in size until they reach what is known as the bubble resonance size range, at which point they collapse. This formation, growth and collapse of a bubble due to the influence of ultrasound, is known as acoustic cavitation [5].

Of interest to material synthesis, the collapsing bubbles produce localised regions of extreme temperature and intense physical shearing. Bubbles driven at low ultrasonic frequency (~ 20-100 kHz), may collapse extremely violently, releasing sufficient energy to produce temperatures up to 10,000 K within the bubble core and pressures of several hundred atmospheres within a few hundred micron of the bubble collapse point [11]. This can lead to the formation of highly reactive radicals which can be used to promote chemical reactions. In water for example, hydrogen and hydroxyl radicals can be formed due to the splitting of the water molecule by pyrolysis. Both the physical shear and radical formation can be beneficially exploited to create materials with a range of desired functionality.

The ultrasound frequency regime ranges from 16 kHz to 500 MHz, although the frequency range most suitable for processing fluids is typically between 16-3000 kHz. When ultrasound is applied to fluids the cavitation effects are highly dependent on the frequency. The intensity of bubble collapse (i.e. amount of energy released) and the maximum bubble size prior to collapse (resonance size) are correlated and approximately inversely proportional to the applied frequency [12] (see Figure 1).

A simple relationship that can relate the resonance size of the bubble with the frequency is given by:

$$F \times R \approx 3 \tag{1}$$

where F is the frequency in Hz and R is the bubble radius in m. Note that this equation gives only a very approximate theoretical resonance size and that there are other factors which may control the resonance size of the bubble [5, 13].

A more accurate version of (1) is the linear resonance radius which can be calculated using the following equation [13]:

$$R_r = \sqrt{\frac{3\gamma p_\infty}{\rho_L \omega^2}} \tag{2}$$

where γ is the specific heat ratio of the gas inside the bubble, p_∞ is the ambient liquid pressure, ρ_L is the liquid density and ω is the angular frequency of ultrasound (all in SI units). In practice, the size for an active bubble is usually smaller than this radius due to the nonlinear nature of the bubble pulsation [14].

Ultrasound can be categorized into several different regions along the frequency spectrum. The *power ultrasound* region [12] spans the low frequency range between 16 – 100 kHz. It is characterized by large bubble resonance sizes followed by intense bubble collapse, often resulting in extremely strong physical effects including localized shear and high temperatures. This category of ultrasound delivers high energy density in the order of 10-1000 W/cm^2. Power ultrasound is often selected for material processing and to some extent in synthesis, owing to its strong physical shear and intense local temperature effects. Examples of processes in this

region include emulsification [15], homogenization [16], cell disruption [17] and polymerization [18].

The region between 100 - 1000 kHz is usually labelled *intermediate ultrasound*. This region results in only moderately intense bubble collapse, but importantly produces the most 'sonochemically active' bubble population that results in highly efficient radical production. Koda et al. [19] and Mason et al. [20] have shown that peak radical production occurs somewhere between 400 - 800 kHz, although it also depends on the power applied and the physical and chemical properties of the fluid system. This intermediate ultrasound region is selected when chemical modification is the primary goal.

Above 1000 kHz, the physical effects of bubble collapse become relatively benign due to small bubble resonance size prior to collapse and a reduced proportion of bubbles undergoing cavitation due to an increased cavitation threshold. The cavitation threshold refers to the pressure (or size) above which bubble nucleation, a necessary precursor to cavitation, occurs. However, despite a reduction in cavitation, radical formation is still possible at frequencies around 1000 kHz [21] provided that sufficient energy intensity is employed. This regime, typically labelled the *diagnostic* or *megasonic* region, is used if only gentle physical effects are desired. It is particularly suitable for applications such as selective particle separation [22], where the aim is to also preserve the natural integrity of the separated product.

2.2 Radical formation and sonochemistry

The concentrated energy released during bubble collapse can split solvent/solute molecules that have diffused into the bubbles, to form radical species. For water, the following reaction may take place [23]:

$$H_2O \rightleftharpoons \dot{H} + \dot{OH} \tag{3}$$

That is, water molecules can be split into highly reactive hydrogen and hydroxyl radicals. Direct splitting of water as described above requires high temperatures resultant from high intensity bubble collapse typically seen only in the power ultrasound region. Alternate reaction pathways in water have been described by Yasui et al. [24] that allow for hydroxyl radical production even at relatively low bubble temperatures that are typical of intermediate ultrasound.

These radical species can be used to induce a whole range of redox reactions. As such, ultrasound can be used in organic synthesis reactions in which radicals are used to initiate and increase the reaction rates. Ultrasound has also been successfully used to increase yield by inducing modified reaction pathways that favor the formation of specific reaction products [4].

The radicals formed through cavitation can be used to initiate and accelerate the rates of free-radical polymerization and copolymerization [18], meaning that in some cases the use of ultrasound can obviate the need for a chemical initiator. Methyl methacrylate for example, can be polymerized by ultrasound without the use of an initiator [25], creating polymers with a molecular weight of up to 400,000 Da. Ultrasound-induced polymerization can however be complicated by the fact that the resulting polymers can also be simultaneously broken down by the intense shear forces resulting from the collapsing bubbles. These fragmented polymers may subsequently react to form side-products that may be quite different to conventional polymerization in the absence of acoustic cavitation.

