1 **Ultrasonic Encapsulation – A Review**

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8 **Highlights**

9 • Ultrasonic preparation of encapsulated functional materials is reviewed.

10 • Mechanisms responsible for expression of functional properties are described.

11 • Promising applications for ultrasonically synthesized materials are identified.

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

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18 **Abstract**

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

1. Introduction

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

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

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

2. Theory of applied ultrasound

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

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

60 *2.1 Characteristics of ultrasound*

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

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

78 Of interest to material synthesis, the collapsing bubbles produce localised regions of extreme
79 temperature and intense physical shearing. Bubbles driven at low ultrasonic frequency (~ 20-
80 100 kHz), may collapse extremely violently, releasing sufficient energy to produce
81 temperatures up to 10,000 K within the bubble core and pressures of several hundred
82 atmospheres within a few hundred micron of the bubble collapse point [11]. This can lead to
83 the formation of highly reactive radicals which can be used to promote chemical reactions. In
84 water for example, hydrogen and hydroxyl radicals can be formed due to the splitting of the
85 water molecule by pyrolysis. Both the physical shear and radical formation can be beneficially
86 exploited to create materials with a range of desired functionality.

87   The ultrasound frequency regime ranges from 16 kHz to 500 MHz, although the frequency

88   range most suitable for processing fluids is typically between 16-3000 kHz. When ultrasound

89   is applied to fluids the cavitation effects are highly dependent on the frequency. The intensity

90   of bubble collapse (i.e. amount of energy released) and the maximum bubble size prior to

91   collapse (resonance size) are correlated and approximately inversely proportional to the applied

92   frequency [12] (see Figure 1).

93   A simple relationship that can relate the resonance size of the bubble with the frequency is

94   given by:

95
$$F \times R \approx 3 \tag{1}$$

96   where F is the frequency in Hz and R is the bubble radius in m. Note that this equation gives

97   only a very approximate theoretical resonance size and that there are other factors which may

98   control the resonance size of the bubble [5, 13].

99   A more accurate version of (1) is the linear resonance radius which can be calculated using

100   the following equation [13]:

101

102
$$R_r = \sqrt{\frac{3\gamma p_\infty}{\rho_L \omega^2}} \tag{2}$$

103   where γ is the specific heat ratio of the gas inside the bubble, p_∞ is the ambient liquid

104   pressure, ρ_L is the liquid density and ω is the angular frequency of ultrasound (all in SI

105   units). In practice, the size for an active bubble is usually smaller than this radius due to the

106   nonlinear nature of the bubble pulsation [14].

107   Ultrasound can be categorized into several different regions along the frequency spectrum. The

108   *power ultrasound* region [12] spans the low frequency range between 16 – 100 kHz. It is

109   characterized by large bubble resonance sizes followed by intense bubble collapse, often

110   resulting in extremely strong physical effects including localized shear and high temperatures.

111   This category of ultrasound delivers high energy density in the order of 10-1000 W/cm^2. Power

112   ultrasound is often selected for material processing and to some extent in synthesis, owing to

113   its strong physical shear and intense local temperature effects. Examples of processes in this

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

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

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

132 **2.2 Radical formation and sonochemistry**

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

136
$$H_2O \rightleftharpoons \dot{H} + O\dot{H} \tag{3}$$
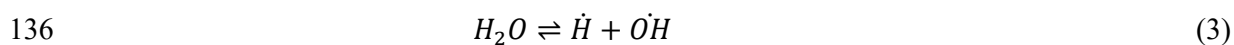
137 That is, water molecules can be split into highly reactive hydrogen and hydroxyl radicals.
138 Direct splitting of water as described above requires high temperatures resultant from high
139 intensity bubble collapse typically seen only in the power ultrasound region. Alternate reaction
140 pathways in water have been described by Yasui et al. [24] that allow for hydroxyl radical
141 production even at relatively low bubble temperatures that are typical of intermediate
142 ultrasound.

