

Recent progress on the preparation processes of hollow polymer nano and microspheres

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ABSTRACT

Hollow polymer nano- or microspheres are of great interest in the fields of drug delivery, cosmetics, catalyst carrier, and microencapsulation. This review is devoted to the progress made in recent years in the fabrication and application of hollow polymer nano and microspheres. The preparation methods including emulsion processing, self-assembly technique, emulsion polymerization, and templating method, and their applications are presented. Fundamental aspects of these formation processes and their effects on the particle properties are also discussed in this paper. Polymer nano and microcapsules are one of the most extensively used materials for encapsulation system. This review also provides a brief description of current production methods and introduces encapsulation applications of formed particles.

KEYWORDS: hollow polymer microspheres, solvent evaporation, self-assembly, seeded polymerization, templating

1. INTRODUCTION

The control of the morphology of polymer particles is of great interest both from an academic and practical perspective. Recently, hollow polymer nano or microspheres have attracted considerable attention due to their unique properties.

These particles have a large surface to volume ratio making the adsorption of active substances more easy, which can be potentially applied as capsules for controlled release drug deliveries and catalyst carriers [1, 2]. They also can be used as light-weight fillers for low density property. The void within the hollow particles not only provides useful spacious compartments but also unique light scattering properties [3]. These particles have been widely used in encapsulation, cosmetics, paper coatings, and so on [4]. Their composites with inorganic particles can provide added functionality in hybrid structures, such as magnetic, electronic, and catalytic properties [5, 6]. Progress on preparation methods of hollow polymer microspheres allows the synthesis of polymers with well-controlled structures and compositions, obtaining the final particles with desired properties.

The aim of this review is to summarize recent fabrication processes of producing hollow polymer nano and microspheres. The fundamental formation mechanism of each method is firstly given and their updated progresses on different polymer materials and applications are pointed out. The advantages and differences of one approach compared with the others are briefly introduced. The understanding of different preparation methods of hollow structures is useful for future development and application of these materials and their functions.

2. Emulsion processing

Emulsion processing is one of the traditional methods to fabricate the hollow polymer particles,

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usually combined with a subsequent solidification, such as phase separation or solvent evaporation. Quintanar-Guerrero *et al.* first developed the emulsion-diffusion method [7]. In this two-step process, polymer containing oil phase is emulsified in the water phase and the organic solvent contained in it is then eliminated by extraction or evaporation. The removal of organic solvent hardens the particle and reduces the particle size.

Double emulsion method is widely applied in the microencapsulation technology, producing liquid microcapsules that contain a liquid or a gas core. Rosca *et al.* produced poly (lactide-co-glycolide) (PLGA) microparticles with different morphologies by double emulsion solvent evaporation method [8]. Hollow and porous microparticles have been generated depending on the formulation conditions. However, multi-core morphology is not able to provide effectively entrapped volume and efficient mass transfer across the polymer shells. Wang and Ma *et al.* reported an emulsion ripening process to obtain single-core W_1/O globules from their multicore precursors in $W_1/O/W_2$ emulsions [9]. Subsequent suspension polymerization ensures the encapsulation of water phase in the biocompatible hollow poly(methyl methacrylate) (PMMA) microcapsules. This method involves many procedures and is costly and time consuming.

A conventional single emulsion process can also prepare hollow polymer particles (see Figure 1) [10]. Polymer/solvent/oil mixture is emulsified in the non-solvent phase, where oil acts as the co-solvent having poor solubility for the polymer in

the mixture. The capsules are formed during the solvent out-diffusion step, leaving the polymer and oil concentrated in the droplets. The polymer continuously solidifies as a shell at the interface between the dispersed and continuous phase. Subsequent removal of the oil by freeze-drying results in the formation of the polymer shell in the appropriate morphology. The size and membrane thickness of capsules by the emulsion-diffusion method depends on the concentration of oil, polymer, and stabilizer and the volume of the solvent [11]. The solidification of the polymer shell is not only obtained by diffusing the solvent, but also by removing or freezing the water [11]. Chevalier *et al.* showed the geometric relationship between the primary emulsion and the final nanocapsule size [12]. The formulation and processing parameters of the primary emulsion, such as the oil-to-polymer ratio and the mixing shear rate, can influence the properties of nanocapsules. Recently our group demonstrated a facile emulsion diffusion process to fabricate poly (lactic acid) (PLA) hollow microspheres driven by viscous turbulent fluid flow, as shown in Figure 2. Based on one-step emulsification, turbulent regime and emulsification temperature have been used to control the shape and size of polymeric particles from nanospheres to hollow microspheres [13]. In the drug delivery technology, single emulsion process usually obtains hollow polymer particles containing oil in the core which are suitable for encapsulating hydrophobic drugs. It is possible to prepare water containing polymer particles by double or multiple emulsion method where hydrophilic molecules can be carried. Generally the hollow

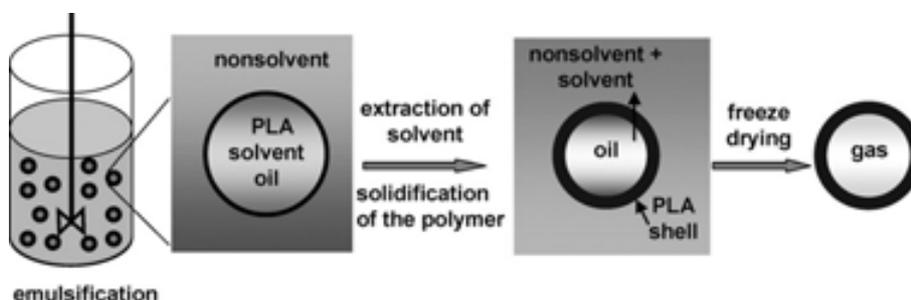


Figure 1. Schematic representation of the emulsion solvent-evaporation/ extraction preparation method of hollow PLA microcapsules. Reprinted from Sawalha, H. *et al.*, Chemical Engineering Journal, 169(1-3), 1-10, Copyright (2011) with permission from Elsevier.