Proteins are biological polymers that can be cross-linked to form larger networks and structures by ultrasound. These networks can be used to coat bubbles, droplets or other templates, forming rigid spheres that can be used for encapsulating materials for applications such as drug delivery [8]. The formation of protein microspheres by application of ultrasound results from a combination of shear-induced emulsification and radical formation [26, 27]. The high shear and temperature can partially unfold the proteins [28] which can then accumulate at the air or organic phase boundary and undergo cross-linking [27]. The protein cross-linking can be reversible, for instance through hydrophobic interactions and hydrogen bonding, or irreversible if covalent links are produced, for example disulphide bonds. In the latter case, this can potentially be facilitated by free radicals generated through ultrasonic cavitation [29].

Ultrasound can also be used to lower the temperature or pressure of some reactions, or reduce the requirement for solvents, which are expensive and often toxic. As such, ultrasonic synthesis techniques are often considered as ‘green chemistry’ alternatives for many applications [25].

2.3 Physical effects of ultrasound

Physical modification of materials by ultrasound can arise from the shear forces generated during bubble collapse that are associated with pressure shockwaves, liquid microjets and acoustic streaming. Acoustic streaming is the propagation of disturbances in the fluid caused

by the ultrasonically induced oscillation of gas bubbles. This results in localized shear forces in the immediate vicinity of the bubbles. Liquid microjets result from the asymmetric and extremely rapid collapse of bubbles during cavitation, leading to unidirectional expulsion of high velocity jets into the surrounding fluid. Naude and Ellis [30] first hypothesized that the observed pitting of solid surfaces and particle size reduction of colloids on exposure to ultrasound was in fact due to the formation of microjets during assymetric bubble collapse. It has since been shown that microjets with velocities in the order of 100 m/s can be formed [31], and that these can create pitting and erosion of surfaces [25]. Microjetting is also the primary cause of ultrasound-induced bulk mixing. Symmetric bubble collapse generates shockwaves that propagate radially outwards from the collapse point into the surrounding fluid. These shockwaves can be used to increase the rates of mass transfer across interfacial boundaries, enhancing the efficiency of multi-phase reactions [25]. All of these physical effects are commonly utilized in laboratory ultrasonic baths to facilitate cleaning of surfaces and dissolution of solids.

Although collapsing bubbles may reach temperatures of many thousands of degrees Celsius, these extreme temperatures are confined to small areas at the core of the collapsing bubble and near the bubble surface [32]. In the bulk solution, the increase in temperature resultant from a single bubble collapse is small. Nevertheless, the dissipation of heat from many cavitation bubbles, vibrating transducer surfaces, shockwave propagation and acoustic streaming can all contribute to incremental increases to the surrounding bulk temperature. If required, temperature control (e.g. a cooling jacketed reactor) can be used to prevent undesired temperature effects, e.g. denaturation of proteins in foods.

The physical forces resultant from cavitation can increase particle interactions in suspensions [25]. Solid powders suspended in fluids, may experience an increase to their momentum in the vicinity of a cavitation bubble, which can cause them to collide together with greater force than under quiescent conditions. Inorganic solids can be fractured and disrupted upon collision, leading to a reduction to their average particle size [25]. The minimum size achievable is dependent on characteristics of the solid, solvent and cavitation intensity. The lower limit is reached when the momentum of the particles become too small to create further impacts to cause particle fragmentation.

Ultrasound can be used to form encapsulating particles over a broad range of sizes, from around 100 nm to 20 μm in diameter. The particle size can be controlled to a large extent by selecting

appropriate sonication conditions such as power intensity, frequency and reactor configuration. The duration of processing [33] , the type of reaction vessel [15] and sonifier used [34] are also variables that control the size of the particles that are formed. Importantly, in addition to being able to target a desired average particle size, ultrasound is able to produce particles with a narrow size distribution. For example, it has been shown that the use of a flow-through horn system could generate lysozyme coated nanospheres of very narrow size distribution ranging between 550-650 nm, compared with a larger 3 mm ultrasound horn that resulted in formation of particles with a broader range between 850-1200 nm [34]. Zhou et al. [35] also used high frequency ultrasound as a post-sonication technique to further narrow down the size distribution of ultrasonically-generated microspheres. By using 213 kHz ultrasound, lysozyme microspheres with a distribution of initially 0.5-4 μm were narrowed to 0.5-2 μm due to selective breakage of the larger microspheres by the ultrasound .