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

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

156 Proteins are biological polymers that can be cross-linked to form larger networks and structures
157 by ultrasound. These networks can be used to coat bubbles, droplets or other templates, forming
158 rigid spheres that can be used for encapsulating materials for applications such as drug delivery
159 [8]. The formation of protein microspheres by application of ultrasound results from a
160 combination of shear-induced emulsification and radical formation [26, 27]. The high shear
161 and temperature can partially unfold the proteins [28] which can then accumulate at the air or
162 organic phase boundary and undergo cross-linking [27]. The protein cross-linking can be
163 reversible, for instance through hydrophobic interactions and hydrogen bonding, or irreversible
164 if covalent links are produced, for example disulphide bonds. In the latter case, this can
165 potentially be facilitated by free radicals generated through ultrasonic cavitation [29].

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

169 *2.3 Physical effects of ultrasound*

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

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

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

195   The physical forces resultant from cavitation can increase particle interactions in suspensions
196   [25]. Solid powders suspended in fluids, may experience an increase to their momentum in the
197   vicinity of a cavitation bubble, which can cause them to collide together with greater force than
198   under quiescent conditions. Inorganic solids can be fractured and disrupted upon collision,
199   leading to a reduction to their average particle size [25]. The minimum size achievable is
200   dependent on characteristics of the solid, solvent and cavitation intensity. The lower limit is
201   reached when the momentum of the particles become too small to create further impacts to
202   cause particle fragmentation.

203   Ultrasound can be used to form encapsulating particles over a broad range of sizes, from around
204   100 nm to 20 μm in diameter. The particle size can be controlled to a large extent by selecting

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

3. Applications of ultrasonic encapsulation

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

3.1   *Functional food emulsions*

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

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

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

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

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

259 Higher frequency ultrasound (midsonic to megasonic) has however been reported useful at
260 forming nano-size emulsion droplets when applied following low frequency ultrasound
261 through a process known as *tandem acoustic emulsification* [39, 40]. Oleic acid/water nano-
262 emulsions were prepared by Kamogawa et al. [40] using this technique, while Nakabayashi et
263 al. [39] also reported the production of transparent emulsions of ethylenedioxythiophene
264 (EDOT) monomer formed by sequential emulsification at 20 kHz, 1.6 MHz and 2.4 MHz
265 ultrasound. The nano-emulsions formed by Nakabayashi et al. were stable even in the absence
266 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

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

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

347 **3.2   *Formation of polymeric particles for controlled drug release***

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

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

361   review of ultrasonically enhanced synthesis of polymers, readers are invited to read the review

362   by Price [18].

363   As described in Section 2, acoustic cavitation leads to both chemical and physical phenomena

364   that can be controlled to create polymers with improved rates of reaction and more defined

365   characteristics such as molecular weight. Radical polymerization is one of the most studied

366   [18] sonochemically-enhanced polymerization processes. The radicals formed during acoustic

367   cavitation can be used to initiate the polymerization process in place of conventional initiators

368   [60, 61]. A particular system in which this has been successful is in vinyl monomers such as

369   methyl methacrylate [62]. Another notable advantage of generating radicals using ultrasound

370   is the ability to perform the reaction at reduced temperatures (i.e. between -10 to 60 $^{\circ}$C

371   compared to between 50 to 100 $^{\circ}$C for more conventional radical polymerization reactions of

372   PMMA).

373   The physical effects of ultrasound can be used to control various properties of the resulting

374   polymer. The intensity of the ultrasound applied, which influences the strength and number of

375   acoustic cavitation bubbles, is one variable that can be modulated to control the yield of

376   polymer produced as well as the final molecular weight of the resulting polymer [63]. A larger

377   number of collapsing bubbles creates more radicals, which can increase the frequency of

378   polymer initiation events. Simultaneously, the shearing forces resultant from the collapse of

379   bubbles can break apart some of the long polymer chains that are formed, effectively reducing

380   the molecular weight of the final polymer. The intensity of collapse, and the duration over

381   which sonication is applied, can control the molecular weight of the polymers [63]. The ability

382   to influence the polymerization process by manipulating ultrasound variables provides scope

383   to transform conventional polymerization processes to form new materials. It should be noted

384   though that sonication has little to no effect on the actual propagation reaction of the polymer

385   formation. The main effects are largely confined to the initiation process and subsequent chain

386   breakage of the formed polymer chains.

