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Review

Hollow Polymer Nanocapsules: Synthesis, Properties, and Applications

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Hollow polymer nanocapsules (HPNs) have gained tremendous interest in recent years due to their numerous desirable properties compared to their solid counterparts. Dramatically increased surface area, extremely low densities, and myriad tailorable functionalities make HPNs a target of numerous research efforts. Herein, this review focuses specifically on organic, polymeric-based, hollow particles on the nanometer size scale. This review aims to cover the diverse array of synthetic techniques for the fabrication of HPNs, the unique properties displayed by these particles, and the fascinating applications being envisioned and realized by these materials, with particular focus on work conducted in the past three years.

Introduction

Hollow polymer nanocapsules (HPNs) are an exciting class of materials which are of significant interest for a variety of applications ranging from high efficiency targeted therapeutics to ultra-sensitive sensing devices. Because of the hollow nature of these materials, they display exceptionally high surface areas, are capable of highly efficient loading and encapsulation, and from the wide variety of routes for their design, can be synthesized with myriad structural and functional motifs. Herein, we define HPNs as materials which consist of covalently linked or otherwise disassemblable polymer material, which in dilute conditions display the absence of chain exchange, consist primarily of a hollow void and thin polymeric shell, and most importantly are on the nanometer size scale (*i.e.* 1-1000 nm).

The topic of hollow materials is quite broad,[1] and several excellent reviews have been published concerning non-polymer hollow structures, such as silica,[2,3] carbon,[4] platinum,[5] and metal sulfides.[6] Methods for the synthesis of these various hollow structures have been reviewed, including through self-assembly,[7] templating,[8] and precipitation polymerization.[9] Several reviews have focused specifically on the potential of hollow nano- and microcapsules as catalytic [10,11] and biomedical materials.[8,12] The focus of this review concerns polymer-based HPNs, on the nanometer size scale, and primarily discusses work from the last three years (*i.e.* 2017-2015), and serves as an update to a similar review published in 2011.[13] With the ever expanding abilities of synthetic chemists to create a vast array of polymer architectures of myriad compositions coupled with advances in polymer characterization, the field of HPNs is rich with recent examples demonstrating the elegance of the modern polymer chemist, as shown in Figure 1. These examples are highlighted here, where we begin with a thorough discussion of the variety of synthetic protocols for the production of HPNs including inorganic nanoparticle templating, emulsion polymerization techniques, and other unique strategies. The hollow nature and the properties this imbues on HPNs are highlighted in the

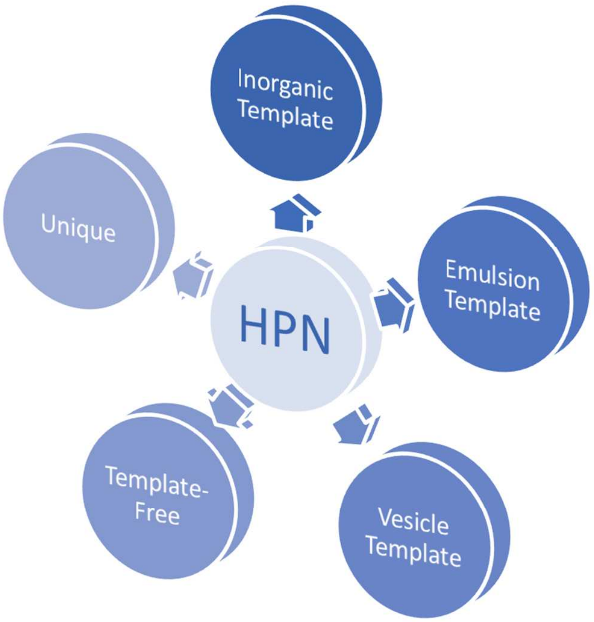

Figure 1. Summary of the various synthetic methods towards hollow polymer nanocapsules (HPN).

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proceeding section, including surface area and swelling. Applications of HPNs are then introduced which demonstrate the incredible potential of HPNs as next-generation materials in a multitude of arenas, such as biomedical, energy, and membranes. Finally, we close with a brief outlook of the future directions of hollow polymer nanocapsules.

Synthesis

Inorganic nanoparticle templating

Inorganic nanoparticles are an ideal template from which to construct a variety of polymer architectures, due to the extremely diverse functionalities that can be imparted onto the surface, ease of synthesis and processing, and controllable size.[14–18] Furthermore, core removal is typically quite straightforward with cores such as silica being easily etched with hydrofluoric acid, and many metal nanoparticles etched with hydrochloric acid or other acidic media. The groundwork for synthesizing HPNs from inorganic nanoparticles began with layer-by-layer grafting of polymers onto inorganic substrates. Much of the pioneering work in this field was conducted by Mohwald and Kotov who demonstrated the ability to create discreate polymeric capsules using this methodology.[19–22] This work was proceeded by some of the first examples of the ability to covalently graft polymeric material to nanoparticle substrates by Prucker and Rühe in the late 1990s.[23,24] This work coincided with the development of controlled radical polymerizations, which naturally led to the merger of these fields in the early 2000s, with Pyun, Patten, Benicewicz, and others using atom transfer radical polymerization (ATRP) and reversible addition-fragmentation chain-transfer (RAFT) polymerization on solid surfaces to grow well defined polymers.[25–29] One of the first examples to demonstrate using inorganic nanoparticles to create HPNs was carried out by Blomberg and coworkers.[30] Using a nitroxide-mediated polymerization technique of styrene and a activated ester or benzocyclobutene functionalized monomer from silica nanoparticle (SiNP) surfaces, followed by either chemical or thermal crosslinking of these respective blocks led to a crosslinked polymer shell around the surface of the nanoparticle. Treatment with hydrofluoric acid gave well defined hollow crosslinked nanoparticles. Contemporaneously, Kamata synthesized hollow polymer nanocapsules containing a gold nanoparticle in the core using ATRP techniques to control polymer growth from the surface of silica covered gold nanoparticles followed by treatment with HF.[31] The field has expanded significantly since then, and the recent advances in the field are discussed below.

In a recent example of using inorganic nanoparticle templates to synthesize well-defined HPNs, Bentz and coworkers used SiNPs as sacrificial templates for the synthesis of poly(caprolactone-*b*-ethylene glycol) (PCL-*b*-PEG) HPNs.[32] Using hydroxy-functionalized SiNPs,[33] crosslinked PCL was grafted-from the surface, followed by conjugation of PEG using carbodiimide coupling chemistry. Core removal was accomplished using hydrofluoric acid. This reaction sequence is shown in Figure 2. It was shown that the hydrodynamic radius of the polymer modified SiNP increased from 70 nm to 125 nm after growing crosslinked PCL on the surface. Subsequent addition of PEG onto the surface and digestion of the silica core yielded an HPN with a size that varied from 50 nm in water to 219 nm in THF. In these studies, the aqueous HPN size was less than the original SiNP, while the large size in THF was a result of releasing constraint on surface-tethered chains.

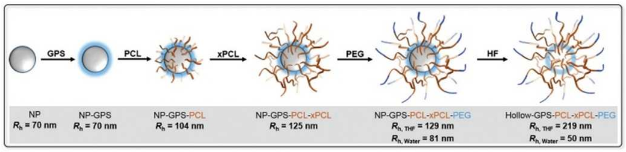

Figure 2. Schematic of hollow amphiphilic nanocapsules synthesized from sacrificial silica nanoparticle templates. Particle hydrodynamic radii are shown for each part of the synthesis. Reproduced from Ref. 32 with permission from the Royal Society of Chemistry. [DOUBLE COLUMN]

SiNP templates have been used to construct HPNs from polyacetylene by Lin and coworkers.[34] After first synthesizing SiNPs and functionalizing with acetylene groups, a seeded emulsion polymerization was conducted with a crosslinking molecule and either a chiral substituted acetylene or phenylacetylene in the presences of PEG *t*-octylphenyl ether surfactant and $(nbd)Rh^+(C_6H_5)_4$ as the catalyst. Subsequent treatment with HF gave polyacetylene HPNs.

Li and coworkers produced double-shelled HPNs from silica nanoparticle templates by first synthesizing particles with vinyl functional groups.[35] Following synthesis of the nanoparticles, polymer was grafted from the nanoparticle surface using traditional radical polymerization with propargyl methacrylate, methacrylic acid, and ethylene glycol methacrylate. Subsequent addition of thiol-functional PEG using thiol-alkyne click chemistry, followed by treatment with hydrofluoric acid gave hollow double-shelled HPNs. Zhou and coworkers synthesized double-shelled HPNs from SiNP templates with an inner layer of tin dioxide and outer layer of poly(ethyleneglycol dimethacrylate-*co*-methacrylic acid) (P(EGDMA-*co*-MAA).[36] SnO was first deposited onto the SiNP surface using a hydrothermal technique,[37] followed by copolymerization of ethylene glycol dimethacrylate and methacrylate acid to give crosslinked polymer shells *via* a distillation precipitation process. Following removal of the SiNP core (160 nm), the resulting double-shell HPNs were measured to have a diameter of 220 nm *via* TEM measurements. However, in aqueous conditions, the hydrodynamic size was determined to be 418 nm, indicating that the polymer shell was highly swollen, as expected from the release of surface tethered chains and osmotic swelling.

Polydopamine copolymer HPNs containing an indazole ligand were constructed by Fan and coworkers using sacrificial SiNP templates.[38] Using oxidative polymerization of dopamine and an indazole-containing monomer, 5,6-dihydroxy-1*H*-indazole in the presence of silica nanoparticles, crosslinked polydopamine copolymer was grafted to the particle surface. Following core removal in using hydrofluoric acid, copolymer polydopamine particles were obtained, as shown in Figure 3. These particles were shown to have enhanced binding of copper(II) in solution, as well as negligible cytotoxicity.