3. Applications of ultrasonic encapsulation

Ultrasonics can be used to promote specific functionality in different materials. For example, in foods comprising emulsions, the shelf-stability and physical appearance are dependent on the droplet size of the dispersed phase. Ultrasonics can be used to disperse different organic/oil phases into various aqueous phases in a controlled manner, to create emulsified products that are very shelf-stable and attractive in appearance [6]. Ultrasonics can also be used to promote the formation of polymer systems that are responsive to specific environmental conditions, such as pH and temperature. These polymer systems are useful for controlling drug release in biological systems. A combination of emulsification and polymerization can be promoted by ultrasound to form protein cross linkages, resulting in the formation of protein microspheres. These entities can be made biocompatible and biodegradable to enable their use as drug-delivery vehicles. This section will describe the effect of ultrasound on important functional properties of food emulsions (3.1), polymer particles for controlled drug release (3.2), and protein microspheres (3.3).

3.1 Functional food emulsions

Droplet size and polydispersity are key attributes that govern the functionality and stability of emulsions. The intense shear forces generated during ultrasonic cavitation can be used to create emulsions with very small and relatively uniformly sized droplets [36]. Two mechanisms are responsible for the emulsification effect of ultrasound. First, the application of the sound field

produces interfacial waves, which become unstable resulting in the dispersion of the oil phase into the continuous water phase as mid- to large-sized droplets. Secondly, the physical effects resultant from cavitation break up these initially formed droplets of dispersed oil into droplets of sub-micron size [25].

Ultrasonics is particularly useful for the production of, for example, food emulsions. In food emulsions, the size of the emulsified droplets influences its visual appearance, mouth-feel and shelf-life stability among other things [6]. Whereas large sized emulsion droplets are characterized by a 'milky' opaque appearance, emulsions with emulsion droplet size (EDS) smaller than ~ 100 nm, can appear translucent and almost clear [15] due to the reduction in light scattering by the smaller droplets.

While emulsions are inherently thermodynamically unstable, when the droplets are smaller than ~ 100 nm they become kinetically stable [37]. At these sizes, the Brownian motion of the droplets overcomes the natural buoyancy force of the droplets to rise and cream. The instability is dependent instead on colloidal forces such as Ostwald Ripening [38] and droplet-droplet collisions that leads to coalescence and eventual phase separation. These are usually very slow processes, such that nano-sized emulsions are shelf-stable for many months [39].

The formation of nano-sized droplets requires the application of strong shear forces to break apart the liquid droplets. This is typically achieved using low frequency ultrasound in the *power ultrasound* region (20-100 kHz) delivered at high energy intensity > 10 W/cm^2. The emulsified droplets then need to be stabilized by a surfactant in the system, to prevent spontaneous phase separation by coalescence [15]. Midsonic and megasonic frequencies > 400 kHz are usually ineffective at forming emulsions, due to insufficient physical shear forces arising from the collapse of smaller resonance size bubbles at these frequencies.

Higher frequency ultrasound (midsonic to megasonic) has however been reported useful at forming nano-size emulsion droplets when applied following low frequency ultrasound through a process known as *tandem acoustic emulsification* [39, 40]. Oleic acid/water nano-emulsions were prepared by Kamogawa et al. [40] using this technique, while Nakabayashi et al. [39] also reported the production of transparent emulsions of ethylenedioxythiophene (EDOT) monomer formed by sequential emulsification at 20 kHz, 1.6 MHz and 2.4 MHz ultrasound. The nano-emulsions formed by Nakabayashi et al. were stable even in the absence of additional surfactant for 1 to 2 years. These nanoemulsions are not only stable and attractive

267 in appearance, but can be used to conduct direct electropolymerization (see Section 3.2) in the
268 absence of additional surfactant [41].

269 It was proposed that the small droplets achieved in tandem acoustic emulsification upon
270 application of higher frequency ultrasound was not due to destructive shear forces such as
271 microjets and shockwaves prominent at low frequency ultrasound. Instead, it is due to the
272 enhanced acceleration of solvent and the emulsion droplets caused by acoustic radiation forces
273 and acoustic streaming [40] such that they collide together and break apart into smaller
274 droplets. These acceleration forces become stronger with increased frequency, and the
275 sequence in which the different frequencies of ultrasound are applied is noted to be important,
276 with reversal of the order (i.e. high frequency followed by low frequency) resulting in
277 ineffective emulsification.

278 Oil-in-water and water-in-oil emulsions can both be produced successfully using the tandem
279 emulsification technique. Although the application of tandem acoustic emulsification has yet
280 to be reported for food applications, it would be an attractive avenue for creating nano-sized
281 surfactant-free emulsions.

282 For foods, the EDS plays a significant role in the sensory characteristics [42]. In general,
283 emulsions containing smaller droplets have a higher viscosity [42] which are purported to
284 provide improved sensory properties such as ‘creamier’ mouthfeel [6] in a range of products
285 such as cheese [43] and creams [44].

286 Emulsions can be used to load hydrophobic or amphiphilic materials with biological
287 functionality or nutritional benefit into an aqueous fluid. In the case of amphiphilic materials,
288 it may be desirable to maximize the surface area of the droplets by reducing the emulsion
289 droplet size. Smaller droplets are also better at retaining a larger amount of volatile material
290 within the oil phase of an emulsion during spray drying for the production of encapsulated
291 microparticles [45]. This is because the smaller emulsion droplets are less likely to be broken
292 apart by the atomizer within the spray dryer [45]. Spray dried encapsulating microparticles can
293 be used to create products that are able to mitigate the release of undesirable odors or smells
294 e.g. fish oil powders.