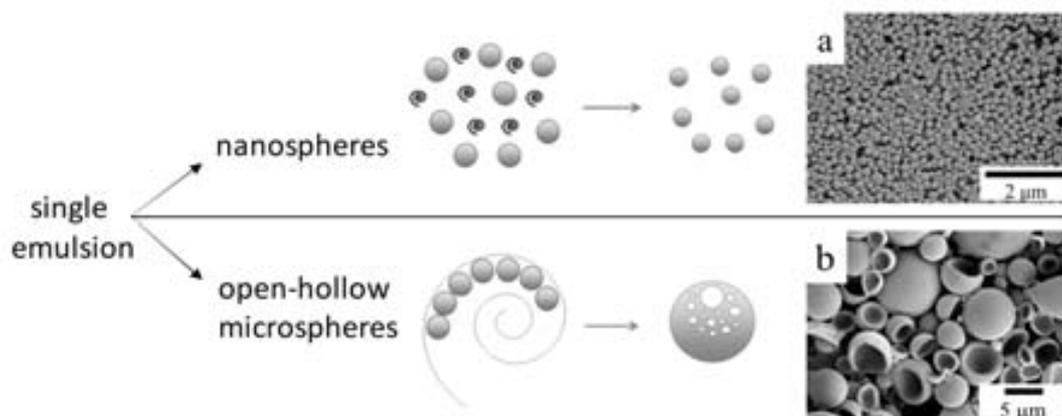


Figure 2. Transitional behavior of polymeric hollow microsphere formation in turbulent shear flow by emulsion diffusion method. Reprinted from Ji, S. *et al.*, *Polymer*, 53, 205-212, Copyright (2012) with permission from Elsevier.

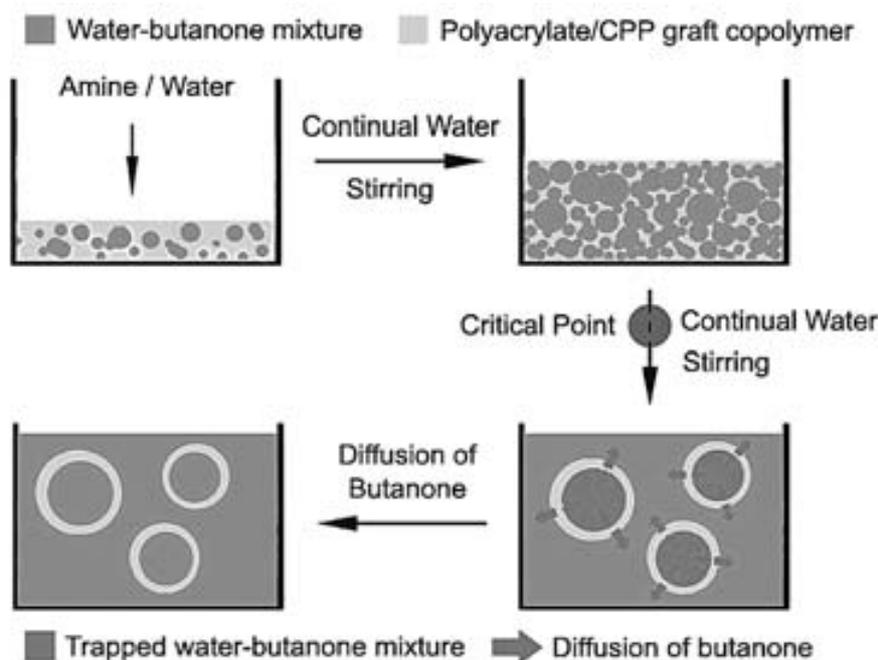


Figure 3. Schematic formation mechanism of hollow microspheres via the phase-inversion method. Reprinted with permission from Cao, Y. *et al.*, *Langmuir*, 26(9), 6115-6118. Copyright (2010) American Chemical Society.

particles formed from double or multiple emulsions are larger in size than those from single emulsions.

Phase inversion is another approach to fabricate hollow polymer microspheres. The one-step single emulsification process is directly related to multiple emulsions formation during phase inversion [14] (see Figure 3). You and Wu *et al.*

grafted hydrophobic chlorinated polypropylene with hydrophilic methyl methacrylate, butyl acrylate, and acrylic acid parts [15]. The solvent containing the modified polymer was diluted by water which induced the phase inversion beyond the critical point and then formed the hollow structure after evaporation. They took advantages of the

semimiscibility of butanone with water and the carboxyl group content in the polymer to entrap the water-butanone compartments in the hydrophobic emulsion droplets as well as lead to the complete phase separation and generation of both inner and outer sphere interfaces.

Conventional emulsification techniques, such as magnetic stirring, sonication, and homogenization, cannot provide a good control over the size and size distribution of hollow particles. The membrane emulsification is used to prepare monodisperse emulsions by passing premixed emulsion droplets through the pores of the glass fibre membrane [16, 17]. Combined co-solvent single emulsification with membrane extraction, narrowly dispersed hollow polylactide microcapsules with sizes 0.35-5 μm were prepared from a polylactide/dichloromethane/dodecane solution in alcohol-water mixtures.