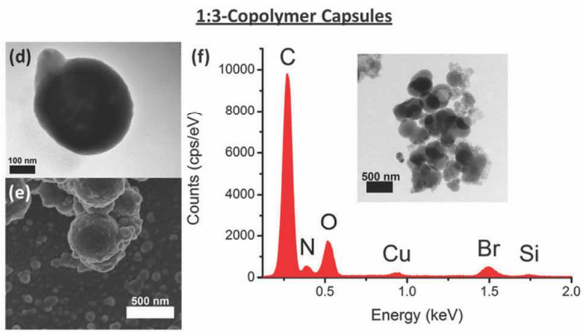

Figure 3. Synthesis of polydopamine copolymer HPNs containing an indazole ligand via oxidatative polymerization and sacrificial silica nanoparticle templates. Reproduced from Ref. 38 with permission from the Royal Society of Chemistry.

Using a unique reactive interface-guided co-assembly methodology, Liang and coworkers synthesized mesoporous HPNs from resol, a type of phenolic resin, and Pluronic F127.[39] Resol and F127 were found to form micellar assemblies in solution, which when introduced to suspensions of functionalized SiNPs reacted to form phenolic networks on the nanoparticle periphery with micelles of F127 located throughout. Removal of F127 and subsequent etching of the silica core afforded HPNs with periodic pores with diameters of about 5 nm. The methodology was extended to include Au@SiNP templates, which gave hollow, yolk-shell architectures.

Thermoresponsive polymers are attractive materials from which to construct HPNs, as they have been shown to be useful in a variety of applications such as drug delivery and smart materials.[40] Temperature responsive hollow double-shell HPNs were synthesized by Dubbert and coworkers[41] using silica nanoparticle templates. After surface functionalization with methacryloyl groups, a layer of poly(*N*-isopropylacrylamide) (PNIPAM) crosslinked with *bis*-acrylamide was grown from the surface, followed by a second layer of poly(*N*-isopropylmethacrylamide) (PNIPMAM) crosslinked with *bis*-acrylamide. Core dissolution using sodium hydroxide gave discrete nanogel HPNs with hydrodynamic radii of 387 nm at 20 °C. At 40 °C, above the LCST of PNIPAM but below the LCST of PNIPMAM, the nanogel HPNs had hydrodynamic radii of 269 nm, and at 50 °C, above both LCSTs, the hydrodynamic radius was 179 nm, consistent with chain collapse of each block above its corresponding transition temperature. In a separate study,[42] neutron scattering experiments fit to a core-shell-shell model showed similar particle radii at the corresponding temperatures. The study also coupled molecular dynamics (MD) simulations to show how cycling between LCST of each block in the presence of guest molecules provides an extremely efficient loading and release mechanism. Li and coworkers synthesized photo- and themo-responsive, molecularly imprinted HPNs from SiNP templates.[43] Following a modified Stöber synthesis to impart the SiNPs with ATRP initiators, crosslinking was performed *via* the polymerization of a small shell of ethylene glycol dimethacrylate in the presence of 4-((4-methacryloyloxy)phenylazo)pyridine and 2,4-dichlorophenoxyacetic acid. The template and residual copper and ligand were removed and successive polymerizations of *N*-isopropylacrylamide and hydroxyethyl methacrylate were carried out, and the silica core was subsequently removed with HF to yield photo- and thermo-responsive HPNs.

In a unique form of inorganic nanoparticle templating, Xiang and coworkers used a zeolitic imidazole-based metal-organic framework (MOF), ZIF-8,[44,45] as a template on which to construct HPNs of polydopamine.[46] To form the MOF, 2-methylimidazole and Zn^{2+} ions were mixed, along with PVP surfactant-functionalized gold nanorods which were included to impart photothermal properties to the resulting HPNs. After formation of ZIF-8, dopamine was introduced and subsequently polymerized in a chelation competition induced polymerization (CCIP) method, resulting in polydopamine HPNs. Because of the affinity of dopamine for Zn^{2+}, competitive binding between dopamine and the MOF results, which disintegrates the surface of the MOF while simultaneously causing polymerization of dopamine at the MOF surface. The process of CCIP for polydopamine-based HPNs is outlined schematically in Figure 4.

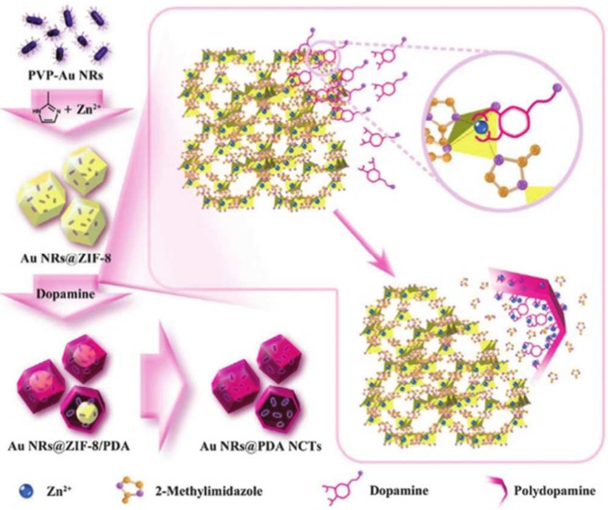

Figure 4. Schematic of formation of polydopamine HPNs from a chelation competition induced polymerization (CCIP) methodology. Reproduced from Ref. 46 with permission from The Royal Society of Chemistry.

Sonogashira coupling of tetrakis(4-ethynylphenyl)methane and 1,4-diiodobenzen in the presence of SiNPs gave nanoporous polymer shells around the nanoparticle in a form of a precipitation polymerization templating.[47] Following core removal with HF, the aromatic rings were sulfonated by treatment with chlorosulfonic acid, as shown in Figure 5.

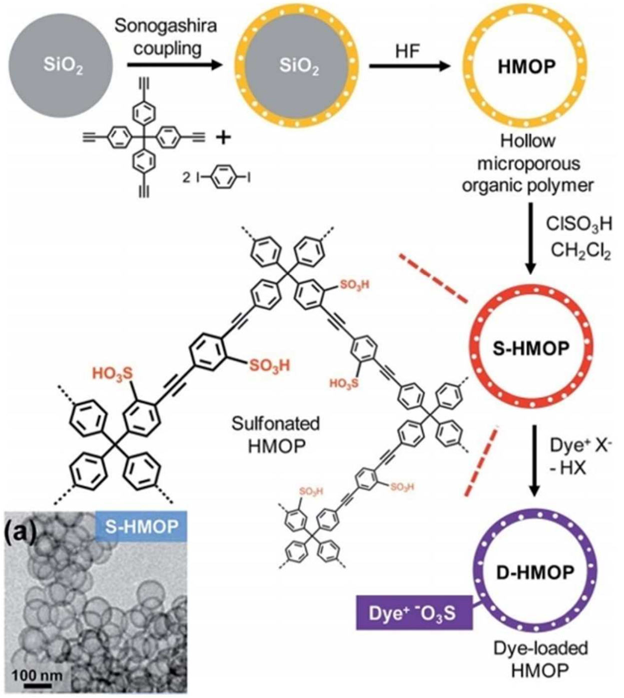

Figure 5. Schematic of formation of nanoporous HPNs from sonogashira polymerization and subsequent removal of sacrificial silica nanoparticle cores. Inset: TEM image of nanoporous HPN (S-HMPO). Reproduced from Ref. 47 with permission from The Royal Society of Chemistry.

Emulsion templating

Emulsion polymerization is one of the oldest techniques used to create polymer nanoparticles, and is as such is very well-studied and highly versatile.[48] Recently, the field of emulsion polymerization has expanded to include unique types of techniques such as nano-emulsions and non-aqueous.[49–51] The use of emulsions as soft templates for the formation of hollow polymer nanocapsules has been used extensively, especially for the synthesis of micron-sized HPNs.[52–57] This method offers numerous advantages such as the ability to synthesize hydrophobic monomers/polymers in primarily aqueous media, highly spherical particle morphologies, and mild reaction conditions. This method does, however, suffer from difficulty in controlling particle size dispersity as well as synthesizing particles less than 100 nm in diameter, even at high surfactant concentration.[58] This is often a direct result of partitioning of the emulsifier into the particle interior, leading to a reduction of active stabilizer, resulting in higher particle sizes.[59] Despite these disadvantages emulsion templating is one of the more commonly employed methods for the synthesis of HPNs. For a general review regarding hollow latex particles, the reader is directed elsewhere.[60]

Redox-responsive monodisperse polyvinylcaprolactam (PVCL) HPNs were prepared by Bian and coworkers using an emulsion droplet-mediated precipitation polymerization method.[61] Emulsion templates of dimethyldiethoxysilane were first synthesized using a base-catalyzed hydrolysis and condensation, followed by functionalization with (trimethoxysilyl)propyl methacrylate. Polymerization of vinylcaprolactam, with and without methacrylic acid, and disulfide-containing crosslinker *N*,*N*′-bis-(acryloyl)cystamine in the presence of emulsion templates, followed by core removal yielded HPNs of PVCL, as shown in Figure 6. The authors demonstrated that the HPNs were readily degraded in the presence of 10 mM glutathione, and that doxorubicin loaded HPNs caused significant cell death in HeLa cells, but non-drug loaded particles displayed negligible cytotoxicity.

