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# Design and synthesis of organic–inorganic hybrid capsules for biotechnological applications†

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Organic–inorganic hybrid capsules, which typically possess a hollow lumen and a hybrid wall, have emerged as a novel and promising class of hybrid materials and have attracted enormous attention. In comparison to polymeric capsules or inorganic capsules, the hybrid capsules combine the intrinsic physical/chemical properties of the organic and inorganic moieties, acquire more degrees of freedom to manipulate multiple interactions, create hierarchical structures and integrate multiple functionalities. Thus, the hybrid capsules exhibit superior mechanical strength (*vs.* polymeric capsules) and diverse functionalities (*vs.* inorganic capsules), which may give new opportunities to produce high-performance materials. Much effort has been devoted to exploring innovative and effective methods for the synthesis of hybrid capsules that exhibit desirable performance in target applications. This *tutorial review* firstly presents a brief description of the capsular structure and hybrid materials in nature, then classifies the hybrid capsules into molecule-hybrid capsules and nano-hybrid capsules based upon the size of the organic and inorganic moieties in the capsule wall, followed by a detailed discussion of the design and synthesis of the hybrid capsules. For each kind of hybrid capsule, the state-of-the-art synthesis methods are described in detail and a critical comment is embedded. The applications of these hybrid capsules in biotechnological areas (biocatalysis, drug delivery, *etc.*) have also been summarized. Hopefully, this review will offer a perspective and guidelines for the future research and development of hybrid capsules.

**Key learning points**

(1) The structure and function similarities between biological cells and artificial hybrid capsules;
(2) The synthetic chemistries (polymer chemistry, supramolecular chemistry, sol–gel chemistry, biomineralization chemistry, catechol chemistry, metal–organic coordination chemistry, *etc.*) used in the design and synthesis of hybrid capsules;
(3) The synthetic methods (layer-by-layer assembly, sol–gel reaction, molecular self-assembly, biomineralization, bioadhesion, Pickering emulsion, *etc.*) and materials (metal–organic frameworks (MOFs), graphene, gold, *etc.*) used in the design and synthesis of hybrid capsules;
(4) The representative applications of hybrid capsules in biotechnological areas;
(5) Future outlook and perspectives in the design and synthesis of hybrid capsules.

## 1. Introduction

Capsules are a class of hollow materials with a unique core–shell structure, which affords a high surface-to-volume ratio and short mass transport distance. The inner hollow core can be loaded with diverse cargoes or can act as a confined space, whereas the outer semi-permeable wall can be endowed with versatile functionalities. The capsule size can be range from nanometres to millimetres. In the past decade, over 30 000 research articles (data from web of science) related to "capsules" have been emerged. The potential applications of capsules are quite broad, spanning from catalysis, separation, and sensing, to controlled delivery, *etc.* To achieve high performance as well as superior stability, the capsules should possess a semi-permeable, robust, and flexible but tunable structure.

Traditionally, capsules can be categorized into organic capsules (mainly polymeric capsules) and inorganic capsules based on the chemical composition of the capsule wall. Several recently published reviews have highlighted the important advancement and

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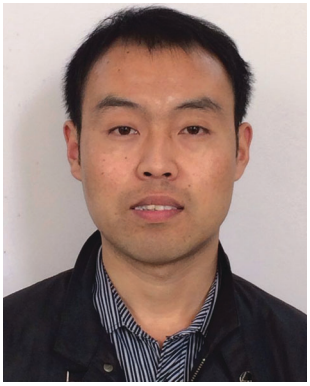

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potential applications of organic capsules.[1–5] Since the capsule wall is fully composed of organic building blocks, the organic capsules usually exhibit multifunctional and tunable properties, but poor mechanical strength. In comparison, inorganic capsules have the superior physical, chemical, mechanical stabilities, whereas the rigidity and inertness often restrict their broad applicability. Several excellent reviews have featured the recent research progress in the preparation and applications of inorganic capsules.[6–8]