3. Emulsion polymerization

In general, the polymer shell surrounding the core can be formed either by precipitation of a preformed polymer at the top of emulsion droplets or polymerization occurring at the interface between the dispersed and continuous phase. The latter usually includes conventional emulsion polymerization, inverse emulsion polymerization, miniemulsion polymerization, dispersion polymerization, and microemulsion polymerization [18]. Due to the possible production of polymers with unique properties and the environmental advantages with waterborne products, the emulsion polymerization has been used to prepare a variety of commercial polymers. The earliest work of fabricating hollow polymer particles was developed by Kowalski and co-workers at The Rohm and Hass Company [19]. They prepared the core-shell polymer particles by sequential emulsion polymerization. The core containing carboxylic acid groups was then swollen and extracted by a volatile base, forming microvoids in the particles. Followed by this concept, McDonald *et al.* encapsulated a non-solvent hydrocarbon within an emulsion which induced the phase separation of the polymer with the dispersed mixture during polymerization due to the immiscibility between the formed polymer and hydrocarbon [20] (see Figure 4). The encapsulated hydrocarbon was then removed by vacuum or steam to generate the inner void

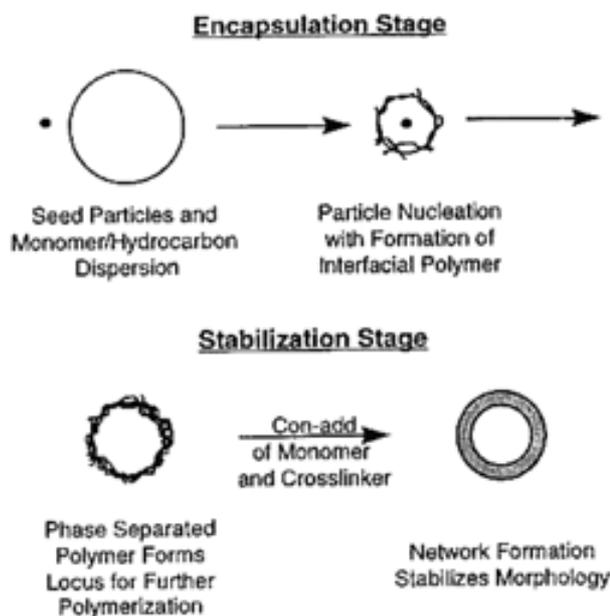


Figure 4. Schematic of two-stage voided latex particle process. Reprinted with permission from McDonald, C. J. *et al.*, *Macromolecules*, 33, 1593-1605. Copyright (2000) American Chemical Society.

structure. No high shear stress was required to control the particle size which was considered mainly related to the surfactant or a nucleating latex seed concentration.

The similar process can also be applied to prepare core-shell structured particles. The core polymer and the surrounding secondary polymer layer are synthesized by the sequential conventional emulsion polymerization. The core materials are degraded or extracted to leave the hollow spheres. Zheng *et al.* consecutively condensed bi- and tri-functional organosilicon onto the poly(dimethylsiloxane) (PDMS) microemulsions [21]. The linear PDMS chains in the core were removed by tetrahydrofuran (THF), forming hollow polysiloxane microcapsules. Similarly, pH-sensitive hollow poly(N,N'-methylene bisacrylamide-co-methacrylic acid) (P(MBAAm-co-MAA)) microspheres with defined size below 200nm and shell thickness in the range of 8-26nm were prepared by a distillation precipitation polymerization, which can be used as the controlled release carriers [22].

Miniemulsion polymerization has been widely applied in the nano/microencapsulation. One of its

advantages is the direct encapsulation while forming the polymeric capsules. γ -ray radiation was used to induce the miniemulsion polymerization of styrene and at the same time N-vinyl pyrrolidone (NVP) was reacted by graft copolymerization onto polystyrene (PS) [23]. The graft reaction between PS and PVP increased the hydrophilicity of the polymer and reduces the interfacial tension, which facilitated the formation of PS nanocapsules with phase-separated dodecane as the liquid core. Shirin-Abadi *et al.* encapsulated hexadecane (HD) in the PMMA nanocapsules via miniemulsion polymerization as one example of the hydrophobic agents [24]. With the aid of theoretical calculations by using differential scanning calorimetry (DSC), dynamic light scattering (DLS), and microscopy, processing parameters such as HD:MMA ratio and the usage of the cross-linking agents, were considered to mainly affect the encapsulation process. Combining with the templating technique, emulsion polymerization can be extended to produce core-shell hybrid particles generating the hollow structure after the removal of the inorganic core. The details will be discussed in the later section.

4. Block copolymer self-assembly

Self-assembling features have been found in amphiphilic block and graft copolymers, which opens up an efficient way to form polymeric micelles with a variety of novel morphologies and functions [25]. Block copolymers act as surfactants when dispersed in the solution. The shape of self-assembled hollow structures is determined by the size of hydrophobic moiety to the hydrophilic part. The aggregation of block copolymers is triggered by minimizing energetically unfavorable contact between the insoluble blocks and the selective solvent [26]. Aggregates with a spherical morphology usually consist of an insoluble core and a soluble corona (see Figure 5). Due to their good stability and toughness, polymeric micelles can be tailored to suite physical, chemical, and biological requirements by varying experimental parameters, such as the block copolymer composition, block length, chemical structure, solvent composition, copolymer concentration, etc. [26, 27].