387   Ultrasound can promote emulsion polymerization to form latex particles of approximately

388   equal size to the emulsion droplets [64]. The latex particles formed by ultrasound are typically

389   smaller than those formed by conventional emulsion polymerization, resulting in an increased

390   surface area [65]. Further, the use of ultrasound removes the need for chemical initiators or co-

391   stabilizers, reduces the required reaction temperature, increases the rate of polymerization and

392   results in higher monomer conversion and potentially higher molecular weights. As a number

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

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

401 Temperature responsive polymers of poly(N-isopropylacrylamide) and poly(N-
402 vinylcaprolactam) have been prepared using ultrasound, and their swelling behavior in the
403 presence of different concentrations of surfactant (SDS) studied [67]. The potential for these
404 types of polymers to be used as drug delivery vehicles was demonstrated by their ability to
405 entrap rhodamine B dye. The structure of these polymers is temperature dependent. At 20 ^{o}C,
406 the polymer chain is an expanded coil that is soluble in water resulting in clear aqueous
407 solutions. When heated to 32 ^{o}C, the chains collapse to a globular structure which decreases
408 the solvation properties causing the polymer solution to become turbid. The release kinetics of
409 the entrapped rhodamine B was consequently found to be dependent on the temperature, with
410 higher release rates occurring at 40 ^{o}C compared with 20 ^{o}C [67]. The release of dye was found
411 to follow Fickian diffusion kinetics, with the diffusion coefficients being 4×10^{-12} and $3.6 \times$
412 10^{-11} m^2/s at 20 ^{o}C and 40 ^{o}C respectively i.e. an order of magnitude increase in release rate.
413 There was an apparent limit to the maximum amount of dye release (approximately 62 %),
414 which was attributed to the concentration gradient of the dye within the polymer and bulk
415 solution approaching zero.

416 ### 3.3 *Formation of protein-coated microspheres*

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

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

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

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

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

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

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

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

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

478 In addition to promoting the formation of protein microspheres, ultrasound is a potential tool
479 for targeted drug release. Ultrasound has been shown to break apart chitosan/titanium oxide
480 hybrid nanospheres, releasing the entrapped contents [70]. This ability could potentially be
481 used to induce rupture of protein microspheres to increase the localized delivery of a drug to
482 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

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

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

5. Conclusion

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

Acknowledgments

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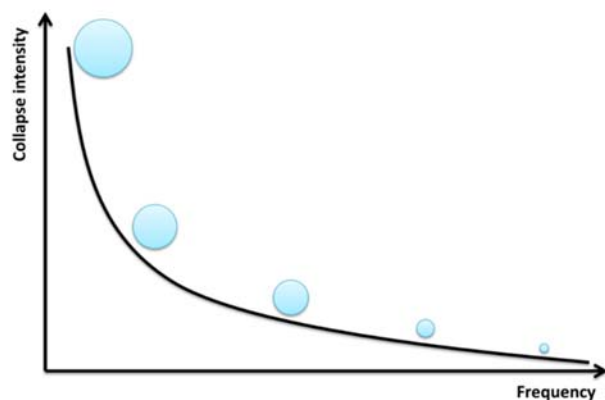
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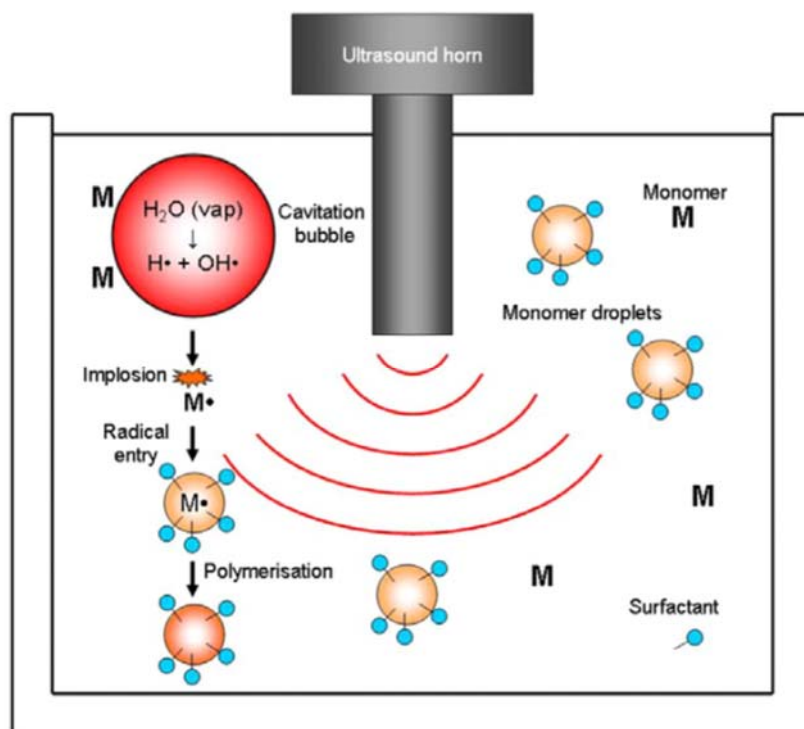