Hybrid capsules, which integrate the merits of organic and inorganic capsules, may offer a competitive and promising alternative. Like most hybrid materials, hybrid capsules can acquire more degrees of freedom to manipulate multiple interactions (hydrogen bonding, covalent bonding, coordinate bonding, *etc.*), create hierarchical structures and integrate multiple functionalities. Therefore, the design and synthesis of hybrid capsules with tailored structures and superior performance will become a burgeoning research area. Historically, the first artificial hybrid capsule was synthesized by Caruso and co-workers through layer-by-layer (LbL) assembly of polyelectrolytes and inorganic nanoparticles.[9] Till now, a variety of chemical and physicochemical methods, including LbL assembly,[9] sol–gel reaction,[10] molecular self-assembly,[11] biomimetic mineralization,[12] polyamine–salt aggregate-assisted assembly,[13] Pickering emulsion-assisted assembly,[14] and other interfacial polymerization/reaction,[15,16] *etc.* have been developed for the rational design and synthesis of hybrid capsules comprising different organic and inorganic moieties, which have displayed great application potential in chemical/biological conversions, drug delivery, *etc.* Owing to the diversity of the synthesis methods and variability of the material compositions, it seems rather difficult to summarize and categorize the existing hybrid capsules based on the synthesis methods or materials. Through the structural characteristics analysis of the capsule wall, it can be found that the inorganic moiety in the capsule wall is either metal ions or inorganic nanoparticles, whereas the organic moiety in the capsule wall is either small organic molecules or polymers. Obviously, the size of metal ions or small organic molecules is on molecular scale, while the size of nanoparticles or polymers is on the nanoscale. Therefore, the following classification is adopted (Fig. 1): if the size of any one of the two moieties is on the molecular scale, the capsules are denoted as molecule-hybrid capsules; if the size of the two moieties is on the nanoscale, the capsules are denoted as nano-hybrid capsules. In other words, upon the size of the two moieties in the capsule wall, the hybrid capsules can fall into two categories in this tutorial review: (i) molecule-hybrid capsules and (ii) nano-hybrid capsules. Correspondingly, the hybrid form of the organic and inorganic moieties can be denoted as (i) molecule-scale hybridization and (ii) nanoscale hybridization, respectively (Fig. 1). To further understand these two types of capsules, additional explanations are presented as follows. The molecule-hybrid capsules are formed through either (1) the assembly of organic moiety-containing molecules and inorganic moiety-containing molecules or (2) the assembly of molecules containing both organic and inorganic moieties (Fig. 1, left part). The nano-hybrid capsules are fabricated through the following four routes (Fig. 1, right part): (3) assembly of polymers and inorganic particles; (4) assembly of polymers and inorganic precursors; (5) assembly of organic precursors and inorganic particles; (6) assembly of organic precursors and inorganic precursors. Hopefully, this categorization can offer readers a basic outline of hybrid capsules and the corresponding formation processes, and offer researchers a preliminary framework for designing and synthesizing high-performance hybrid capsules.

Collectively, this *tutorial review* primarily focuses on the design and synthesis of hybrid capsules for biotechnological applications. We will firstly present a brief description of the capsular structure and hybrid materials in nature. Then, we will devote a detailed discussion to the design and synthesis of hybrid capsules by summarizing the typical examples based on two categories and the subordinate six formation routes. For each route, the synthesis methods will be presented in detail

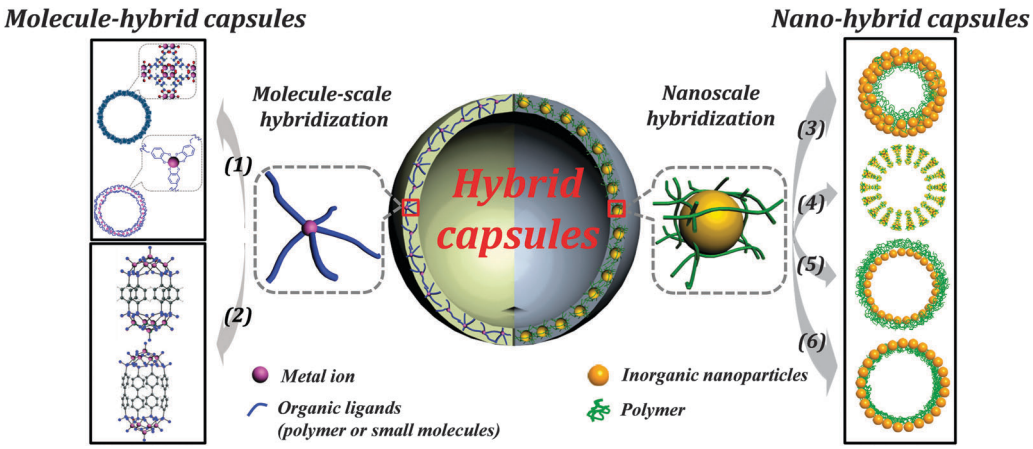


Fig. 1 Schematic illustration of the hybrid capsules in this *tutorial review*. Molecule-scale hybridization means that the size of any one of the organic and inorganic moieties is on the molecular scale, which can be acquired by two routes (1 and 2); whereas nanoscale hybridization means that the size of the organic and inorganic moieties is on the nanoscale, which can be acquired by four routes (3, 4, 5 and 6).

 

and a brief comment will be incorporated. By the end of this *tutorial review*, the biotechnological applications (including biocatalysis, drug delivery, *etc.*) of the hybrid capsules will be introduced.

## 2. Capsular structures and hybrid materials in nature

Getting inspiration from nature is one of the most efficient pathways to acquire high-performance materials, since nature is well known as the most powerful manufacturer for synthesizing materials with hierarchical structures, multiple phases and multifunctional properties. Capsular structures and hybrid materials can be widely found in nature. For instance, biological cells represent exquisite and unrivalled capsular structured materials. Compartmentalization in cells is one of the most powerful tools in nature's arsenal to construct metabolic and signalling pathways. Compartmentalization can ensure a high level of control over enzyme reactions and protect the cell against the exotic attack. In addition, compartments can serve as scaffolds for the precise decoration with biomolecules, which can act as recognition elements on the surface, as catalysts in the interior of the compartment, and as selective channels in the compartment's membrane. These unique configurational and inherited properties of cells have great implications for the design and synthesis of artificial capsules.