Eisenberg *et al.* first showed the dependence of block copolymer morphologies on the molecular

architecture, e.g. block lengths [25]. The formation of polystyrene-*b*-poly (acrylic acid)(PS-*b*-PAA)micelles is strongly dependent on the ratio of PAA and PS block lengths. When the PAA content is decreased, the morphology changes from spherical micelle-like to rod-like aggregates, or even further to vesicular. The solvent can also influence the morphology of those block copolymers which is related to the polymer-solvent interaction [28]. When tetrahydrofuran (THF) is used as solvent, both micelles and vesicles are obtained, whereas only spherical micelles exist under N,N-dimethylformamide (DMF). A lot of work has been reported on the regular amphiphilic block copolymers, such as polystyrene-block-poly(4-vinylpyridine) (PS-*b*-P4VP) [29], poly(ethylene oxide)-block-poly(*n*-butylacrylate) (PEO-*b*-PnBA [27], poly(ethylene oxide)-block-poly(ethyl ethylene) (PEO-*b*-PEE) [30] and poly(butadiene)-block-poly(ethylene oxide) (PBD-*b*-PEO) [31]. Discher *et al.* integrated the hydrolysable and non-cross-linkable diblock, poly(ethylene oxide)-poly(lactic acid) (PEO-PLA) into bilayer vesicles of PEO-PBD copolymer to offer the controlled destabilization property to the solid polymer shell and facilitate the encapsulant release as degradable delivery agents [32]. Amphiphilic copolymers with complex structure can broaden their potential applications. In order to mimic the natural membrane with oriented proteins, artificial membrane which is in the asymmetric vesicular structure, was build up by ABC triblock copolymer, poly(ethylene oxide)-poly(dimethyl siloxane)-poly(methyl oxazoline) (PEO-PDMS-PMOXA), in the aqueous solution [33].

In the assembly strategies, coil polymer chains are commonly used as building blocks. However, the stiff rod-like blocks can also affect the macromolecular packing and facilitate the vesicle formation. The first work of vesicle formation by a multiblock copolymer was reported by Holder *et al.* [34]. Amphiphilic poly(methylphenylsilane)-poly(ethylene oxide) (PMPS-PEO) copolymer was synthesized and vesicles were well formed in the water with narrow size distribution. PMPS chains in the vesicle walls were orientated perpendicular to the air/water interface and packed as rod-like layer which promoted the formation of

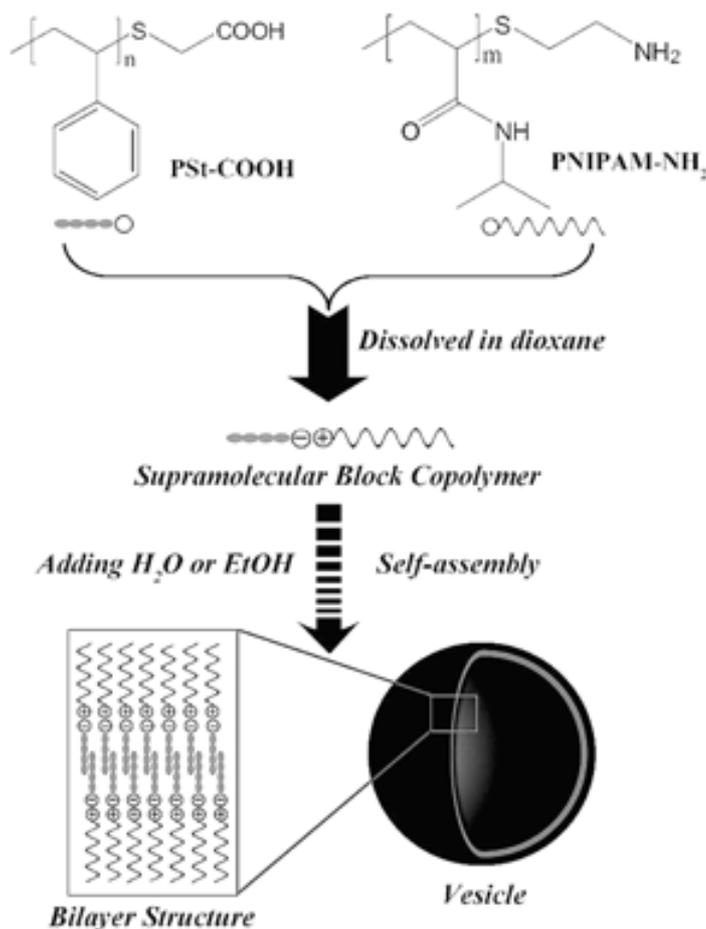


Figure 5. Illustration of vesicle formation from supramolecular block copolymers. Reprinted with permission from Qian, J. and Wu, F. P. *Macromolecules*, 41, 8921-8926. Copyright (2008) American Chemical Society.

a hollow spherical structure. Jenekhe and Chen also reported the self-assembly of synthetic rod-coil diblock copolymer, poly(phenylquinoline)-block-polystyrene (PPQ-b-PS) in a selective solvent, trifluoroacetic acid (TFA), which is good for PPQ under different solvent compositions and solution drying rates. The hollow microcavities observed from large micron size spherical aggregates show the potential application in encapsulating the fullerene molecules or generating ordered microporous materials [35]. Li *et al.* also extended this idea onto two amphiphilic liquid crystal block copolymers consisting of a side-on nematic polymer block and a PEG block with different hydrophilic/hydrophobic ratios. Polymer vesicles were obtained from block copolymers at large hydrophilic/hydrophobic

ratios [36]. A mixing of rod-like homopolymer polyimide (PI) and coil-like homopolymer poly(4-vinyl pyridine) (PVPy) in their common solvent chloroform produced the hollow spherical aggregates within nano-scale, which was proposed that grafts with enough stiffness are necessary for the formation of hollow structure even in the non-selective solvents [37].