Anisotropy in colloidal particles is a highly sought-after property in materials chemistry.[62–67] Early work in the development of anisotropic colloidal particles was originally carried out by Kim and coworkers using crosslinked polystyrene latex seeds, but the resulting Janus particles had dimensions on the micron size scale.[68] To reduce the dimensions of these particles to the nanometer size scale, Park and coworkers,[69] used non-crosslinked polystyrene cores synthesized from conventional emulsion polymerization, followed by sequential addition of styrene and 3-(trimethoxysilyl) propyl methacrylate, to give core-shell structures. The particles were then swollen with additional styrene, which during heating and polymerization collapses to form a lobe on the core-shell particle surface, endowing the particles with anisotropic character.

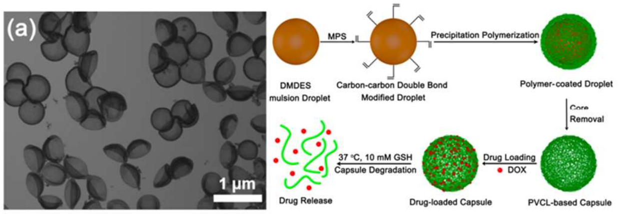

Figure 6. Synthesis of redox-responsive polyvinylcaprolactam HPNs using an emulsion droplet-mediated precipitation polymerization method. Reprinted with permission from *Chem. Mater.* **2015**, *27*, 1262–1268. Copyright 2015 American Chemical Society.

Extending these examples to the focus of hollow particles, crosslinked PNIPAM-based Janus HPNs were synthesized by Chu and coworkers using similar conditions as described above, but with the addition of a crosslinked PNIPAM shell.[70,71] Treatment with THF remove to PS core gave the Janus particles hollow character, as confirmed by cryo-TEM, scanning force microscopy, and dynamic light scattering. Additionally, depolarized dynamic light scattering (DDLS) showed high intensity scattering, indicative of anisotropic particles. Because of the thermoresponsive character of PNIPAM, the particles showed not only distinct temperature dependent behavior on their size, but also their aspect ratio, owing to their anisotropy. At 10 °C the hydrodynamic radii of the particles were approximately 250 nm, but when the temperature was increased to 50 °C the hydrodynamic radii of the particles dropped below 150 nm. Furthermore, the aspect ratio (given as the ratio of the center-to-center distance of each sphere component in the Janus particles to the overall diameter of the HPNs) of the particles increased from 0.21 to 0.38 over the same temperature span.

Casein-based HPNs were synthesized by Zhang and coworkers[72,73] using an emulsion polymerization method in which caprolactam-modified casein was used at the emulsifying agent. Methacrylic acid (MMA), butyl acrylate, and methyl methacrylate were then introduced, along with ammonium persulfate initiator to yield polyacrylate-casein core-shell particles. To obtain hollow core structures, the nanoparticles were subjected to slightly basic, aqueous conditions (pH ~ 10) causing a migration of hydrophilic chains to the particle periphery and creating a hollow void in the particle interior. By varying the quantity of MAA during particle synthesis, visible-light transmittance was tuned in resulting particle films. Hollow, natural rubber-based HPNs were synthesized in a similar manner by Wichaita and coworkers.[74] First, natural rubber latex particles were swollen with divinylbenzene monomer and tetraethylene pentaamine and *t*-butyl hydroperoxide redox initiators. Subsequently methyl methacrylate and acrylic acid monomers were added and the polymerization was continued. While polymerization occurred predominately on the NR latex surface, appreciable amount of polymer was formed in the NR core, which induced a phase-separation phenomenon to occur between the rubber and synthesized polymer, leading to the formation of a hollow interior. The hollow void size was increased with increasing mass ratio of monomer to NR latex core, with a void of 155 nm being formed in a 298 nm particle at a 4:1 ratio.

Shen and coworkers[75] combined emulsion polymerization with post-polymerization acid-base treatment to synthesize HPNs of poly(styrene-*s*-*N*,*N*'-dimethylaminoethyl methacrylate). After traditional emulsion polymerization with styrene and *N*-*N*'-dimethylaminoethyl methacrylate, the latex particles were treated with acid, which induced swelling of the particles due to protonation of amino groups. Base was then introduced, which deprotonated the amino groups, and increased the interfacial tension between polymer and water, maintaining the swollen size. In order to minimize free energy, the interfacial area was reduced by forming pools of water in the particle interior, giving rise to HPNs.

The Shirasu porous glass (SPG) membrane emulsification technique[76,77] has been utilized for the formation of hollow polymer nanocapsules. This method utilizes glass membranes of highly uniform pore sizes on the order or 0.1 to 20 µm in diameter, through which emulsions are pushed using nitrogen gas pressure to produce very monodisperse droplets. An example synthesis by Zhai and coworkers[78] utilized the SPG method to form hollow nanocapsules of polydopamine. Emulsions of toluene, hexadecane, and sodium dodecyl sulfate (SDS) were formed using SPG membranes with average pore sizes of 300, 800, and 1,500 nm. Following emulsion formation, dopamine and tris(hydroxymethyl)aminomethane (tris) were introduced to the emulsion and allowed to react, forming polydopamine in an oxidative polymerization method. Dialysis yielded monodisperse hollow polydopamine nanocapsules. Shin and coworkers have also used the SPG membrane-method for the synthesis of hollow spheres of polystyrene-*b*-polybutadiene.[79] Monodisperse HPNs were obtained when the operating pressure was between 1.3 and 2.3 times greater than the critical pressure required for emulsion formation. Furthermore, unique internal morphologies of the block polymers comprising the HPNs were observed when internal solvent was evaporated, including onion-like, or even coiled cylinders when homopolymers were added.

Polydopamine HPNs were synthesized by Zhai and coworkers using a mini emulsion technique in which toluene droplets acted as a soft template for the polymerization of dopamine.[80] Both core and shell size were tuned by either adjusting the size of the initial toluene droplets, or initial quantity of dopamine, respectively.

Sudjaipraparat and coworkers[81] demonstrated the synthesis of non-spherical HPNs using a seeded emulsion polymerization technique in a one-pot manner. Either additional styrene or methyl methacrylate monomer were introduced after the synthesis of crosslinked latex particles of poly(styrene-*s*-divinylbenzene-*s*-acrylic acid). The additional monomer caused non-spherical swelling of the particles, which following polymerization, gave rise to particles with a hollow core. The non-spherical nature was understood by a negative spreading coefficient, S_M, which is related to the interfacial tension between particle-water, particle-monomer, and monomer-water.

Polystyrene HPNs containing a hole in the capsule were first were synthesized by Im and coworkers, using standard emulsion polymerization of styrene followed by swelling with solvent, freezing, and thawing,[82] and similarly by Hyun and coworkers.[83,84] Similar particles were constructed in a facile manner by Kano and coworkers[85] using a standard emulsion polymerization with styrene and SDS with a fluorocarbon oil, perfluoro-*n*-octane (PFO). During emulsion formation, due to the immiscibility of PFO and styrene, the PFO component segregated to a droplet on the styrene droplets. Following polymerization of styrene and workup of the particles, the PFO droplet was removed to give hollow cup-type HPNs, where both hole size and particle size could be tuned by polymerization time. Several other polymers have been formed into hole-containing HPNs using similar methodologies such as poly(3,4-ethylenedioxythiophene),[86] poly(acrylamide-ethylene glycol dimethacrylate),[87] and poly(methylsilsesquioxane).[88]

An elegant and simple method designated as the supersaturated gas-cored instant polymerization (SGCIP) method by Matsubayashi and coworkers exploited the formation of nanobubbles created when mixing water and acetone to form polycyanoacrylate HPNs.[89] When water and acetone are mixed, the gas solubility of the mixture is less than the sum of the pure liquids, which results in supersaturation of the mixture and ultimately formation of bubbles on the nanometer size scale. When ethyl cyanocacrylate (ECA) was dissolved in acetone and water was introduced, phase separation of ECA to the gas/solution interface was induced with the ethyl group directed towards the gas phase and the relatively polar cyano group directed towards the solution phase. Because polymerization of cyanoacrylates occurs extremely quickly and is initiated spontaneously upon exposure to even small amounts of water, polymerization is induced immediately upon addition of water. The authors demonstrated that the size of the HPNs could be easily tuned by varying the water content in the mixture, with sizes ranging from 13 to 1830 nm, as shown in Figure 7.

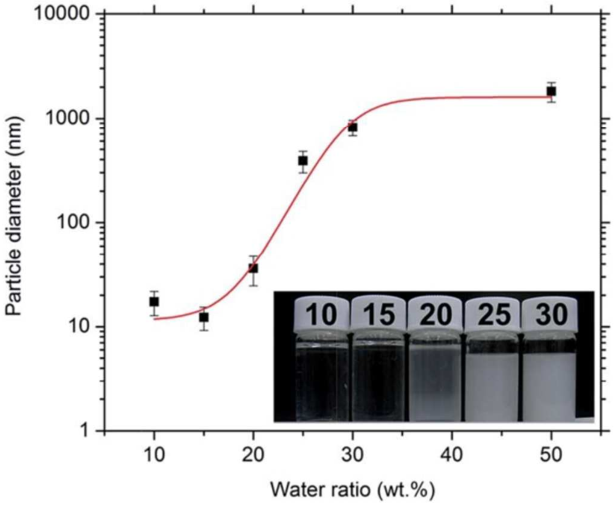

Figure 7. Particle sizes of polycyanoacrylate HPNs using super-saturated gas-cored instant polymerization (SGCIP) method; inset shows optical photographs of resulting HPNs synthesized at varying percentages of water. Reproduced from Ref. 89 with permission from The Royal Society of Chemistry.