Meanwhile, to obtain materials with optimal trade-off relations between durability, mechanical properties and other functions such as density, permeability, colour, hydrophobicity, *etc.*, nature synthesizes fascinating organic–inorganic hybrids, such as crustacean carapaces, mollusc shells and bone, teeth, mussel byssus, *etc.*, by using soft and sustainable synthetic approaches. The molecule-scale hybridization and the nanoscale hybridization can be clearly recognised from these biological prototypes. Typically, cells or organelles can utilize organic molecules to synthesize biominerals under ambient conditions. These biominerals are usually the composites of biomacromolecules and inorganic components (biosilica, $CaCO_3$, *etc.*), which can be defined as the nanoscale hybridization as mentioned above. Taking diatoms as an example (Fig. 2),[17] besides their elegant appearance, the silica outer shells are robust enough to protect diatoms against predators, are transparent enough for the photosynthetic activity of the cell, and more importantly, have moderate porosity to allow nutrients and metabolites to diffuse in and out freely.

Alternatively, the typical molecule-scale hybridization is also ubiquitous in nature. Mussel byssus is regarded as a great representative. It is found that iron and 3-(3,4-dihydroxyphenyl) alanine (dopa) are co-localized in the cuticle (a thin outer coating of the mussel byssus). More specifically, the form of $[Fe(dopa)_3]$ complex in the cuticle is shown in Fig. 3.[18] It is accepted that this complex plays two unique roles in the formation of the cuticle. In the threads, Fe–dopa bonds in $[Fe(dopa)_3]$ complex can improve the mechanical performance, whereas in the case of plaques, the $[Fe(dopa)_3]$ complex is responsible for formation of the material and also contributes to adhesive bonding. Biomineralization and mussel chemistry (bioadhesion) are the two typical methods for manufacturing hybrid materials; other fascinating methods will be also revealed in this *tutorial review*. Collectively, incorporating the hybrid materials as well as their formation strategies inspired from nature into the synthesis process of capsules will offer an ingenious way for preparing hybrid capsules with highly desired performance. Moreover, hybrid capsules can be constructed from different materials and methods, leading to diverse structures and versatile properties, which should have great implications for the broad scientific communities with chemistry, materials science, chemical engineering backgrounds.

## 3. Design and synthesis of organic–inorganic hybrid capsules

### 3.1 Molecule-hybrid capsules

Molecule-hybrid capsules refer to those capsules composed of organic and inorganic moieties being hybridized on a molecular scale in the capsule wall, and at least one of the two moieties is a small molecule. The interaction between the organic and inorganic moieties is mainly through coordinate bonding, which can either originate from the original hybrid building blocks (such as polyoxometalate) or be generated alongside the formation of the hybrid capsule wall. Moreover, two routes can be adopted to synthesize the hybrid capsules: assembly of two types of molecules (organic moiety-containing and inorganic moiety-containing molecules) and the assembly of single type of molecules (molecules containing both organic and inorganic moieties in one molecule). This section will give detailed examples and characteristics of the molecule-hybrid capsules which are synthesized through the following two routes.

**3.1.1 Assembly of organic moiety-containing molecules and inorganic moiety-containing molecules.** This route is mainly inspired by the delicate structure and amazing performance of natural materials, where one of the most prominent examples is protein–metal ion complexes, such as metallic enzymes, adhesive proteins, *etc.* Introducing metal ions into these proteins to form protein–metal ion hybrids would either enhance the mechanical strength (adhesive proteins) or confer the protein with catalytic activity (dehydrogenases, ferrohemoglobin, *etc.*). Under the framework of this molecule-scale hybridization, several hybrid capsules have been synthesized. Particularly, in our previous study, a novel method to make polymer–inorganic hybrid capsules was developed through incorporating metal–organic coordination into LbL assembly (see Fig. S1 in ESI†).[19] Specifically, alginate was firstly activated *via* *N*-ethyl-*N*′-(3-dimethylaminopropyl) carbodiimide (EDC) and *N*-hydroxy succinimide (NHS) coupling chemistry, and then reacted with 3,4-dihydroxyphenethylamine (dopamine). Subsequently, the dopamine-modified alginate and titanium(IV) bis(ammonium lactato) dihydroxide (Ti-BALDH) were alternately deposited onto $CaCO_3$ templates. The coordination reaction between the catechol groups of dopamine-modified alginate and the Ti(IV) of Ti-BALDH allowed the alternative assembly to form multilayers.