Besides the structural difference among the covalently connected segments, secondary interactions between the polymer tectons, such as charge interactions, H-bondings, dipolar interactions, etc., can also control the intermolecular conformation. Jiang group have studied a series of building block polymers and successfully prepared hollow spheres with different homopolymer pairs via inter-polymer

H-bonding, such as PVPy and hydroxyl-containing PS in a selective solvent, PVPy and carboxy-terminated PI in their common solvent, and PVPy and carboxy-terminated poly(amic acid) ester (PAE) [37, 38]. Qian and Wu connected hydrophilic poly(N-isopropylacrylamide) with amino end groups (PNIPAM-NH₂) and hydrophobic PS with carboxylic end groups (PSt-COOH) through the ionic interaction. These amphiphilic supramolecular block copolymers formed spherical vesicles in the dioxane/H₂O system. Increasing temperature induced the transformation of worm-like vesicles to spherical vesicles in the dioxane/ethanol system [39].

5. Templating process

Templating method is a simple process which includes the synthesis of the polymer shell on the dispersed template and the removal of the template core particle [40] (see Figure 6). PS latexes, emulsion droplets, inorganic colloids, or gas bubbles are commonly used as templates. Polymer particles prepared by this method are usually monodispersed. The process of fabricating hollow polymer microspheres by osmotic swelling method was originally from Kowalski *et al.* as described above, which produces the submicron-sized hollow particles with water and ionized

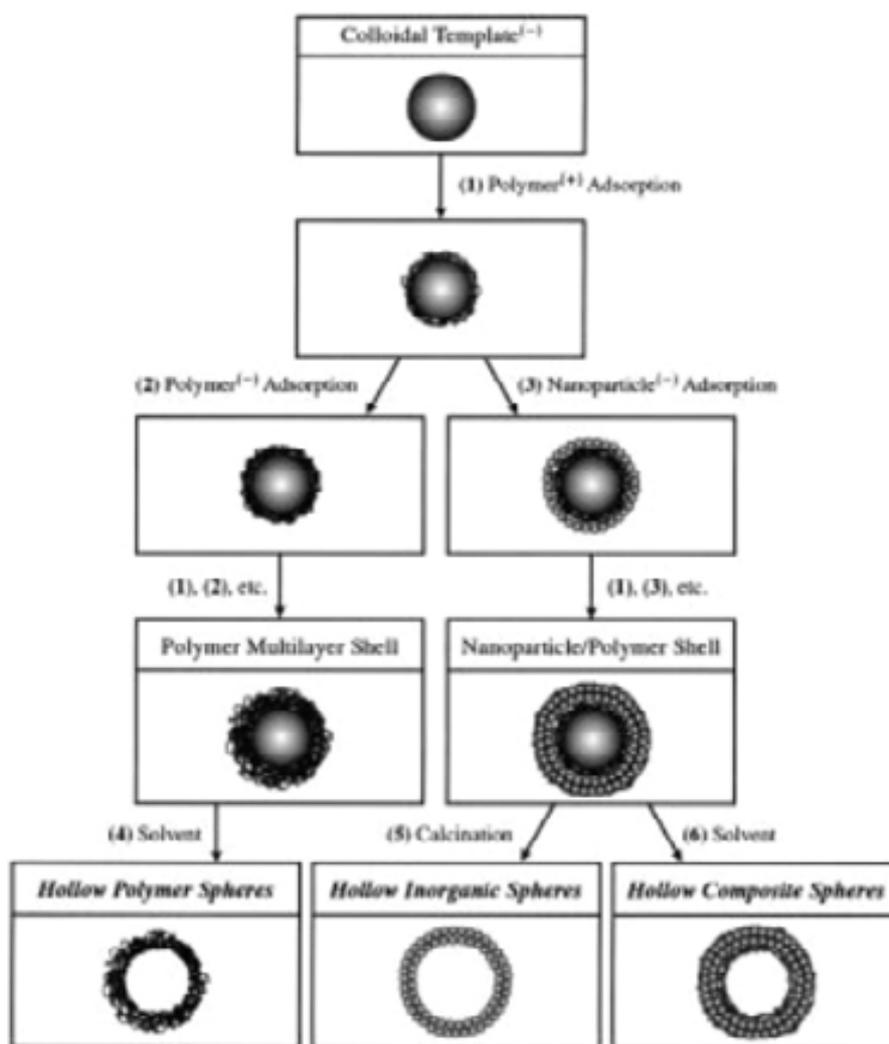


Figure 6. Schematic diagram for hollow capsule production by exploiting colloidal templating and self-assembly methods. Reprinted from Caruso, F. 2000, Chem. Eur. J., 6(3), 413-419, with permission from John Wiley and Sons.

polymer inside [19]. Okubo group has proposed the stepwise alkali/acid and alkali/cooling treatments on the carboxyl-containing latex particles for forming the multihollow structure [41-43]. In the alkali/acid treatment, poly(styrene-butyl acrylate-methacrylic acid) (P(St-BA-MAA)) was prepared as the seed particle by emulsion copolymerization and carboxylic acid groups in the core PS particle were neutralized and swollen under alkaline condition. Entrapped water coalesced to form bigger one, resulting in the hollow structure during the acid treatment. It has been shown that the initial pH value, temperature, and time in the post-treatment processes have great effect on the particle morphology. In order to simplify the polymerization process and lower the impact of BA on the glass transition temperature, strength, and rigidity of polymer latex particles, Kan *et al.* further synthesized the porous P(St-MAA) particles via batch soap-free emulsion polymerization, followed by stepwise alkali/acid post-treatment. MAA amount was considered as a crucial factor to control the size and morphology of prepared latex particles [44]. Recently, sulfonated polystyrene (SP) particles have attracted much attention as the template. Wang and Ge *et al.* successfully prepared multihollow PMMA particles by one-step radiation emulsion polymerization, the structure of which was determined by the initial location of SP template particles before emulsification [45]. When SP particles located in the water phase, pickering emulsion was formed giving the cage-like hollow structure. If dissolved in the monomer phase, SP particles were entrapped in the multiple emulsions and multihollow structure would be generated (see Figure 7).