295 Another way to encapsulate materials in emulsions is to create what is known as a double
296 emulsion. Double emulsions are emulsions entrapped within emulsions. Their capacity to
297 encapsulate aqueous components within oil droplets makes them promising delivery vehicles

298 for bioactives, for flavour masking and for fat reduction in foods [46]. The entrapped inner
299 phase is protected from degradation by environmental factors in the external phase, and release
300 of inner material can be delayed until it enters the digestive system, thereby masking potentially
301 undesirable flavours. Fat reduction can achieved without compromising the sensory properties
302 of the fat phase by displacing fat without reducing the apparent volume fraction of the fat
303 droplets.

304 There is significant commercial interest, with a large number of examples having been
305 developed for the production of flavour-enhanced and reduced-fat salad dressings [47], and
306 also reduced-fat cheese [48-50]. Instability is a potential issue for using double emulsions in
307 food applications. Rapid phase separation can arise due to the relatively large droplets
308 (typically greater than 20 μm) [51] that are formed at the low shear rates which are required to
309 avoid release of the entrapped material. This issue may be resolved to an extent by use of
310 ultrasonication as reported by Tang et al. [52, 53]. Ultrasonication was successfully used to
311 form double emulsions of sub-micron size range for the purpose of aspirin encapsulation,
312 achieving both high stability (1 month prolonged storage) and entrapment yield (up to 99%
313 encapsulation) [53].

314 The use of ultrasonics has been compared with most conventional and state of the art
315 emulsification techniques. Some of the more common methods applied in industrial
316 emulsification are rotor-stator systems [54] and high pressure homogenization [55]. In addition
317 to conventional high pressure homogenization, a modified technology known as the
318 Microfluidizer^{TM} involves impinging two pressurized streams against each other. The
319 Microfluidizer^{TM} (MF) has been shown to be highly effective at nano-emulsion preparation
320 [56-58]. MF has relatively high energy efficiency for producing emulsions with very small and
321 narrowly distributed EDS [57] and is commonly used in the pharmaceutical industry to make
322 nano-emulsions. Madhi Jafari et al. [57] have compared emulsion preparation using US at
323 matched specific energies with MF, and found comparable performance. It was found that
324 when using matched 20 kJ/kg energy input, particle size reduction by MF achieved mean
325 volume-weighted particle size of 0.83 μm compared with 1.02 μm for ultrasonication at 20
326 kHz.

327 Emulsification by ultrasonication and MF occurs via common causal mechanisms including
328 cavitation and shear [58]. Although MF has been noted to be superior in size reduction and
329 generating emulsions with more narrow size distributions, ultrasonication is deemed to be

significantly easier to operate, clean and maintain [57]. With extended duration of processing, ultrasonication has been shown to be able to achieve comparably small emulsion droplets to MF [58]. Leong et al. [15]. demonstrated the capability of ultrasound to produce emulsions with comparable particle size to microfluidization, provided that the energy density and surfactant system was optimized.

Typically, the formation of emulsions requires a large amount of surfactant to cover the newly formed surfaces and hence stabilize the dispersed droplets. The tandem-emulsification technique reported by Nakabayashi et al. [39] and Kamogawa et al. [40] is exceptional in that ultrasound can produce nano-sized emulsions in the absence of surfactant, although the technique is yet to be proven for a wide range of oils. Recently, Shanmugam et al. [59] have shown that ultrasonic emulsification can be used to create stable food-based emulsions of flax seed oil directly in skim-milk without the requirement for additional surfactants. The native milk proteins are partially denatured (less than 1%) by the ultrasound and allowing them to effectively coat the formed oil droplets, stabilizing the emulsion for at least 7 days. Emulsification could not be achieved in the absence of ultrasound even when using matched applied energies in a rotor-stator system, suggesting the importance of acoustic cavitation to the stabilization process.

3.2 Formation of polymeric particles for controlled drug release

In the treatment of certain diseases, drugs must be delivered at rates corresponding to the physiological needs of the patient. In conventional drug delivery, the concentration of the drug within the patient's blood stream rises, peaks then declines. Each drug has a different concentration above which it becomes toxic and below which it is rendered ineffective. Controlled drug release is desirable in treating certain illnesses, as it enables maintenance of a drug within a desired therapeutic range with a single dose that is responsive to the needs of the patient.

Polymer-based materials that are sensitive to environmental factors such as temperature, pH and ionic strength, have potential to be used as responsive drug delivery vehicles [7]. If the structure of the polymer can be externally regulated (e.g. by magnetic, ultrasonic, thermal and electric stimulation) or self-regulated (i.e. by changing environmental conditions), it is possible to release the entrapped drug in a controlled manner. Ultrasonics has been investigated as a tool to assist in synthesizing such polymers with a range of functionality. For a more detailed

review of ultrasonically enhanced synthesis of polymers, readers are invited to read the review by Price [18].