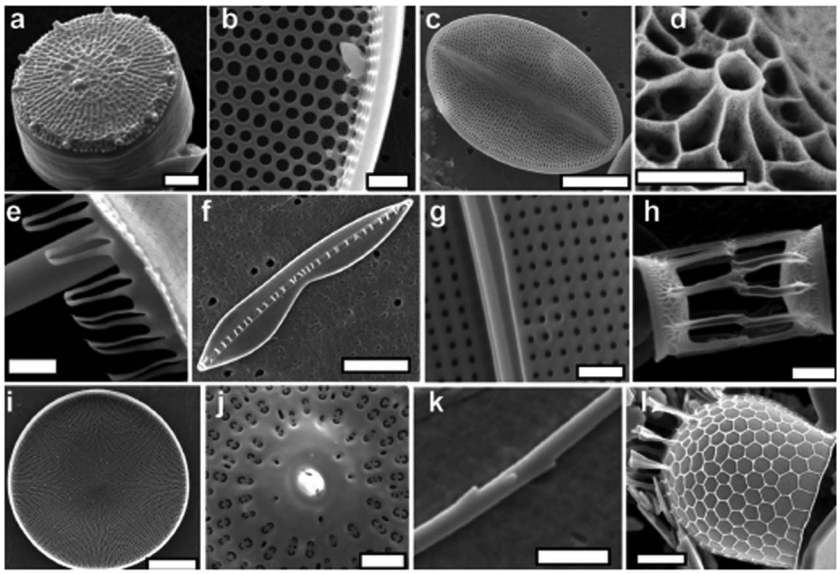


Fig. 2 Diversity of diatom silica structures. Acid-cleaned material from (a) *Thalassiosira pseudonana*, bar = 1 μm; (b) close up of *Coscinodiscus wailesii*, bar = 5 μm; (c) *Cocconeis sp.*, bar = 10 μm; (d) *rimoportula* from *Thalassiosira weissflogii*, bar = 500 nm; (e) corona structure of *Ditylum brightwellii*, bar = 2 μm; (f) *Bacillaria paxillifer*, bar = 10 μm; (g) close up of pores in *Gyrosigma balticum*, bar = 2 μm; (h) *Skeletonema costatum*, bar = 2 μm; (i) valve of *C. wailesii*, bar = 50 μm, (j) close up of pores in *D. brightwellii*, bar = 2 μm; (k) seta of *Chaetoceros gracilis*, bar = 1 μm; and (l) *Stephanopyxis turris*, bar = 10 μm. Reprinted with permission from ref. 17. Copyright 2008 American Chemical Society.

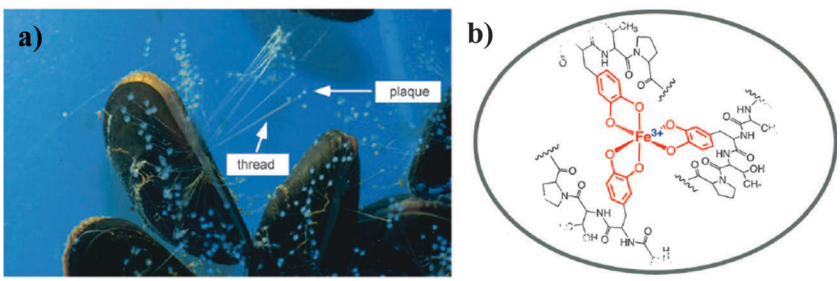


Fig. 3 (a) Mussels adhering to glass (the picture shows the byssal adhesive system which consists of threads and plaques); (b) an $[Fe(dopa)_3]$ complex existence in the cuticle (a thin outer coating of threads in the mussel byssus). Reprinted with permission from ref. 18. Copyright 2010 Wiley-VCH.

After removal of the templates, the alginate–titanium hybrid capsules were obtained. Osmotic pressure experiment and thermogravimetric (TG) analysis indicated that the hybrid capsules possessed high mechanical stability and superior thermal stability. Besides, the wall thickness and the physical/chemical properties of the hybrid capsules can be tuned by altering the number of deposited layers. Because of the ubiquity of metal–organic coordination and the wide applicability of LbL assembly, this method may be suitable for preparing a variety of polymer–inorganic hybrid materials.

Based on the coordination interactions between metal ions and catechol groups, another recent breakthrough has given us a great encouragement for synthesizing hybrid capsules. Caruso and co-workers fabricated polyphenols–metal molecule hybrid capsules through just one-step coating of coordination complexes of natural polyphenols (including tannic acid (TA), (−)-Epigallocatechin gallate, *etc.*) and metal ions (including iron(III), vanadium(III), gadolinium(III), chromium(III), *etc.*) on sacrificial spherical templates.[11] The particle size of the capsules ranges from nanometres (<50 nm) to micrometres (>10 μm), which was strongly dependent on the diameter of the templates. The formation of the capsule wall was primarily ascribed to the unique structure of polyphenols and its coordination with the metal ion. Taking TA as an example, it was actually a mixture of polygalloyl glucose molecules with different degrees of esterification. Three galloyl groups from TA can react with each Fe(III) ion to form a stable octahedral complex, allowing each TA molecule to react with several Fe(III) centres to form a cross-linked film (Fig. 4a). The coordination between Fe(III) and TA was pH-dependent, and the resultant capsules exhibited pH-dependent disassembly behaviour, which can be attributed to transitions among mono-, bis-, and tris-complex states (Fig. 4b). Actually, at low pH, most of the hydroxyl groups were protonated, which led to a rapid destabilization of the cross-links and disassembly of the capsule wall. For example, at pH 2.0, the Fe(III)–TA capsules shrank immediately and disassembled. At pH 3.0, all capsules have disassembled within 4 hours, whereas at pH 4.0, 6 days of incubation were needed to disassemble the