Figure 1: Schematic representation of the relationship between ultrasonic frequency applied and the relative intensity and size of the collapsing bubbles. Not drawn to scale.
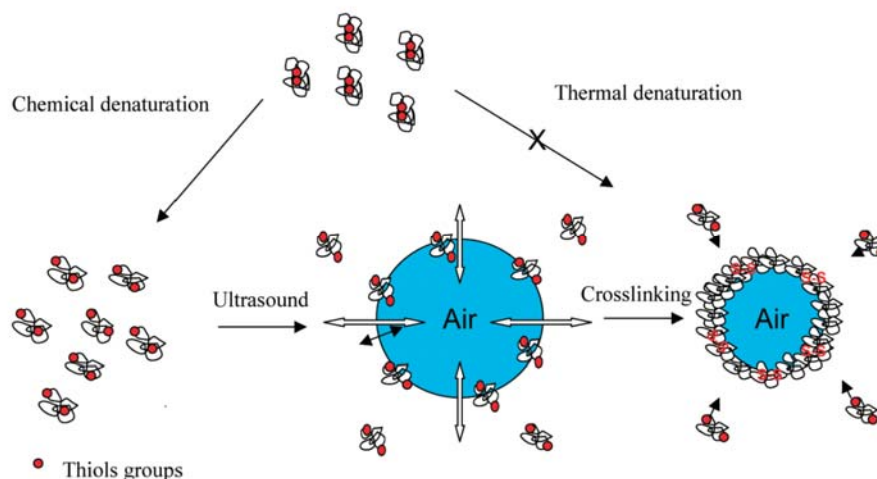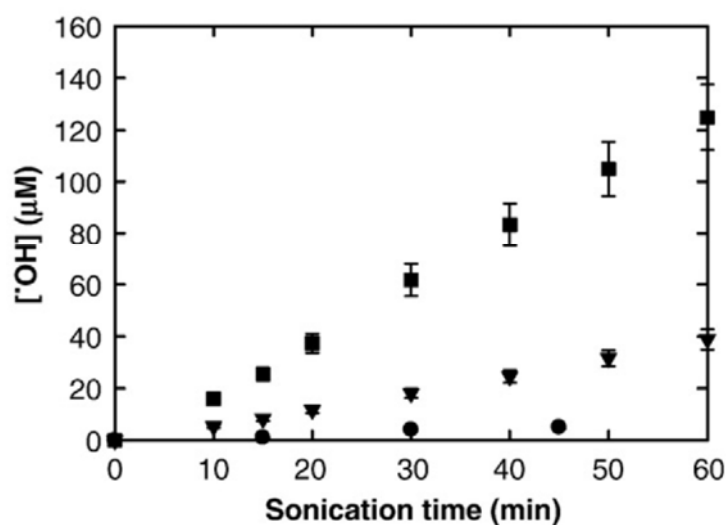

Figure 2: A schematic diagram of a proposed emulsion polymerization process. Reprinted from Teo et al. [64], Copyright 2008, with permission from Elsevier.

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.

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