Polymersomes and vesicle templating

The field of polymersomes is rich with examples of amphiphilic polymers that undergo self-assembly to form hollow vesicle-type architectures in close analogy to biological liposomes. Early examples demonstrated the broad utility of synthetic polymers to mimic nature and form well-defined morphologies, specifically hollow vesicles.[90,91] Inspired by these early efforts, researchers began to more fully understand the balance between hydrophilic and hydrophobic balance in synthetic polymers to create even more well-defined and predictable structures.[92] As the field advanced, polymersomes have been used for a wide variety of applications, especially in the biomedical field.[93]

The crosslinking of polymersomes gives rise to HPNs in the context discussed in this review, where dilution will not cause disassembly of the particles. A common approache towards the crosslinking of polymersomes is through UV photo-crosslinking. Such an example is the photo crosslinkable group poly(3,4-dimethyl imidobutyl methacrylate), as demonstrated by the Voit and Appelhans groups.[94,95] By systematically varying the content of hydrophobic poly(*n*-butyl methacrylate) and hydrophilic poly(2-(diethylamino)ethyl methacylate), followed by photocrosslinking, pH responsive crosslinked vesicles were obtained. Importantly, a sharp transition between swollen and collapsed vesicles as a function of pH was shown, with highly tunable pH depending on block composition, as shown in Figure 8. Recently, Deng and coworkers designed polymersomes, which upon exposure to intracellular H_2O_2 underwent a cascade reaction to cause crosslinking of the vesicle bilayer.[96] This was achieved through oxidative self-immolation of boronic ester polymer side chains to reveal primary amines which caused bilayer crosslinking through interchain amidation reactions. Additionally, this cascade reaction lead to a switch in the bilayer hydrophilicity, and ultimately highly stable intracellular polymersome HPNs. A major issue commonly encountered with crosslinked vesicles is decreased membrane permeability.[97,98] Significant strides have been taken towards the synthesis of crosslinked polymersomes with controlled membrane permability. In crosslinked polymersomes containing poly(2-(diethylamino)ethyl methacylate), synthesized by Iyisan and coworkers, changes in pH were able to significantly change the membrane thickness, with a membrane thickness of 19 nm at pH 9 and 27 nm at pH 5.[99]

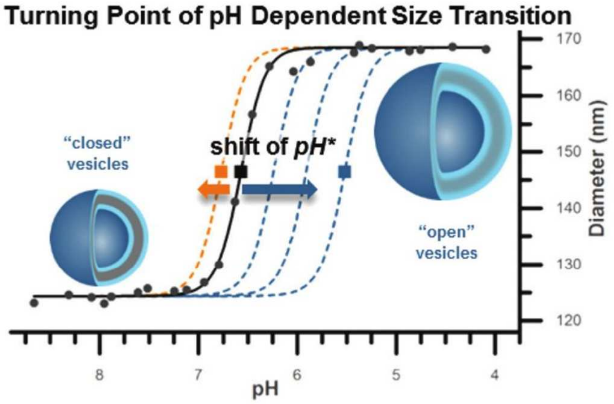

Figure 8. Hydrodynamic diameters of crosslinked PEG-*b*-poly(2-(diethylamino)ethyl methacylate)-*co*-poly(*n*-butyl methacrylate)-*b*-poly(3,4-dimethyl imidobutyl methacrylate) polymersomes. A sharp and tunable pH responsive transition in swelling state is achieved by varying the ratios of poly(2-(diethylamino)ethyl methacylate)-*co*-poly(*n*-butyl methacrylate) in the copoltner. Reproduced from Ref. 94 with permission from The Royal Society of Chemistry.

Other approaches towards hollow vesicle-type HPNs have involved the use of templates onto which polymer structures are attached or grown. This approach has several advantages in that the amphiphiles from which the HPNs are constructed typically are very well-studied and can form vesicles of very well-defined and predictable sizes. Sui and coworkers[100] used vesicles of cetyltrimethylammonium bromide (CTAB) and dodecylbenzenesulfate (SDBS), to serve as templates for the polymerization of 3,4-ethylenedioxythiophene, which upon surfactant removal resulted in hollow nanospheres of PEDOT ranging in size from 50 to 950 nm. Kim and coworkers[101] prepared acrylic and styrenic hollow nanocapsules starting with the coassembly of SDBS, cetyltrimethylammonium (CTAT), peroxide initiator, and the requisite monomers (*t*-butylmethacrylate, butylmethacrylate, and ethylene glycol dimethacrylate or *t*-butylstyrene and divinylbenzene). After assembly into bilayer-membrane vesicles, thermal initiation caused polymerization of monomer located in the vesicle bilayer resulting in hollow polymer nanocapsules, as shown in Figure 9.

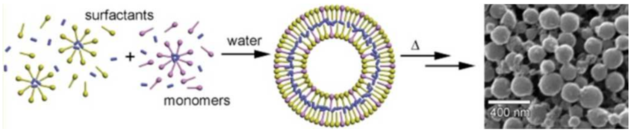

Figure 9. Synthesis of hollow acrylic and styrenic nanocapsules from vesicle-templated synthesis. Reprinted with permission from *Langmuir*, **2015**, *31*, 2561–2568. Copyright 2015 American Chemical Society.

Strong interactions of β-cyclodextrin and various guest molecules have been used to synthesize a variety of HPNs. Samanta and coworkers exploited the host-guest interactions between cyclodextrin and adamantane to create highly stable HPNs which were capable of encapsulating small hydrophilic monomers.[102] Vesicles of amphiphilic β-cyclodextrin were prepared by extrusion in buffer, with resulting hydrodynamic diameter of 128 nm. Separately, adamantine end-capped poly(acrylic acid) of DP = 81 was introduced to the vesicles, increasing the size to 142 nm through the host-guest grafting reaction. Crosslinking was accomplished through carbodiimide-mediated coupling of the PAA acid groups and 2,2'-(ethylenedioxy)bis(ethyleneamine), which resulted in a modest increase in hydrodynamic diameter to 150 nm, indicating that negligible particle-particle crosslinking occurred. Finally, the vesicle template was removed through treatment with Triton X-100 surfactant and dialysis. The reaction pathway towards these particles is shown schematically in Figure 10. In another example involving β-cyclodextrin hosts, Zhang and coworkers used azobenzene guest molecules as a route towards photo-responsive HPNs.[103] They first synthesized β-cyclodextrin terminated poly(2-(diethylamino)ethyl methacrylate) and a azobenzene terminated block polymer which contained a thermoresponsive block and crosslinkable block, poly((itaconoyloxy)ethyl methacrylate)-*b*-poly(*N*-isopropyl acrylamide). Following the host-guest interaction between the two end-capped polymers, self-assembly was induced to form swollen spherical assemblies at slightly basic pH and collapsed assemblies in slightly acidic conditions. Crosslinking of the itaconoyl groups was accomplished *via* radical-mediated coupling and polymerization through the pendant groups. Finally, the core was removed to yield HPNs by irradiation with 365 nm UV light to induce photoisomerization of the azo compound, which is known to dissociate the interaction.[104]

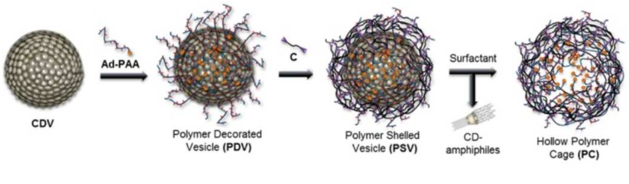

Figure 10. Synthesis of HPNs using β-cyclodextrin/adamantane host-guest interactions and subsequent amide crosslinking. Adapted with permission from *J. Am. Chem. Soc.* **2015**, *137*, 1967–1971. Copyright 2015 American Chemical Society. [DOUBLE COLUMN]

Template-free

Template-free methodology is a highly convenient route towards HPNs as fewer synthetic steps are typically required, and less waste is generated. While there are fewer examples demonstrating this method, some early examples of this technique were demonstrated with various metal-oxides,[105,106] as well as polymers.[107] Recently, Fan and coworkers[108] demonstrated the template- and additive-free synthesis of polystyrene hollow nanospheres using γ-ray irradiation-assisted self-assembly. By simply dispersing styrene into deionized water and irradiating with ^{60}Co γ-rays, hollow nanospheres with average diameter of 300 nm were formed in 15 hours. Because initiation of styrene is induced by either hydrogen or hydroxyl radicals, the polystyrene chain ends contain hydrophilic residues that induce self-assembly into vesicles in solution. Continued polymerization forms the nanospheres which are stable and dispersible in water, ethanol, DMSO, toluene, and DMF.

In a single-step utilizing an inside-out Ostwald ripening process, Kandambeth and coworkers synthesized HPNs from covalent organic frameworks (COFs) of 2,5-dihydroxyterephthalaldehyde (Dha) and 1,3,5-tris(4-aminophenyl)benzene (Tab), as shown schematically in Figure 11.[109] In the early stages of the network formation, π-π stacking interactions begin assembling the networks into rod-like structures, which in turn bundle into aggregates of aligned fibers, as shown in Figure 11b, 12 and 24 hours. Following fiber formation, spherical assemblies result, and the early stages of this process are evident in the TEM images in Figure 9b, 24 hours. After assembly into spheres, inside-out Ostwald ripening causes the spheres to develop into hollow particles after about 72 hours. While this phenomenon has been observed in inorganic metal oxide particles, examples with organic, polymeric material are exceedingly rare.[110,111]

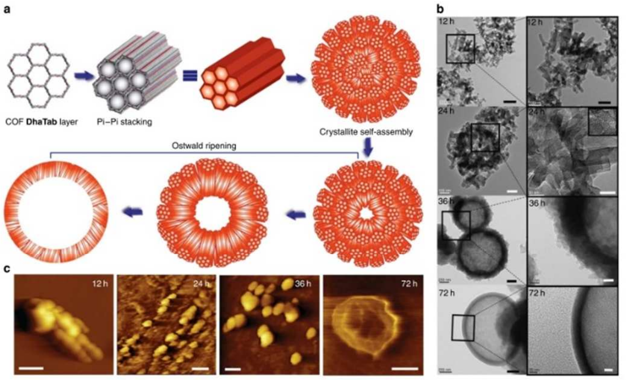

Figure 11. Synthesis of covalent-organic framework HPNs. a) Proposed mechanism of HPN formation from inside-out Ostwald ripening; b, c) TEM and AFM images, respectively, at various reaction times of HPN synthesis. Scale bars, (b) 12 h (200 nm, 100 nm), 24h (100 nm, 50nm), 36 h (200 nm, 50nm), 72 h (200nm, 20nm) and (c) 12 h (500 nm), 24h (500 nm), 36 h (100 nm), 72 h (100 nm). Used from Ref. 109 with permission from Macmillan Publishers Limited.