 

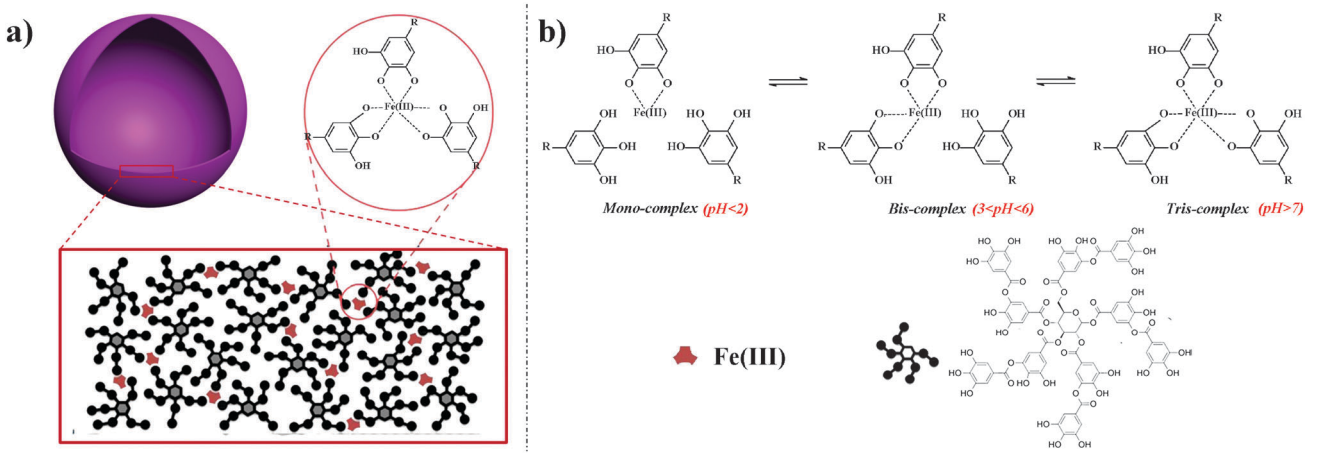


Fig. 4 (a) Molecular structures of the Fe(III)–TA capsule wall; (b) pH-dependent transition of dominant Fe(III)–TA complexation state. *R* represents the remainder of the TA molecule.[11]

majority of the capsules. By contrast, ~70% and ~90% of the capsules still remained intact after 10 days of incubation at pH 5.0 and pH 7.4, respectively. Besides, the cytotoxicity of the Fe(III)–TA capsules was found to be negligible. Collectively, this simple preparation method and the consequent biologically controllable physicochemical properties of the metal–polyphenol capsules will demonstrate a platform technology for preparing advanced materials for a broad range of applications.

In recent years, metal–organic frameworks (MOFs), a class of crystalline materials that are synthesized through forming coordination bonds between metal ions and organic ligands, have been recognized as a promising candidate in applications that require selective permeation through uniform micropores, such as membrane separation, sensor technology and so on. Due to its unique structure, formation mechanism, as well as superior performance, MOFs may provide an efficient building motif for capsule walls. In a typical example, De Vos and co-workers synthesized MOF capsules through interfacial reaction of the organic ligands and inorganic precursors.[20] Specifically, as shown in Fig. 5a, two kinds of immiscible liquids (one liquid consists of Cu(II) ions and the other consists of 1,3,5-benzenetricarboxylate (BTC) ligands) were supplied through syringe pumps to a T-junction, where the formation of aqueous solution droplets in the continuous organic phase took place. The $[Cu_3(BTC)_2]$ capsule wall (dark blue in Fig. 5a, the schematic representation of the $[Cu_3(BTC)_2]$ structure can be found in Fig. 5e) was then generated at the liquid–liquid interface through the interfacial reaction of BTC and Cu(II) ions. The as-synthesized capsules had a uniform diameter of $375 \pm 15$ μm with a uniform thickness of 1.5–2 μm (Fig. 5c and d). One advantage of the interfacial growth of the MOF capsule wall was that the metal ions and organic ligands approached the growing MOF layer from opposite directions, which allowed the growth to self-complete in one step (Fig. 5b). Besides, during the growth process, diffusion of the two precursors was faster at the defects than through the already formed layer, thus fresh crystallites would be formed mainly at such defect sites. This mechanism also ensured the thickness of the capsule wall was uniform. Considering the intrinsically hybrid nature of all MOFs, this interfacial growth method can be also extended to other MOF and the relevant structures (such as ZIF-8). In addition, owing to the uniform pore size of the MOF layer in the wall, this capsule showed size-selective permeability