Okubo group also developed a seeded emulsion polymerization method, named the “dynamic swelling method” (DSM) [46, 47]. PS particle was used as the seed and swollen by toluene with dissolved divinylbenzene (DVB) monomers. PDVB was polymerized and precipitated near the interface, forming a cross-linked PDVB shell. Dissolving PS built up the uniform inner shell against the PDVB shell after the evaporation of toluene under reflux (see Figure 8). Processing parameters, such as DVB content [6], polymerization temperature [48], addition of

emulsifiers, and PS molecular weight [49], were investigated to control the size and morphology of prepared polymer particles. Xia *et al.* applied the similar concept to form hollow PS and PMMA particles with controllable holes on their surfaces for the potential application in the micro-encapsulation [50]. They utilized the toluene volume shrinkage from liquid to solid phase to generate a void inside the swollen PS solid particles. A hole was formed after the evaporation of toluene. Recently decane droplets were used instead of swelling solvents in the seeded dispersion polymerization to prepare monodispersed dimple and hemispherical PS particles [51]. Processing temperature, stirring rate, and medium composition were studied to explain the formation mechanism. Adsorption of decane droplets into PS particles was carried out by heating spherical PS particles beyond the glass transition temperature of PS in the aqueous medium. During the cooling process, PS particles phase separated with decane and formed non-spherical structure after its removal.

Layer-by-layer (LbL) self-assembly is suitable for controlling polymer shell thickness and compositions [52]. As its name implies, it is based on the consecutive deposition of oppositely charged polyelectrolyte layers onto a charged particle surface (see Figure 9). The adsorption is mainly dependent on the electrostatic force. Poly(styrene sulfonate) (PSS), poly(allyamine hydrochloride) (PAH), poly(ethyleneimine) (PEI), and poly(diallyldimethylammonium chloride) (PDAC) are usually used as polyanion and polycations [53, 54]. Template particles, such as PS latex particles modified with sulfate, melamine formaldehyde (MF) microparticles, or inorganic particles, can be dissolved by organic solvents or acid solutions after LbL coating. Multilayer capsules can be functionalized by assembling materials of interest. Micrometer sized hollow silica-polymer spheres were obtained by LbL self-assembly of silica nanoparticles and PDAC layers [55]. The shell thickness can be easily tuned by the adsorption layers, while the template particles can affect the size and shape of final hollow spheres. Similarly, Li and coworkers have built a PEI/PAA-gold hollow nanocomposite capsule system by LbL self-assembly process which is