As described in Section 2, acoustic cavitation leads to both chemical and physical phenomena that can be controlled to create polymers with improved rates of reaction and more defined characteristics such as molecular weight. Radical polymerization is one of the most studied [18] sonochemically-enhanced polymerization processes. The radicals formed during acoustic cavitation can be used to initiate the polymerization process in place of conventional initiators [60, 61]. A particular system in which this has been successful is in vinyl monomers such as methyl methacrylate [62]. Another notable advantage of generating radicals using ultrasound is the ability to perform the reaction at reduced temperatures (i.e. between -10 to 60 ^{o}C compared to between 50 to 100 ^{o}C for more conventional radical polymerization reactions of PMMA).

The physical effects of ultrasound can be used to control various properties of the resulting polymer. The intensity of the ultrasound applied, which influences the strength and number of acoustic cavitation bubbles, is one variable that can be modulated to control the yield of polymer produced as well as the final molecular weight of the resulting polymer [63]. A larger number of collapsing bubbles creates more radicals, which can increase the frequency of polymer initiation events. Simultaneously, the shearing forces resultant from the collapse of bubbles can break apart some of the long polymer chains that are formed, effectively reducing the molecular weight of the final polymer. The intensity of collapse, and the duration over which sonication is applied, can control the molecular weight of the polymers [63]. The ability to influence the polymerization process by manipulating ultrasound variables provides scope to transform conventional polymerization processes to form new materials. It should be noted though that sonication has little to no effect on the actual propagation reaction of the polymer formation. The main effects are largely confined to the initiation process and subsequent chain breakage of the formed polymer chains.

Ultrasound can promote emulsion polymerization to form latex particles of approximately equal size to the emulsion droplets [64]. The latex particles formed by ultrasound are typically smaller than those formed by conventional emulsion polymerization, resulting in an increased surface area [65]. Further, the use of ultrasound removes the need for chemical initiators or co-stabilizers, reduces the required reaction temperature, increases the rate of polymerization and results in higher monomer conversion and potentially higher molecular weights. As a number

of these advantages reduce chemical and energy consumption, ultrasonic emulsion polymerisation can be considered a 'green' alternative to conventional polymerization reactions. A proposed mechanism for ultrasonically-promoted emulsion polymerization is presented in Figure 2.

Ultrasonic emulsion polymerization has also been used to create latex coated magnetic nanoparticles using a simple, one-step method [66]. The particles exhibited colloidal stability for up to 12 months with no observed deterioration, and strong magnetic properties. The suspensions behaved as conventional magnetic fluids in their response to a magnetic field.

Temperature responsive polymers of poly(N-isopropylacrylamide) and poly(N-vinylcaprolactam) have been prepared using ultrasound, and their swelling behavior in the presence of different concentrations of surfactant (SDS) studied [67]. The potential for these types of polymers to be used as drug delivery vehicles was demonstrated by their ability to entrap rhodamine B dye. The structure of these polymers is temperature dependent. At 20 °C, the polymer chain is an expanded coil that is soluble in water resulting in clear aqueous solutions. When heated to 32 °C, the chains collapse to a globular structure which decreases the solvation properties causing the polymer solution to become turbid. The release kinetics of the entrapped rhodamine B was consequently found to be dependent on the temperature, with higher release rates occurring at 40 °C compared with 20 °C [67]. The release of dye was found to follow Fickian diffusion kinetics, with the diffusion coefficients being 4 x 10^{-12} and 3.6 x 10^{-11} m^2/s at 20 °C and 40 °C respectively i.e. an order of magnitude increase in release rate. There was an apparent limit to the maximum amount of dye release (approximately 62 %), which was attributed to the concentration gradient of the dye within the polymer and bulk solution approaching zero.

3.3 Formation of protein-coated microspheres

Ultrasonics have been used to prepare protein microspheres, which have a wide range of potential biomedical applications including acting as echo contrast agents for sonography and magnetic resonance imaging, and as vehicles for drug delivery [4]. These microspheres (typically several μm in diameter) consist of a protein shell surrounding a core which can be either a gas or a liquid. The solid shell is a barrier to permeation between the interior phase and the aqueous exterior, conferring long term storage stability to the protein microspheres.

Protein microspheres are formed by a combination of two acoustic phenomena: emulsification and cavitation. In the emulsification stage bubbles or liquid droplets are created, which acts as a 'template' for the protein shell to form around. The radicals produced by acoustic cavitation lead to the formation of superoxide species which promote the formation of intermolecular disulphide crosslinks between the proteins covering the interface. It has been shown that emulsification alone (via vortex mixing) was not sufficient to produce long-lived microbubbles, indicating that chemical cross-linking arising from ultrasonic cavitation was required to produce stable protein microbubbles [26].

One of the first commercially available protein microspheres were albumin-coated microbubbles, marketed under the name Albunex® and Optison™ [8]. These microspheres have been used primarily as contrast agents for ultrasound imaging, with the air-filled core providing enhanced signal response.