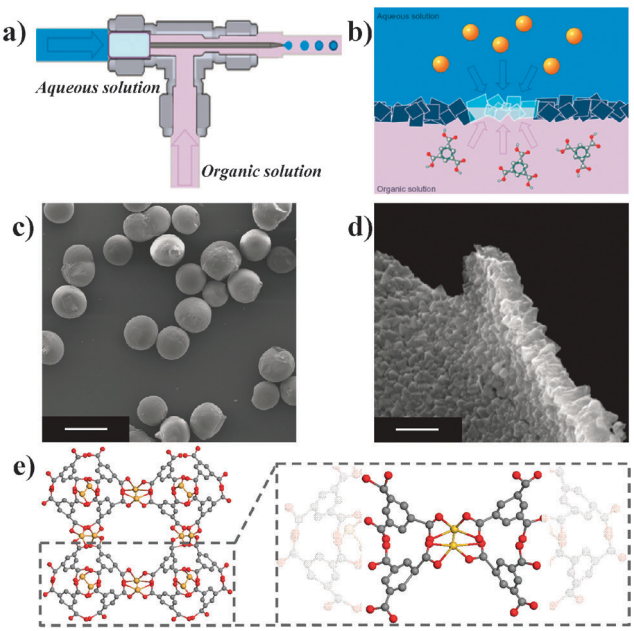


Fig. 5 (a) Schematic synthesis procedure of $[Cu_3(BTC)_2]$ metal–organic framework (MOF) capsules; (b) interfacial reaction between organic and inorganic precursors at the interface between the aqueous and organic phase; (c) overview of several capsules illustrating their monodispersity. The capsules retain their spherical shape upon drying (bar = 500 μm); (d) cross-sectional view of the capsule wall, showing its thin and uniform thickness (bar = 2 μm); (e) schematic representation of the $[Cu_3(BTC)_2]$ structure. The right side shows the unit cell of the crystal lattice with an indication of the crystallographic orientation. The grey and red dots respectively represent the C and O atoms of the BTC ligands. Cu(II) ions are shown as orange spheres. The left side highlights the so-called 'paddle wheel' structural unit. Reprinted with permission from ref. 20. Copyright 2011 Nature Publishing Group.

for molecules (see Fig. S2 in ESI†). Detailed information can be found in Section 4.3.

**3.1.2 Assembly of molecules containing both organic and inorganic moieties.** As illustrated in Section 3.1.1, organic and inorganic moieties in the capsule wall must be prepared separately, which then react with each other to form hybrid capsules. Theoretically, manipulating the assembly behaviour of a single molecule that comprises both organic and inorganic moieties may provide a more facile process to generate molecule-hybrid capsules.[21] As is well known, polyoxometalate is just such a unique molecule, which consists of a transition metal ion core and chemically-linked organic ligands. Unfortunately, most polyoxometalate cannot be directly utilized to form hybrid capsules; and essential functionalization or substitution reaction is needed. For example, Schmitt and co-workers firstly identified a {V–O} motif in $[V_5O_9(O_3AsC_6H_4NH_2)_4]^{5-}$, upon which $[H_2V_{10}O_{18}(O_3PC_6H_4PO_3)_4]^{8-}$ and $[H_2V_{10}O_{18}(O_3PC_{12}H_8PO_3)_4]^{8-}$ were synthesized through substitution of As in $[V_5O_9(O_3AsC_6H_4NH_2)_4]^{5-}$ with phosphonates (Fig. 6). These resultant two polyoxometalates were present in the form of capsular structures in dimethyl formamide (DMF)–water solutions. Moreover, simple extension of the organic ligands could affect the formation of the elongated capsules.[21] Notably, as a result of the rather complicated synthesis process of polyoxometalates, this method is confined to limited applications.

### 3.2 Nano-hybrid capsules

Besides molecule-scale hybridization, the capsules with nano-scale hybridization forms are also extensively investigated. Generally, nano-hybrid capsules refer to those capsules composed of organic and inorganic moieties being hybridized on the nanoscale in the capsule wall, and both of the two moieties must be polymer and inorganic particles (oligomers). In comparison to molecule-hybrid capsules, the interactions between the organic and inorganic moieties in nano-hybrid capsules are more diverse, and include electrostatic force, hydrogen bonding, covalent bonding, or coordinate bonding, *etc.* The interactions are mainly generated accompanied by the formation of the hybrid capsule wall. Moreover, since the building blocks of nano-hybrid capsules are polymers and inorganic nanoparticles, which can be respectively generated from organic and inorganic precursors, four routes can be adopted to synthesize such hybrid capsules: assembly of (a) polymers and inorganic particles; (b) polymers and inorganic precursors; (c) organic precursors and inorganic particles; and (d) organic precursors and inorganic precursors. In this section, four routes to synthesizing nano-hybrid capsules and selected examples are highlighted, with an emphasis on the preparation process and the related mechanisms.