Polyaniline HPNs were synthesized using a self-assembly process in which a polyacid, poly(2-acrylamido-2-methylpropane sulfonic acid) (PAMPS), and aniline assembled into hollow micelles, followed by introduction of ammonium persulfate to oxidize and polymerize the aniline.[112] Depending on the quantity of PAMPS used, morphologies ranging from short nanofibers, to hollow spheres ranging in size from 350 to 430 nm could be obtained.

Using a plasma-enhanced chemical vapor deposition process, Lo Porto and coworkers synthesized polyethylene HPNs in a one-step process.[113] Depending on the method of plasma activation, either continually applied or pulsed, particles in the size range of 400-600 nm or 150-500 nm, respectively. Furthermore, during the aerosolization process used in the plasma reactor, the HPNs were filled with either vancomycin or fluorescein when aqueous solutions were introduced in the synthesis.

Unique morphologies

Anisotropy in colloidal particles is particularly attractive for a variety of applications.[62–67] The hollow nature of HPNs make these materials especially suited for advanced applications due to their high surface areas and ease of functionalization. Towards the development of anisotropic HPNs, Li and coworkers used rod-like SiNPs[114] as a sacrificial template for the synthesis of crosslinked polystyrene HPNs.[115] Using standard emulsion polymerization techniques of styrene and divinylbenzene in the presence of the rod-like SiNPs gave crosslinked polystyrene shells. An additional hypercrosslinking step was performed using Friedel-Crafts conditions to give nanoporous, highly crosslinked PS shells. Finally, the SiNP core was removed to give rod-like PS HPNs.

Sun and coworkers[116] prepared hollow nanotubes from self-assembled copolypeptoid tiles consisting of block polymers of hydrophobic poly-*N*-decylglycine and hydrophilic poly-*N*-2-(2-(2-methoxyethoxy)ethoxy)ethylglycine. Because the block polymers had monodisperse molecular weight (Đ = 1) nanotubes of uniform diameter were formed, and furthermore because of the structural motifs present on the block polymers, no hydrophobic core was formed during the assembly, as shown in Figure 12. At equal weight percent of hydrophobic/hydrophilic blocks (*i.e.* ~50 wt% each block) but with increasing overall molecular weight, the latitudinal periodicity remained constant at 2.4 nm as measured by both wide-angle X-ray scattering and electron microscopy, but the longitudinal stripe periodicity increased from 5.7 nm to 11.1 nm as the molecular weight increased from 3.6 kg/mol to 7.3 kg/mol.

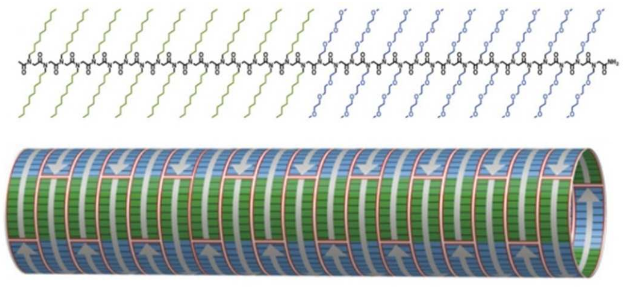

Figure 12. Hollow nanotubes from self-assembled copolypeptoid tiles. Copyright 2016 National Academy of Sciences, *Proc. Natl. Acad. Sci.* **2016**, *113* (15), 3954–3959.

In a particularly elegant example of the synthesis of anisotropic hollow particles, Qiu and coworkers[117] prepared hollow rectangular platelet micelles from cylindrical micelle seeds. Utilizing a living crystallization-driven self-assembly (CDSA) technique, cylindrical micelles of poly(ferrocenyldimethylsilane)-*b*-poly(dimethylsiloxane) (PFS-*b*-PDMS) were mixed with block polymers of PFS-*b*-poly(2-vinyl pyridine) (PFS-*b*-P2VP) and homopolymers of PFS. In order to overcome previous challenges of poor colloidal stability and irregular edges of resulting assemblies,[118] long corona chains of PDMS were used in the cylindrical micelle seeds. Upon mixing of the three components, the PFS blocks rapidly underwent CDSA to afford highly uniform platelet micelles in about five minutes, and the use of P2VP in the block polymer gave a polar corona. Corona crosslinking was then achieved by the addition of small (~2 nm) platinum nanoparticles which coordinated to the P2VP blocks. Finally, hollow platelets were obtained upon exposure to THF, which selectively solvates both blocks of the initial cylindrical micelle seed, removing it from the assembly. Further demonstrating the modularity of this approach towards hollow particles, the authors added the original cylindrical micelle forming polymer (PFS-*b*-PDMS) to pre-assembled platelet micelles prior to crosslinking, expanding the platelet micelles and imparting them with functionality similar to the starting cylindrical micelle seed (*i.e.* PFS core and PDMS corona). Subsequent addition of PFS-*b*-PDMS and PFS unimers, platinum nanoparticle-induced crosslinking, and exposure to THF gave both hollow, rectangular micelles, and the parent hollow platelet micelles.

Properties of HPNs

High surface area

High surface area materials are highly sought after in a wide variety of applications, such as catalysis, separation, and storage materials.[119,120] By definition, HPNs contain a hollow interior, so it follows that these materials have high surface areas compared to solid-core materials. An example highlighting this is demonstrated by Park and coworkers in HPNs of poly(tetrakis(4-ethynylphenyl)methane-*alt*-1,4-diiodobenzne).[47] They used 83 nm diameter silica particles, which have a surface area of roughly 50 m^2g^{-1}.[121] Following polymerization and core removal, the surface area was found to be 733 m^2g^{-1}, a greater than 14-fold increase, despite a polymer shell thickness of only 8.9 nm. Hollow lignin nanocapsules were synthesized by Xiong and coworkers[122] using a self-assembly technique, and they were shown to have dramatically increased surface areas following core removal. To synthesize the nanocapsules, enzymatic hydrolysis lignin was dissolved in THF, then upon slow addition of water, lignin nanospheres about 400 nm in diameter were formed. Particle diameter could be controlled by either stirring rate, rate of water addition, or pH value, where increasing any of these parameters resulted in decreased diameter. Furthermore, the lignin surface area was increased by up to 30-fold after formation into nanospheres. Synthesis and surface measurements using nitrogen absorption isotherms of hypercrosslinked rod-like polystyrene HPNs were carried out by Li and coworkers.[115] The templating SiNP core and subsequent layer of poly(styrene-*co*-divinylbenzene) showed surface areas of 12 and 15 m^2g^{-1}, respectively. Upon hypercrosslinking and SiNP core removal, the surface areas increased dramatically to 527 and 704 m^2g^{-1}, respectively. In another example, covalent organic framework hollow particles of 1,3,5-triformylphloroglucinol and *p*-phenylenediamine templated from ZnO nanorods showed dramatically increased surface areas before and after core removal.[123] The bare ZnO nanorods displayed a surface area of 31 m^2g^{-1} and increased to 180 m^2g^{-1} after templating the COF onto the particle. Following core removal, the measured surface area increased to 447 m^2g^{-1}. Examples of extremely high surface areas in HPNs have been reported, such as triphenylbenzene HPNs with surface areas of 933 m^2g^{-1},[124] and close to 1,500 m^2g^{-1} have been observed in covalent-organic framework HPNs.[109]

It is important to frame the properties of HPNs with other materials to gain a broader perspective of these materials and the areas for improvement and further research. A natural comparison of HPNs to other high surface area materials are metal-organic frameworks (MOFs), covalent-organic frameworks (COFs), and porous polymers. As described above, fully polymeric HPNs can be synthesized with surface areas approaching 1,000 m^2g^{-1} and up to 1,500 m^2g^{-1} has been reported in COF-based HPNs. Perhaps the most extreme example of high surface area materials are MOFs, which can approach surface areas of 10,000 m^2g^{-1}.[125–127] While traditional MOFs are highly crystalline and consist of small molecule organic linkers with inorganic building block clusters, significant progress has been made on forming polymer-based MOFs, which has tremendous upside for the field of high surface area hollow polymers.[128,129] In COFs and porous polymers, which contain no inorganic component as a main structural unit, surface areas are lower than many MOFs, but still show very high potential for use in HPN materials, with surface areas over 2,000 and 1,500 m^2g^{-1} reported, respectively.[130,131]

Loading capacity

The ability to load material in high capacity is vital for the certain applications such as drug delivery and energy storage. Early work towards polymeric materials with high loading capacity included polymer dendrimers,[132–135] and has since expanded to more controlled morphologies and materials, such as micelles and vesicles, as well as solid materials such as graphene oxide.[136–138] In addition to unique functions of HPNs, their hollow nature allows for high capacity loading of a variety of payloads. Bazylinska and coworkers synthesized PLA and PCL nanospheres and HPNs and compared their encapsulation capacity of a cyanine-type photosensitizer.[139] It was shown that in virtually all conditions tested, the encapsulation efficiency increased going from nanosphere to corresponding HPN, where in some cases the encapsulation efficiency was greater than 90%. Zhang and coworkers[124] used ZnO nanoparticles as templates for the formation of hollow porous organic polymers composed of tetraphenyl porphyrin (TPP), tetrabiphenyl porphyrin (TBPP), or triphenylbenzene (TPB). These particles showed both high loading capacities for hydrophobic dyes, as well as high surfaces areas. In particular, TBPP hollow nanospheres displayed excellent loading of Rhodamine B dye (460 mg/g after 500 minutes).