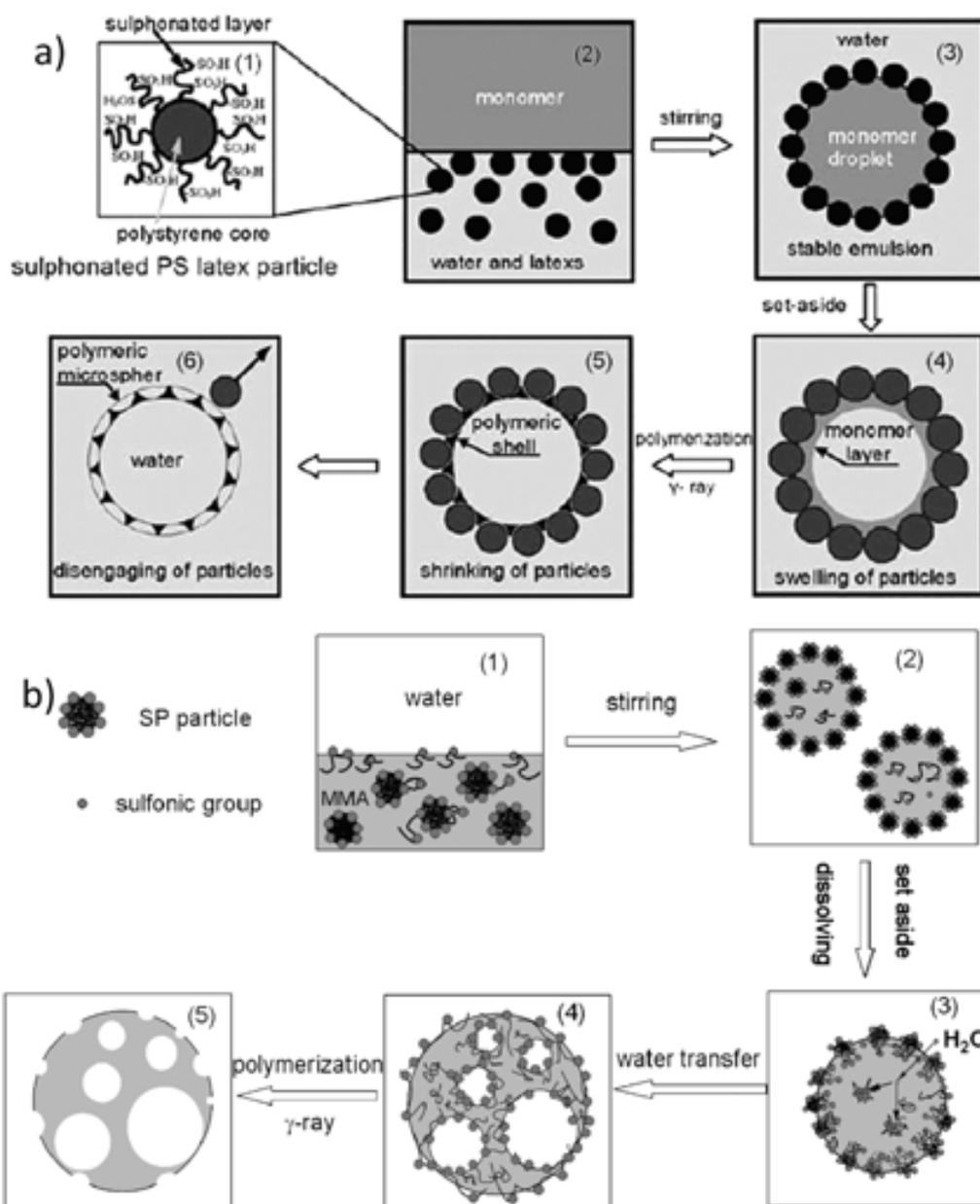


Figure 7. Schematic illustration of the formation of cage-like a) and multiple multihollow structure b) microspheres. Reprinted with permission from Yuan, Q. *et al.*, *Langmuir*, 25, 2729-2735. Copyright (2009) American Chemical Society.

sensitive to near infrared laser light applied in the drug delivery [56]. The pH responsive behavior of PSS/PAH capsules was studied by Dejugnat and Sukhorukov [57]. Swelling and shrinking of the capsules could be achieved under basic and acidic solutions respectively, which serve as a trigger to control the permeability of the polymer capsules. Hollow polyelectrolyte shells can be used on

biological templates, not only for protecting biological interiors but also for mimicking their structures. PSS/PAH layers have been grown on human erythrocytes [58]. After decomposing template proteins, prepared polyelectrolyte shells are considered as the replicas of the original cells. Further deposition of lipids allows the control of the permeability of small polar molecules.

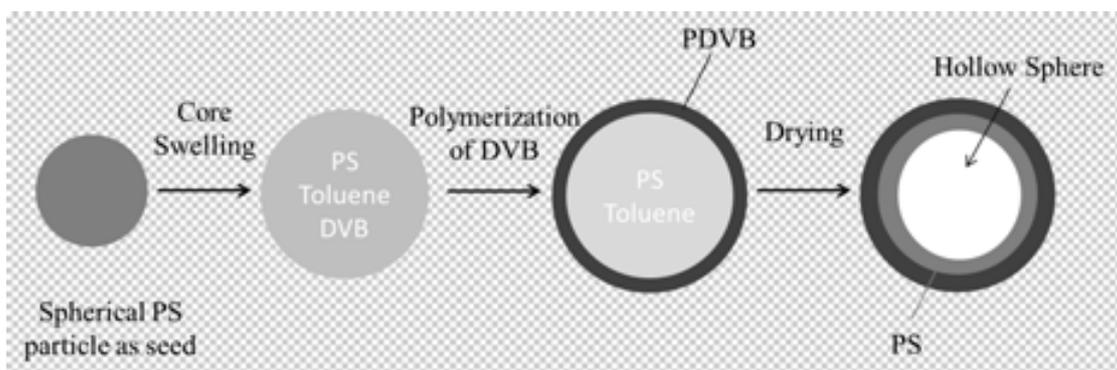


Figure 8. Formation mechanism of monodispersed hollow polymer particles by seeded polymerization for the dispersion of (toluene/DVB)-swollen PS particles prepared utilizing the dynamic swelling method. Adapted from [47].

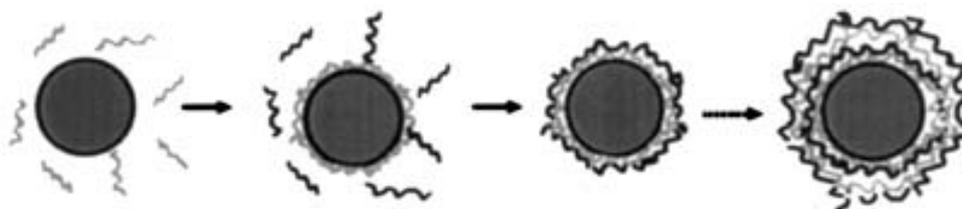


Figure 9. Schema of stepwise colloid particle coating with polyelectrolytes. The grey and black molecules represent polycations and polyanions respectively. Reprinted from Sukhorukov, G. B. *et al.*, 1998, *Polym. Adv. Technol.*, 9, 759-767, with permission from John Wiley and Sons.

Besides the liquid droplets or solid particles, microbubbles have been used as templates for lipid bilayers and polymer films. Microbubbles covered with a lipid bilayer are expected to be used as ultrasound contrast agents [59]. Shchukin *et al.* and Winterhalter *et al.* described the polyelectrolyte microcapsules with a gaseous interior by LbL self-assembly [60, 61] (see Figure 10). Air microdispersion was performed by ultrasound generator. PAH/PSS multilayers were adsorbed at the water/air interface. The size of resulting capsules is in a wide size distribution (1-20 μm). Recently a new preparation method of PAH/PSS microcapsules with microbubble templates in the size of approximate 5 μm has been reported by Daiguji *et al.* [62]. No surfactants were required in this process. By controlling the pH of Na_2CO_3 solution, CO_2 microbubbles covered with R-NHCOO^- and R-NH_3^+ were assembled by a PAH layer and finally deposited a PSS layer.