Protein microspheres can be used as drug delivery vehicles with therapeutic agents either loaded on the surface of air-filled protein microspheres, or if liquid filled, entrapped within the liquid phase of the protein microsphere. Of importance for drug delivery, they are inherently biodegradable and likely to be more biocompatible than microsphere made from synthetic polymers. They can also be functionalized with ligands (e.g. antibodies, peptides or vitamins) to target specific entities within the body.

To achieve further functionality, proteins may be used that infer useful biological properties to the formed microspheres. Cavalieri et al. [27] first reported the formation of lysozyme protein microspheres which were stable for several months using a sonochemical approach. Lysozyme, derived from hen egg white, has natural anti-microbial properties and the microspheres formed from lysozyme were found to retain some of the enzymatic functionality and anti-microbial activity of the native protein. This work by Cavalieri et al. [27] confirmed the need to release free thiol groups via partial protein denaturation in order to initiate crosslinking required to stabilize protein microspheres (Figure 3). Alternatively, the microbubbles can be used as a carrier for antibiotics. Avivi et al. [68] encapsulated tetracycline into bovine serum albumin-coated microspheres using a sonochemical approach, and found that up to 65% encapsulation efficiency could be achieved. Importantly, it was found that the majority of the encapsulated tetracycline, approximately 97%, was loaded within the core of the bubble and not simply adsorbed to the surface of the protein microspheres. Avivi et al. [68] confirmed that the

antimicrobial activity of the entrapped tetracycline when released by gentle heating was identical to equivalent amounts of free tetracycline when applied to different strains of bacteria.

Zhou et al. [69] used the same approach to create liquid-encapsulating lysozyme microspheres loaded with various oils (sunflower oil, tetradecane, dodecane and perfluorohexane). Liquid-filled microspheres can theoretically be loaded with significantly larger quantities of oil-soluble drugs, than air-filled bubbles where the active drug component needs to be functionalized on the surface of the bubble. The type of liquid encapsulated in the microspheres was found to influence the physical properties (i.e. size, polydispersity, and shell wall strength) of the formed microspheres.

The approach used to synthesize lysozyme microspheres can be extended to the synthesis of protein-mimicking polymer-coated microspheres. Cavalieri et al. [29] first reported a one-step sonochemical process to synthesise microspheres made from synthetic thiolated polymers of polymethacrylic acid. Important physical properties of the formed microspheres could be controlled by adjusting the thiol content in the macromolecules. The size, surface roughness, and shell thickness were all found to increase with increasing number of thiol groups in the monomer backbone. Recent work has further demonstrated the versatility of this method with the fabrication of new types of microspheres, including chitosan/titanium dioxide hybrids [70]. These hybrid microspheres have composite properties including high mechanical strength and antibacterial activity.

The size of the active sonochemical region delivering the ultrasound has been shown to effect the size distribution of formed microspheres, offering a means of controlling size [34]. In this study, a novel flow-through sonication horn with a very small active sonochemical region created smaller and more monodisperse microspheres than larger diameter horns with larger sonochemical regions.

In addition to promoting the formation of protein microspheres, ultrasound is a potential tool for targeted drug release. Ultrasound has been shown to break apart chitosan/titanium oxide hybrid nanospheres, releasing the entrapped contents [70]. This ability could potentially be used to induce rupture of protein microspheres to increase the localized delivery of a drug to specific parts of the body.

4 Industry application

Ultrasonics has been successfully used to generate a range of functional food and biomaterials in the laboratory. Industrial uptake of ultrasonics is not currently widespread, but is gaining considerable traction. A number of potential issues identified in early studies are gradually being debunked or resolved. Some of these issues will be discussed in the following section.

4.1 Generation of particulate metal contaminants

The strong physical phenomena generated by cavitation are capable of affecting not just the product, but also the transducer and reactor surfaces. The potential for release of metallic particles into the product that may be too small to remove has raised some health concerns. Recently however, Mawson et al. [71] assessed the production of metal particulates from ultrasonic transducers and found no evidence for the formation of harmful nanoparticles (<80 nm). In their study, no nano-particulate material was observed even after prolonged exposure (up to 7.5 hours) to high intensity ultrasound (20 kHz and 174 J/mL). However, most food or drug related applications involving ultrasound only require a few second of ultrasonic processing [72], meaning the risk of contamination of sensitive products such as foods and pharmaceuticals is minimal. Contamination-free reactors [73] have also been developed, and these can be used for the production of high-valued products that require the utmost purity.

4.2 Degradation of functional properties

The formation of radicals by ultrasonic cavitation can be beneficial in promoting and enhancing sonochemical reactions, but they can also potentially degrade redox sensitive components. This is a particular concern for foods and bioproducts, where the flavor and nutritional properties must be taken into account. Vitamins, fats, and other lipids are particularly susceptible to reactions induced by oxidative radicals. Fatty acid oxidation and lipolysis can significantly modify the flavor profile of the food [74] and produce off-flavors associated with ‘burnt rubber’, ‘grass’ or ‘rancid fruit’. Destruction of vitamins and anti-oxidants in foods may reduce the nutritional value or induce undesirable color changes.