Controlled aggregation of Metal Nanoparticles in HPNs

One of the most desirable properties for colloidal materials to possess is high colloidal stability, *i.e.* exist in solution aggregation-free. However, it is often desirable to control the aggregation state of nature of colloids, to create hierarchical structure,[140,141] impart new functionality,[142] create or act as constrast agents in MRI,[143] to name a few examples.The ability to form small clusters of gold nanoparticles is desirable from a biomedical standpoint, as this permits facile clearance from the body with high wavelengths of light absorption.[144–146] Aggregate size of gold nanoparticles was controlled by the quantity loaded into vesicle-templated hollow nanoparticles, as demonstrated by Dergunov and coworkers.[147] With controlled quantities of gold nanoparticles loaded into the HPNs, the wavelength of absorption was significantly redshifted upon addition of acid. Gold nanospheres grafted with thermoresponsive polymer, poly(oligoethyleneglycol methacrylate-*co*-2-(2-methoxyethoxy)ethyl methacrylate) showed temperature dependent aggregation behavior.[148] Above the LCST of the polymer, although the individual particle diameters decreased, the apparent hydrodynamic diameters increased due to particle aggregation.

Swelling

An interesting feature of HPNs is the ability to reversibly swell and contract in response to various stimuli such as temperature, light, or solvent conditions. Controlled swelling and deswelling is highly desirable for drug delivery applications as well as for mechanical modulation in a variety of materials.[149–152] Because many HPNs consist of only a thin polymer layer or loosely crosslinked networks, steric and excluded volume chain packing effects are significantly diminished compared to traditional polymer assemblies. Furthermore, HPNs synthesized from sacrificial templates can show a significant expansion in size upon core removal due to relief of tethered chain ends. This was shown by Bentz and coworkers in PCL-*b*-PEG HPNs constructed from SiNP templates (hydrodynamic radii = 70 nm).[32] After grafting of amphiphilic block polymers, the hydrodynamic radii of the particles increased to 129 nm when suspended in a good solvent for both blocks (THF). However, when suspended in water, a poor solvent for the PCL block, the hydrodynamic radii decreased to 81 nm. Upon removal of the silica core and release of tethered chain end constrains, the hydrodynamic radii in good solvent increased to 219 nm. Finally, when the

PCL-*b*-PEG HPNs were suspended in water, the HPNs collapsed to hydrodynamic radii of 50 nm, a size lower than the initial SiNP core, illustrating the dynamic swelling character of HPNs. An example of pH responsive swelling was demonstrated by Wang and Sukhisvili.[153] Poly(acrylic acid) HPNs were prepared *via* carbodiimide-mediated crosslinking of PAA with adipic acid dihydrazide on PEO-PPO-PEO micellar templates, followed by core removal using dialysis. The resulting PAA HPNs displayed tunable degrees of swelling in response to pH changes with varying crosslink density, as shown in Figure 13. Particles with low quantities of crosslinks swelled to over twice their initial size when pH was increased from 2 to 7, due to deprotonation of the PAA side groups and resultant electrostatic repulsion. When the crosslink density was increased, the degree of swelling was very limited due to covalent chain constrains, precluding the ability of the polymer cages to swell, even with very high amount of electrostatic repulsion. Zhang and coworkers used temperature to reversibly swell PNIPAM-containing HPNs.[103] At 31 °C the HPNs had a hydrodynamic diameter of about 210 nm, but as temperature was increased to 39 °C, the diameter dropped to about 110 nm. Additionally, the particle could be returned to its original size upon cooling with very little hysteresis, and could be cycled many times. Similar behavior was observed in crosslinked polymersomes containing poly(2-(diethylamino)ethyl methacylate), where cycling between pH 5 and pH 10 caused a swelling of 1.5 fold to occur in acidic conditions due to the protonated amine side chains.[99] Furthermore, this process was shown to be highly reversible, which negligible loss in swelling or deswelling ability after 5 cycles.

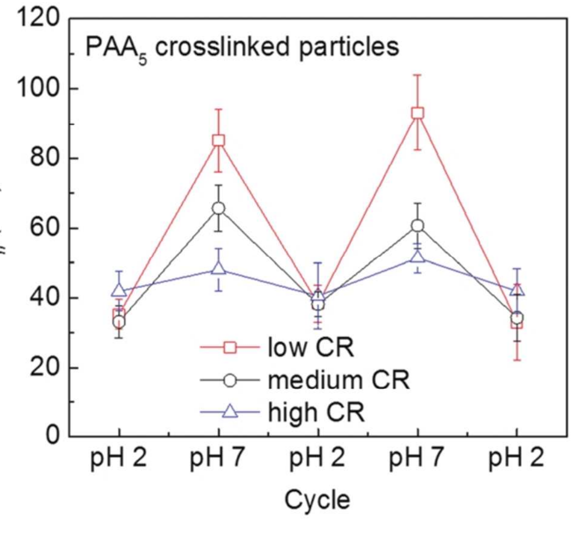

Figure 13. Crosslink density dependent swelling of poly(acrylic acid) HPNs, with hydrodynamic radii given as a function of solution pH. Low, medium, and high CR refers to low, medium, and high crosslink density, respectively. Reproduced from Ref. 153 with permission from The Royal Society of Chemistry.

Liu and coworkers exploited the controllable swelling of HPNs to tune the release kinetics of NO in *S*-nitrosothiol-containing hollow particles of poly((ethylene glycol dimethylacrylate)-*co*-(hydroxyethyl methacrylate)).[154] In the dry state, as measured by TEM analysis, the hollow particles had an average diameter of 169 nm. However, in real bovine serum the measured size as determined by dynamic light scattering was 420 nm. The swelling of the particles was even more enhanced in PBS buffer where the hydrodynamic size was 1794 nm.

Applications

Biomimetic HPNs

As hollow polymer materials with highly tunable size, functionality, and high storage capacity, HPNs are excellent materials for a variety of biomedical applications.[155] Given the hollow nature of HPNs, their ability to be efficiently loaded with cargo, and highly tunable surface properties, these materials are obvious choices for biomedical, drug delivery, and biomimetic applications The hollow nature of polymer capsules offers tremendous opportunity to begin creating cell mimicking devices. Significant progress has been made towards synthetic cellular systems in both polymer and inorganic material designs.[156–158] In order to create synthetic cells, however, communication between intraparticle and extraparticle environment is essential. Dergunov and coworkers have synthesized HPNs with porous walls which allow for communication between dye molecules inside and outside of the shell, which when interacting, create rotaxane-like structures.[159] Located inside the particle was 1,3,5-tri(4-acetylphenyl)isocyanurate which could undergo a Mannich reaction with a derivatized fluorescein molecule containing a variable length alkyl spacer with terminal amine. When the isocyanurate-containing particles were mixed with ethyl linker fluorescein and subsequently washed no change in fluorescence was observed compared to the pure isocyanurate-containing HPNs. However, when hexyl and decyl linkers were used, a significant wavelength shift in fluorescence maxima was observed, as shown in Figure 14. An example by Tamate and coworkers used crosslinked polymersome HPNs to create self-oscillating synthetic cells.[160] A block polymer consisting of PEG, and a thermo-responsive $Ru(bpy)_3$-containing block was effectively assembled into vesicle morphologies and crosslinked. Following this, changes in temperature and redox state of the Ru could effectively alter the size of the resulting HPNs. Finally, the oscillatory Belousov-Zhabot chemical reaction was used to give rise to HPNs with autonomous swelling and deswelling behavior, much like natural cellular systems. These results highlight important steps toward mechanisms by which synthetic cells may become viable.

While siRNA has emerged as a promising candidate for therapeutic applications such as gene suppression and treatment of a variety of genetic disorders, actual delivery of the nucleic acid to the target site remains a significant challenge.[161–163] An elegant example of such was demonstrated by Zou and coworkers who synthesized virus-mimetic chimaeric polymersomes composed of reversibly crosslinked PEG-*b*-poly(trimethylene carbonate-*co*-dithiolane trimethylene carbonate)-*b*-polyethyleneimine, and loaded with siRNA.[164] To impart the cell targeting ability of natural viruses to these particles, the cyclic peptide cNGQ, which shows high affinity for $\alpha_3\beta_1$-integrin-overexpressing tumor cells, was end-functionalized to a fraction of the assembling polymers, such that it was expressed on the particle surface. Additionally, This copolymer was found to effectively assemble into spherical vesicles with a radius of gyration of 49 nm. When loaded with varying amounts of siRNA, the R_g increased up to 175 nm. Finally, *in vivo* studies with mice bearig A549 human lung tumors demonstrated the highly effective nature of these particles to undergo receptor-mediated endocytosis, efficient payload release, and ultimately boost survival time of this mice significantly. Additionally, Kumar and coworkers used mesoporous polycaprolactone-based HPNs to load and effectively deliver siRNA to HepG2 cancer cells.[165] The HPNs were capable of loading 400 ng of siRNA per 1 mg of HPN, with delivery efficiencies up to 93%.