6. Other methods

Many other fabrication methods have been developed for hollow polymer particles. Spray drying technology is a simple and efficient process to obtain products in narrow size distribution [63]. It is based on accumulating solute at the sprayed droplet surface which diffuses relatively slowly than the solvent during the drying process, resulting in forming the solid shell. Spray drying process was applied to produce PLGA microcapsules encapsulating the volatile solid, ammonium carbonate, for use as ultrasound contrast agents [3].

Microfluidics has attracted attention in recent years offering low cost and easy use for controlling fluid flow. The droplet size can be highly controlled and the particles are monodispersed since droplets solidify during the emulsion preparation [64]. Biodegradable PLLA capsules with a narrow size distribution were prepared by optimizing the flow rate of the

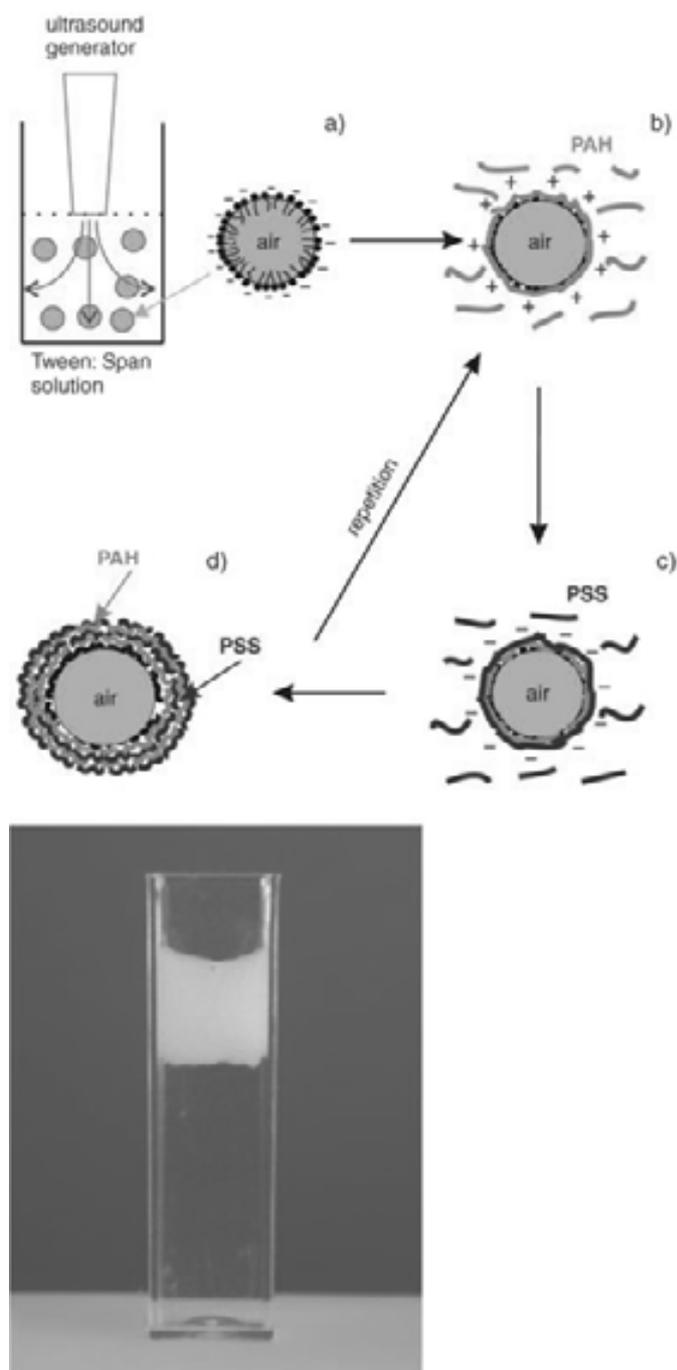


Figure 10. Schematic illustration of the formation of polyelectrolyte capsules on an 'air' core. a) The Tween/Span mixture is used to form air microbubbles; b-d) Microbubbles are stabilized by the electrostatic assembly of PAH/PSS multilayers. The photograph shows air-containing polyelectrolyte capsules in aqueous solution after centrifugation. Reprinted from Shchukin, D. G. *et al.*, 2005, *Angew. Chem. Int. Ed. Engl.*, 44(21), 3310-3314, with permission from John Wiley and Sons.

continuous phase and PLLA molecular weight in the microfluidics system [65].

A new method to prepare particulate polymeric carriers in nano- and micro-meter size has been studied, named electrohydrodynamic atomization (EHDA). No templating or the use of surfactants are required making the process more efficient.

A liquid is slowly injected through a capillary which is applied at certain voltage and injected flow rate. The liquid emits from the cone vertex and breaks up into fine droplets [66, 67]. The primary droplets are monodispersed and their size is controlled by either spray rate or the electrical conductivity of the liquid.

CONCLUSIONS

Due to their unique properties, such as high specific surface area, low density, and useful inner void, hollow polymer particles have been widely used as drug delivery carriers, catalysts, coatings, etc. This review highlights the diversity of methods that have been developed to fabricate this class of materials, together with their progresses. Although a number of polymers were mentioned here, the methods described can be applied into a broader range. Polymers with various compositions and properties can be successfully prepared by one or combined processes. However, the commercialization of existing methods is still a big challenge. Economic considerations on equipment and operation cost, processing time, and complexity of fabrication process need to be emphasized. Regarding the hollow polymer structure in nano- and micro-meter size, its stability and functionality also need to be enhanced. The development of new polymer and composite materials will impart new functionalities and applications to the hollow polymer particles.

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