However, these problems can be mitigated by selecting operation at lower frequency ultrasound and employing shorter exposure times [72]. As can be observed in Figure 4, radical formation at 20 kHz has been shown to be minimal relative to mid and high frequency ultrasound, and at short sonication times essentially negligible and unlikely to result in any significant change to

513 the functionality of biomaterials. For instance, for a solution of 5 % protein, the radical
514 concentration resultant from sonication at 20 kHz for 5 min would typically be approximately
515 less than 10 ppm (i.e. 10 moles of radical per million moles of protein). A recent study
516 performed by Juliano et al. [75] showed that by limiting the duration of sonication (i.e. low
517 specific energy), off-flavor volatiles from oxidation of milk fat could be kept below detectable
518 sensory thresholds, even when operating with mid (400 kHz) or high (1 MHz) frequency
519 ultrasound. The reason is because many natural food products such as milk contain natural anti-
520 oxidants, which mitigate detrimental changes to the product.

521 ***4.3 Augmentation or replacement of current industrial techniques***

522 Ultrasound can be used to replace or complement conventional techniques such as
523 emulsification and polymerization that are used to create encapsulating particles in aqueous
524 systems. Acoustic cavitation can provide efficient high-shear processing and radical
525 polymerization as described in sections 3.1 and 3.2. However, ultrasound cannot replace
526 industrial techniques currently used to create dried encapsulating particles, for example, spray
527 drying, freeze drying, extrusion coating, fluidized bed coating, and coacervation [76]. Although
528 studies have employed ultrasonic atomization as a technique to generate microcapsules at lab
529 scale [77], spray drying is the most feasible method on an industrial scale, particularly for foods
530 [76, 78]. Spray drying is highly energy efficient and effective technique by which internalized
531 materials can be stabilized during storage. Emulsions can be formed as a precursor to
532 encapsulate lipids and oil-soluble material during spray drying. Ultrasound can play a
533 complementary role in aiding the formation of stable small-sized emulsions which may have
534 beneficial outcomes within the spray dried product [45].

535 Hydrodynamic cavitation [79, 80], imparts similar cavitation-borne mechanisms to materials
536 as ultrasonic cavitation, with the advantage of higher throughput due to its more conventional
537 unit design. In some situations, hydrodynamic cavitation can be more efficient due to its ability
538 to generate cavitation over a large volume/region [79].

539 ***4.4 Towards scale-up***

540 Ultrasonic technology is yet to be widely implemented at an industrial scale, not due to
541 uncertainty of its efficacy, but to challenges in scaling up. For a comprehensive review of the
542 design considerations for efficient scale up of sonochemical reactors readers are directed to

Gogate et al. [81]. A key issue for scale-up of sonoprocessing that is worth highlighting is the strong attenuation in effectiveness with distance from the ultrasound source. This complicates scale-up as the effective volume is confined to the active sonochemical regions close to the transducers which, in some cases, can be quite small and narrow. One strategy is to use flow-through cells, where liquid passes through a narrow region close to the transducer to ensure all elements of fluid are subjected to ultrasound. Alternatively, flow chambers incorporating multiple transducer horns can be effective at providing uniform delivery of ultrasound to large volumes of material. Many commercial flow-through sonication products are now available, and can be tailored for a range of applications.

The current cost of the technology, although not prohibitive, is still often higher than conventional alternatives. However, the ability of ultrasound to produce unique, high-value products with improved functionality while reducing chemical and energy consumption in some applications, may compensate for the extra cost. It is envisioned that the continual development of the technology will lead to gradual industrial uptake of ultrasonics and eventually its mainstream use for the production of valuable functional materials.

5. Conclusion

The ultrasonic synthesis of functional food and bio-materials has a bright future with many yet-to-be realized commercial opportunities. Many of the issues identified in early studies are being overcome, paving the way for ultrasonic synthesis of the next generation of drug delivery agents, functional biomaterials and food products.

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Figures

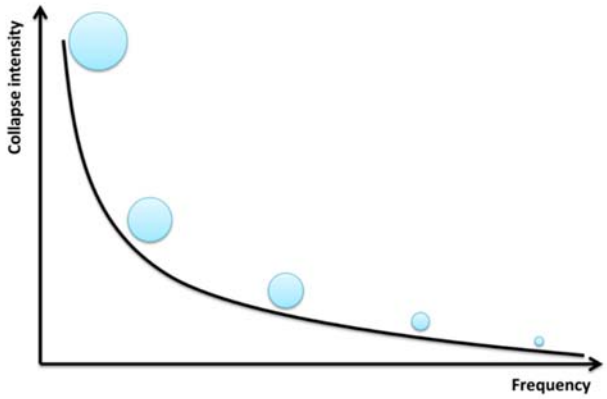

Figure 1: Schematic representation of the relationship between ultrasonic frequency applied and the relative intensity and size of the collapsing bubbles. Not drawn to scale.