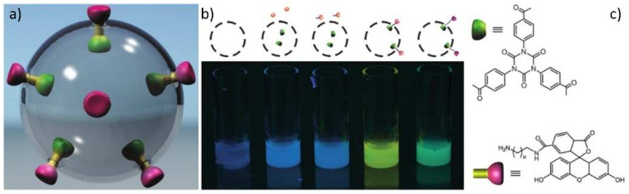

Figure 14. a) Schematic of porous HPNs with rotaxane-like fluorescent moieties threaded through the polymer shell. b) Schematic of various samples of rotaxne-linked HPNs and corresponding optical photograph under UV light. From left-to-right, HPNs with no internal isocyanurate; isocyanurate-containing HPNs treated with 6-amino fluorescein followed by washing; treatment with ethyl, hexyl, and decyl spacer amino-fluorescein, respectively. c) 1,3,5-tri(3-acetylphenyl)isocyanurate (green wedge) and fluorescein with alkyl spacer (pink wedge with yellow rod). Modified from Ref 159 with permission from John Wiley and Sons.. [DOUBLE COLUMN]

Drug delivery

Drug delivery is an extremely important application in the scientific community in general, and especially in the field of HPNs. While the field of drug delivery is far too broad to cover in detail, several excellent general reviews exist, and the reader is directed to those for a more general overview.[166–168] With regards to HPN drug delivery vehicles, Liu and coworkers[169,170] used hollow double-layer nanoparticles decorated with boronic acid and *S*-nitrosothiol groups to effectively target over-expressed sialic acid groups on tumor cells and release nitric oxide (NO) upon decomposition with intracellular glutathione. In the presence of low pH or low glucose concentration, the hollow double-layer nanoparticles selectively bound to human hepatocellular carcinoma cells (HepG2). It was demonstrated that the HPNs had highly tunable release kinetics of NO dependent on both solution tempertaute, and pH, as shown in Figure 15. Prolonged release of NO using hollow nanoparticles was demonstrated by Yamala and coworkers[171] by encapsulating sodium nitroprusside inside 100 to 150 nm hollow spheres of poly(*N*-acryloyl l-phenylalanine methyl ester). In addition to prolonged release of NO, immunomodulatory and adjuvant action in murine macrophages was also facilitated. The pH-responsive release of doxorubicin by crosslinked polymersome HPNs was demonstrated by Liu and coworkers.[172] Following self-assembly of fumarate-di-2,4,6-trimethoxybenzylidene-1,1,1-tris(hydroxymethyl) ethane end-capped PEG into vesicle morphologies in the presence of doxorubicin, crosslinking of the membrane was performed by redox reaction with ammonium persulfate and tetramethylethylenediamine. In acidic conditions the hydrophobic trimethoxybenzylidene moieties were cleaved, rendering the crosslinked HPN entirely hydrophilic, thus reducing the unfavorable interactions of doxorubicin with the HPN membrane.

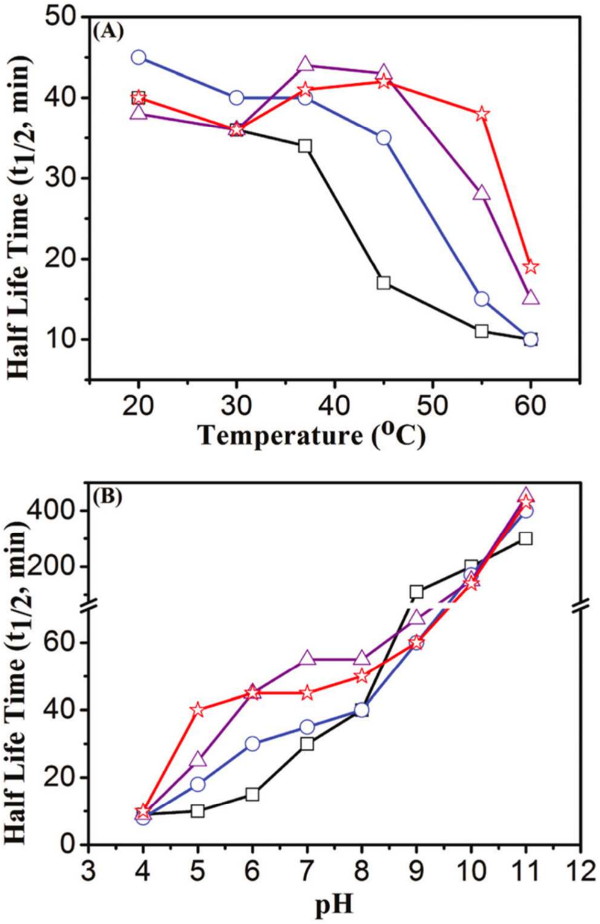

Figure 15. Release kinetics of NO from double-shelled *N*-diazeniumdiolated HPNs as a function of a) temperature and b) pH. Reproduced from Ref. 170 with permission from the Royal Society of Chemistry.

Through inclusion complexation and host-guest interactions, Li and coworkers,[173] prepared hollow spheres from sodium alginate-*g*-poly(*N*-isopropylacrylamide) (ALG-*g*-PNIPAM) and β-cyclodextrin (β-CD) for controlled release of cancer therapeutic 5-fluorouracil. Upon complexation of the isopropyl pendant groups of PNIPAM and β-CD, rod-like segments formed on the sodium alginate backbone coil. Self-assembly after complexation led to hollow spheres which displayed drug entrapment efficiencies of 25% to about 50% as the molar ratio of ALG-*g*-PNIPAM:β-CD increased from 1:1 to 1:5. The authors hypothesized that the loading efficiency increased with decreasing β-CD content due to spatial constraints in the particle interior with additional β-CD present. Drug release kinetics were considerably enhanced both above the LCST of PNIPAM (40 °C *vs.* 25 °C) and at slightly acidic conditions (pH = 5.2 *vs.* 7.0).

Energy and conductive materials

Research towards more efficient energy storage materials and batteries is becoming increasingly more important. Nanomaterials, especially HPNs which exemplify the high surface-to-volume ratio desired in nanomaterials, are extremely promising materials in energy applications.[174–177] Mesoporous HPNs formed from micelle-templated, Suzuki coupling polymerization of tris(4-bromophenyl)amine and benzene-diboronic acid were shown by Zhou and coworkers to be highly effective replacements for traditional oxide fillers used in solid-state lithium ion batteries.[178] The porous and hollow nature of the HPNs allowed for scavenging of impurities which are otherwise present with traditional oxide-containing batteries, thus lowering the impedance compared to cells containing Al_2O_3.

Hollow, ring-shaped assemblies of block polymer blends were used by Park and coworkers to improve performance in phase-change memory (PCM) materials.[179] While PCM is a promising candidate for high density memory storage, a major drawback is the high switching current required in many modern materials. By using coassemblies of PDMS-*b*-PS (cylinder formers) and PS-*b*-PFS (sphere formers) on PCM wafers followed by solvent annealing and reactive ion etching, the desired dot-in-hole morphology was obtained, and an extremely small switching current of 2-3 µA was measured.

Hollow metal nanospheres are of considerable interest due to their excellent conducting properties, combined with their relatively low density compared to their solid counterparts. These materials are especially attractive as conductive coatings formed both from spray-coating and ink-jet printing. A major drawback that limits the commercial viability of such materials is the need for stabilizers before or during the sintering process, as these stabilizers often act is resistive materials. To overcome this, Mir and Ochiai[180] formed hollow Ag nanoparticles with a conducting polymer shell of poly(*N*-vinylcarbazole-*co*-maleic anhydride)-*g*-[poly(propylene oxide)-*co*-poly(ethylene oxide)]. These nanocapsules were able to be ink-jet printed and give conductivities of 8.5×10^5 S/m without the need for thermal annealing.

Separation and membranes

Polymeric materials are widely used as separation membranes in a variety of applications, such as food packaging, water filtration, and gas separation. While many polymer materials demonstrate high selectivity and tunable permeability,[181–183] HPNs make ideal candidates for next-generation gas separation membranes due to their exceptionally high surface areas and low densities. Progress towards these materials was realized in the form of highly porous liquids developed by Zhang and coworkers, who templated PEG-sulfonate to hollow porous silica particles.[184,185] Because the hollow silica particles were functionalized with quaternary ammonium functionalized organosilanes, the polymer conjugation was accomplished via strong ionic interactions between the polymer head group and silica surface. The dynamic nature of the ion pair, combined with the relatively low molecular weight of the PEG (~1,000 g/mol) resulted in a liquid material. These materials were highly effective at separating CO_2/N_2 gas mixtures, due to Lewis acid/base interactions between the PEG and CO_2,[186] allowing the CO_2 to enter the particles where the hollow cavity allows for unimpeded flow.

Qin and coworkers used HPNs with high densities of amine and carboxy groups as pH sensitive absorbents for acidic dyes.[187] Precipitation copolymerization of styrene and maleic anhydride gave nanoparticle templates, from which a second layer of divinylbenzene and maleic anhydride was polymerized to give a crosslinked corona. Acetone wash, followed by reaction with diethylenetriamine gave high densities of both primary and secondary amines, as well as carboxy groups. At high pH, when the carboxy groups were deprotonated, low binding affinity of the dye was observed, with loading levels of 59 mg/g. However, when the pH was lowered, protonating both the carboxy groups and amine groups, loading increased dramatically to 406 mg/g, as shown in Figure 16.

Figure 16. pH modulated absorption of amine and carboxy-functional HPNs. Adapted with permission from *ACS Appl. Mater. Interfaces* **2016**, *8*, 16690–16698. Copyright 2016 American Chemical Society.