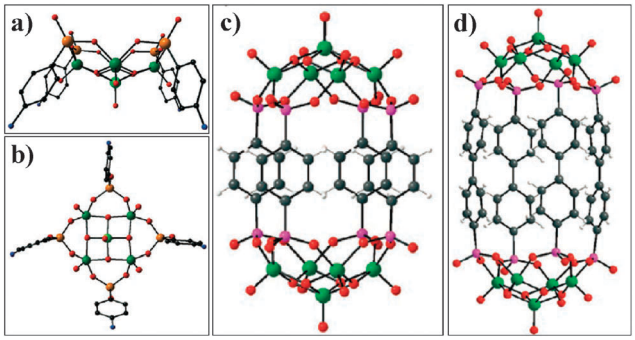


Fig. 6 (a, b) Different perspectives of the $[V_5O_9(O_3AsC_6H_4NH_2)_4]^{5-}$ "calix" structure in DMF–water solution ($V^{IV}$ darker green, $V^{V}$ light green, As orange, O red, N blue, C grey); molecular hybrid capsules of (c) $[H_2V_{10}O_{18}(O_3PC_6H_4PO_3)_4]^{8-}$ and (d) $[H_2V_{10}O_{18}(O_3PC_{12}H_8PO_3)_4]^{8-}$ in DMF–water solution (encapsulated water and DMF molecules have been omitted for clarity. Color code: V green, O red, N blue, C dark grey, P pink). Reprinted with permission from ref. 21. Copyright 2008 Wiley-VCH.

**3.2.1 Assembly of polymers and inorganic particles.** The assembly of polymers and inorganic particles generally leads to a simple mixture of these two candidates, which is an exceptional design of natural materials. For example, Foraminifera, a kind of ancient protozoan, possesses a typical polymer–inorganic hybrid wall, which is formed through the gluing of fine-grained minerals by a secreted macromolecular adhesion. This "gluing" is primarily driven by electrostatic interactions or hydrogen bonding between the organic and inorganic moieties, which affords a simple route for the synthesis of hybrid materials with various structures, including hybrid capsules.

The incorporation of such assembly behaviour of organics and inorganics into traditional LbL assembly processes can provide one important method for preparing hybrid capsules. Caruso and co-workers fabricated the first example of this kind of capsules by consecutively assembling polymers and silica nanoparticles onto colloids and subsequently removing the template (Fig. 7).[9] The basis of this method was the electrostatic attraction between the deposited charged species. The thickness of the capsule walls can be readily controlled by varying the number of deposition layers, whereas the size and shape of the capsules were determined by the dimensions of the employed colloid template. Most importantly, this method can be applicable to a wide variety of charged polymers and inorganic particles ($Fe_3O_4$ nanoparticles,[22] graphene oxide,[23] gold nanoparticles,[24] FePt nanoparticles,[25] *etc.*), thereby enabling the production of diverse hybrid capsules. For example, stimuli-responsive multilayered hybrid nanoparticle–polyelectrolyte capsules were prepared by using gold nanoparticles with carboxyl groups and poly(allylamine hydrochloride) (PAH).[24] These kinds of capsules exhibited pH-dependent properties and can be deconstructed both at low and high pH values. Furthermore, the gold nanoparticles incorporated in the wall of the capsule rendered them responsive to infrared (IR)-light, which can be used at high intensity to destroy the capsules and at low intensity to perform imaging. Magnetic capsules have also been synthesized using $Fe_3O_4$ or FePt nanoparticles as inorganic building blocks through this method, which can be utilized in a magnetically-guided drug delivery system.[22,25]

Although LbL assembly provides an important platform for hybrid capsule preparation, other methods that minimize the number of processing steps and do not require a sacrificial core would be more appealing for the large-scale production of hybrid capsules. One example was demonstrated by Dai and co-workers (see Fig. S3 in ESI†).[26] They assembled only one PAH

 

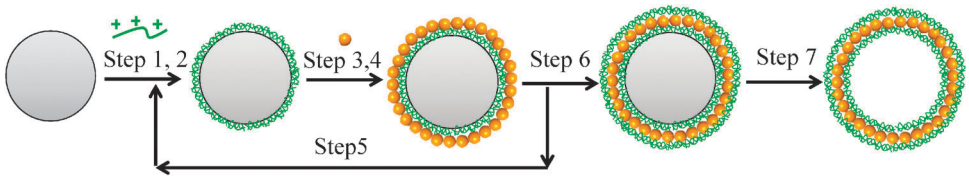


Fig. 7 Schematic fabrication of polymer–silica hybrid capsules through LbL assembly of polymers and silica nanoparticles. Steps: (1) treat with positively charged polyelectrolyte; (2) centrifugation/rinse to remove excess polyelectrolyte; (3) treat with silica nanoparticles; (4) centrifugation/rinse; (5) repeat steps of (1)–(4) to deposit additional layers; (6) template with desired number of layers; (7) removal of the template to form polymer–silica hybrid capsules.