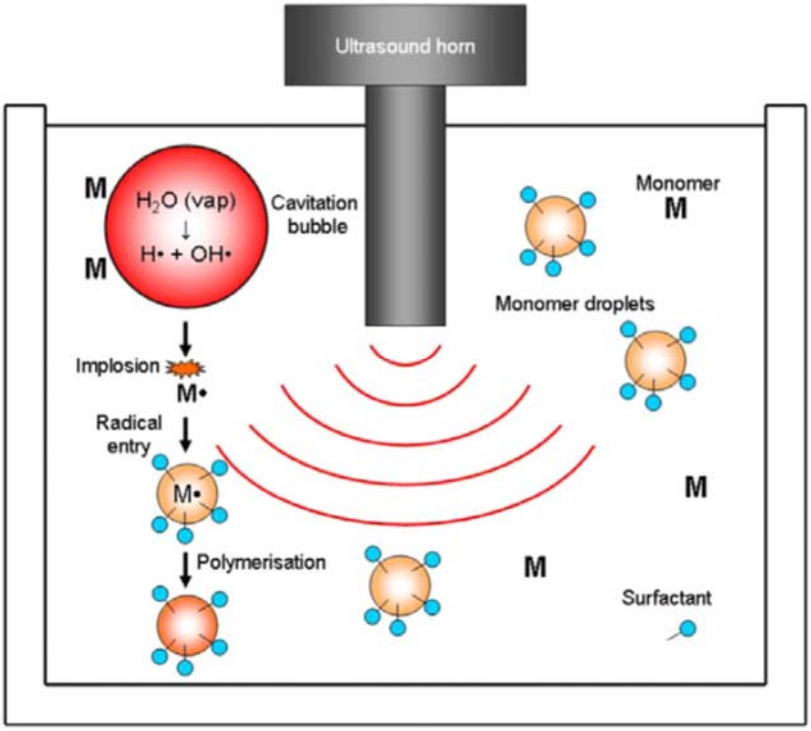

Figure 2: A schematic diagram of a proposed emulsion polymerization process. Reprinted from Teo et al. [64], Copyright 2008, with permission from Elsevier.

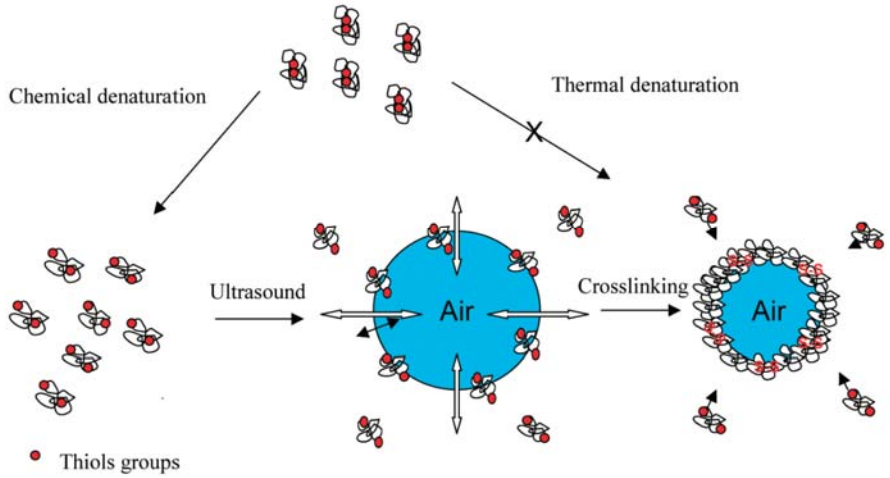

Figure 3: Mechanism proposed for the formation of lysozyme protein microspheres. Reprinted with permission from Cavalieri et al [27]. Copyright 2008 American Chemical Society.

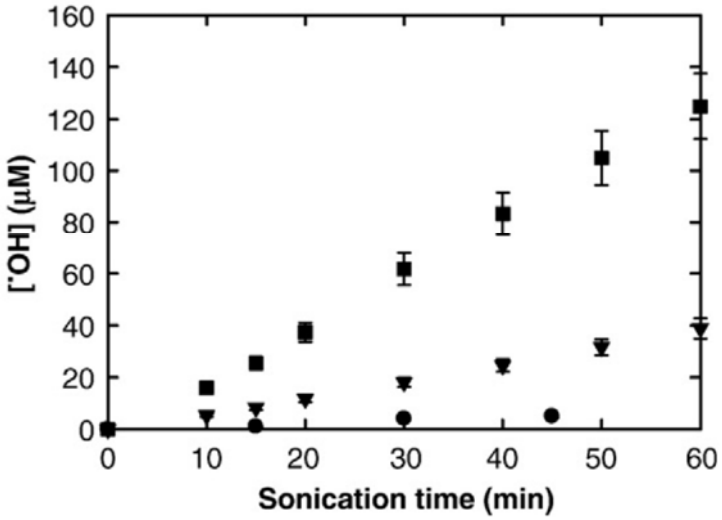

Figure 4: OH radical yield generated in water upon sonication at different acoustic frequencies with matched power 0.9 W cm^{-2}. Adapted from Ashokkumar et al. [72], Copyright 2008, with permission from Elsevier.