Xie and coworkers used hollow molecularly imprinted polymer nanotubes for the selective recognition and separation of chloramphenicol, an antibiotic used in the aquaculture industry that is being found in increasingly high levels in the food chain and drinking water.[188]

Proton exchange membranes (PEM) are an important component in direct methanol fuel cells, and are commonly constructed from sulfonated poly(ether ether ketone) (SPEEK).[189,190] Zhang and coworkers found that conductivity was nearly doubled in SPEEK membranes containing HPNs of sulfonated polystyrene brushes compared to native membranes in the absence of HPNs.[191] Additionally, proton conductivity was measured in SPEEK membranes containing HPNs only consisting of a thin layer of sulfonate-functional groups compared to long brushes of sulfonated polystyrene. The brush-containing membranes not only exhibited higher proton conductivity compared to the thin sulfonated HPNs, but also displayed slightly higher tensile strength and Young's modulus, due to higher compatibility of the HPNs in the SPEEK matrix.

Catalysis

Catalysis using HPNs is one of the most promising applications of these materials. Because of the highly tunable membrane characteristics, ease of functionalization, and high surface area, endowing HPNs with catalytic function is extremely facile. Henderson and coworkers demonstrated the utility of crosslinked polymersome HPNs containing Pt(0) crosslinks to catalyze the hydrosilylation of alkenes.[192] Additionally, the Pt(0) crosslinked HPNs were resistant to disassembly from surfactant, but could be readily degraded in the presence of phosphines. Gräfe and coworkers used enzyme loaded, crosslinked polymersome HPNs consisting of poly(3,4-dimethyl imidobutyl methacrylate)-*b*- poly(2-(diethylamino)ethyl methacylate to carry out the enzymatic reactions of horse radish peroxidase, myoglobin, and glucose oxidase.[193] By simply changing the pH from 6 to 8, the reactions could be switched on or off due to the increased permeability of the protonated amine membrane in acidic conditions. Polymersomes containing the enzyme CalB have also been shown to be effective at catalyzing reactions at the water/oil interface, and show the potential for applications such as environmental remediation.[194]

Incorporation of metal nanoparticles in HPNs has been a desirable method to create nanoreactors for a variety of reactions. Hairy hollow nanocapsules containing platinum nanoparticles for the catalytic reduction of 4-nitrophenol (4-NP) were prepared by Li and coworkers.[195] Alkyne-functional silica nanoparticles were grown around platinum nanoparticle clusters and functionalized with azide-functional β-CD. Finally, HPNs with grafted temperature responsive adamantyl-terminated poly(*N*-vinylcaprolactam) were prepared by β-CD inclusion complexation followed by HF etching. The platinum containing HPNs displayed the expected pseudo-first-order kinetics for the reduction of 4-NP, and no reduction of 4-NP in the absence of the HPNs. Furthermore, the rate of reduction was increased with increasing temperature from 10 °C to 25 °C, after which a 4-fold reduction in rate was observed when the temperature was reduced to 35 °C above the LCST of the polymer. Most importantly, however, was the ability to easily recover the platinum-containing HPNs and demonstrate their ability to catalyze with virtually no loss in efficiency after multiple collection cycles. Similar behavior was observed in gold nanoparticle containing HPNs of poly(ionic liquid) and thermo-responsive poly(2-(dimethylamino)ethyl methacrylate).[196] The particles were shown to effectively catalyze the reduction of 4-NP, where the rate of reduction increased linearly with temperature until the LCST was reached, at which point the rate was significantly reduced.

Zhang and coworkers used HPNs of graphitic carbon nitride polymer (g-C_3N_4) for the photocatalytic splitting of water.[197] In addition to the synthesis of hollow g-C_3N_4 capsules, the authors also incorporated varying amounts of 2-aminothiophene-3-carbonitrile into the polymerization, resulting in nearly three times greater hydrogen output.

Sensing

Owing to their high surface area and tailorable surface functionalities, HPNs are ideal candidates for highly sensitive sensors. Early examples of using hollow structures for sensing applications include polypyrrole hollow spheres for pressure sening,[198] hollow polymer microneedles for transdermal electrochemical sensing,[199] and polypyrrole coated SnO_2 hollow spheres for ammonia sensing.[199] Recently, Gong and coworkers[200] designed photoresponsive, molecularly imprinted HPNs for the detection of trace levels of triamterene, a potassium-saving diuretic banned by the Medical Commission of the International Olympic Committee and World Anti-Doping Agency. To achieve this, a novel azobenzene derivative, 4-[(4-methacryloyloxy)phenylazo]-3,5-dimethyl benzenesulfonic acid (MAPADSA), was copolymerized with *N*,*N*,*N'*,*N''*,*N''*-pentamenthyldiethylenetriamine from the surface of ATRP initiator-functional silica nanoparticles, in the presence of MAPADSA, followed by removal of MAPADSA and silica core with hydrofluoric acid. MAPADSA was shown to be a specific and highly sensitive agent for the binding of triamterene, where the rate of *cis-trans* isomerization is slowed when bound. By exploiting this binding efficiency, the molecularly imprinted hollow nanoparticles were able to detect triamterene at levels less than 0.2 ppm, below the threshold limit as defined by the IOC and WADA.

Prasad and Singh[201] have also used hollow molecularly imprinted polymers for high sensitivity detection of anti-HIV drugs Lamivudine (3TC) and Azidothymidine (AZT). Accurate determination of the levels of these drugs in patients is crucial for clinicians to prescribe proper dosages of these drugs. A sensing molecule with polymerizable vinyl groups, 2,4,6-trisacrylamido-1,3,5-triazine (TAT), was anchored to silica nanoparticle surfaces, followed by polymerization of ethylene glycol dimethylacrylate, core removal using hydrofluoric acid, and deposition on pencil graphite electrodes. The molecularly imprinted HPNs were able to detect 3TC and AZT down to 2.45 and 1.88 ng/mL, respectively, in blood serum samples, and were 1.5 times more sensitive than their core-intact counterparts.

Hollow molecularly imprinted polymers have been used for the detection of the pyrethroid λ-cyhalothrin in environmental water.[202] Silica nanoparticles functionalized with fluorescein isothiocyanate (FITC), followed by polymerization of divinylbenzene in the presence of λ-cyhalothrin, and subsequent core removal resulted in hollow molecularly imprinted polymers which showed significant fluorescence quenching in the presence of various pyrethroids and allowed for detection of λ-cyhalotrin at nanomolar levels.

Conclusions and Future Outlooks

Hollow polymer nanocapsules are an exciting class of material with extremely high potential in a variety of applications such as materials science, biomedicine, and energy. The breadth of the applications for which HPNs may be suitable stems directly from the huge variety of synthetic methods and polymers from which they can be constructed. As shown above, each synthetic method has its unique advantages and disadvantages. Inorganic nanoparticle templating, for example, allows for the precise tuning of the HPN hollow core size, and through judicious choice of core material, the degradation conditions can be tailored for the given application. However, with this method, an additional step is required in the synthetic route towards the desired material, and typically, the core material is unrecovered and is not an atom-efficient process or green process, often requiring harsh, toxic reagents. Emulsion templated methods, conversely, typically require much milder conditions for core removal, often simply water. From this standpoint, the emulsion templated methods can be viewed as a much more green approach towards HPNs. Emulsion templated cores are typically simple surfactants and could be easily recovered if so desired. However, like inorganic templating, an additional step is required in the synthetic route to the final hollow material. Unlike inorganic templates, which have precisely predetermined size, which is often quite narrowly dispersed, emulsions can be quite disperse in size and are more difficult to control. Towards even more efficient routes to HPNs are vesicle-templated and polymersome-based HPNs. In these systems, there is no need for core removal, which eliminates a step in the synthesis. Additionally, because no core material is lost in the synthesis, this is a much more environmentally friendly technique. Finally, template-free and unique morphologies are rarer examples of the synthesis of HPNs, but seek to combine the advantages of the aforementioned techniques. As progress in supramolecular chemistry and controlled synthetic techniques advance, we expect to see the field of template-free and direct access to highly controlled HPNs in few synthetic steps blossom.

In addition to the versatility of the synthetic routes towards HPNs, their unique properties allow for improvement in a wide variety of applications. Because of the exceptionally high surface areas of HPNs, they make ideal candidates as sensing materials and catalytic devices. Furthermore, their hollow nature makes HPNs ideal candidates as nanoreactors and in biomedical applications for their ultra-high storage capacity. As materials and polymer chemistry advances, we expect interest in HPNs to grow accordingly. Progress in imaging techniques and spectroscopy will give researchers in the field improved insights into the mechanisms of formation for HPNs and ultimately lead to improved material design. As synthetic strategies improve, and efficiency increases, the real-world utilization of HPNs dawns. Next-generation biomaterials and membranes, including synthetic cellular nanomachines and molecular separation, are at the forefront of material design for hollow polymer nanocapsules.

Conflicts of interest

There are no conflicts to declare.

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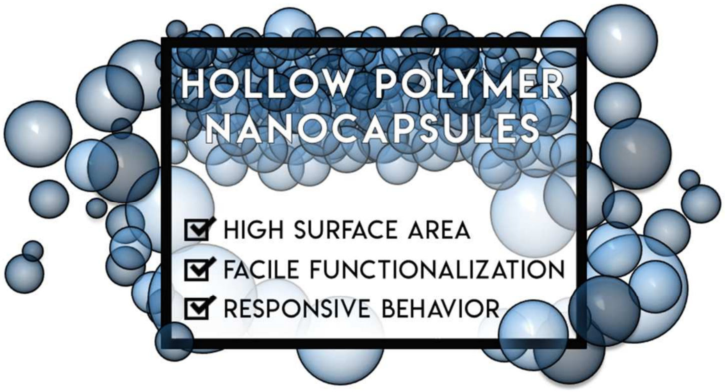

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