layer on the spherical templates which were composed of poly(lactic acid) (PLA) and polyvinyl alcohol (PVA) materials. The resultant particles were then utilized for adsorbing gold nanoparticles, and hybrid capsules with a PAH–gold nanoparticles bilayer were acquired. To obtain an intact gold capsule wall, a further reduction of the gold precursors was implemented at the PAH–gold nanoparticles bilayer. During this process, the gold nanoparticles were considered as the nucleus of a gold coating around the capsule surface, which resulted in the gold-nanoshelled hybrid capsules. In addition, a novel concept of capsule formation process based on polyamine–salt aggregate (PSA) assembly was developed by Wong and co-workers in recent years.[13,27] As shown in Fig. 8, the polyamine chains were first ionically crosslinked with multivalent anionic salts to form polyamine–salt aggregates (PSAs); then the PSAs worked as templates for wall material deposition (inorganic nanoparticles) to form hybrid capsules with a thick multilayered capsule wall (the thickness of capsule wall was up to micrometres). Notably, the resultant hybrid capsules were denoted as nanoparticle-assembled capsules (NACs). The polyamine–salt template can either reside in the capsule interior for further use, or spontaneously disassemble after the capsule wall formation to leave behind a water-filled interior, which was dependent on the polymer and salt types. In addition to inorganic nanoparticles, proteins and anionic polymers can also be deposited on the surface of PSAs, which would form pristine polymeric capsules. Compared to LbL assembly, the cumbersome multiple centrifugation steps for capsule wall deposition were avoided by using the "PSA" assembly method. The main benefits of this method were summarized as follows: (1) the template can be formed *in situ* through the ionic crosslinking of the polyamine and salt under mild processing conditions. The size of the template can be tuned easily by changing the processing parameters (including (i) the ratio of the number of negatively charged groups from the salt to the number of positively charged groups from the polyamine, (ii) the aging time, (iii) the concentration of PSAs, (iv) the temperature and (v) the polyamine molecular weight), which determined the final size of resultant capsules, (2) the composition of the capsules including the polyamine, salt, and the wall forming material can be screened for a specific applications (see Table S1 in the ESI†). More detailed discussions including the current state of this method, the mechanism of the capsule assembly, and the potential applications can be found in Wong's review.[28]

Another important method for preparing hybrid capsules through the spontaneous assembly of polymers and inorganic particles is on the basis of oil–water emulsions.[29–32] During this synthesis process, polymeric moieties react with inorganic particles through electrostatic interaction, metal–organic coordination interaction, or host–guest interaction, subsequently resulting in amphiphilic hybrids, which can be locked on the

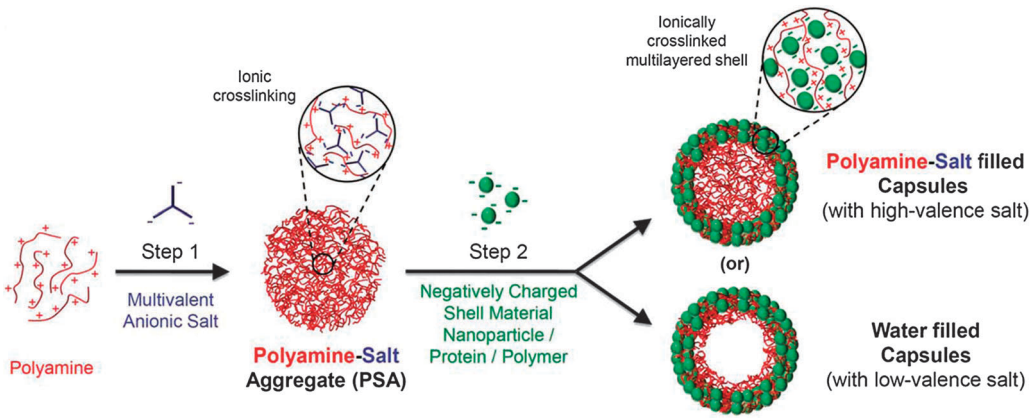


Fig. 8 Schematic fabrication of nanoparticle-assembled capsules (NACs) through the two-step polyamine–salt aggregate (PSA) assembly. Steps: (1) polyamine chains are ionically crosslinked with multivalent anionic salt to form polyamine–salt aggregates (PSAs); (2) PSAs act as a template for wall material deposition (either nanoparticles, proteins or polymers) in a second mixing step to form NACs with a thick multilayered capsule wall. Reproduced from ref. 28. Copyright 2011 Royal Society of Chemistry.

surface of oil–water emulsions, and finally generating hybrid capsules. The assembly process can take place either in one of the two phases or at the interface between the two phases.

For the former case, some research has been reported, two works of which are quite typical. One was from Rotello and co-workers, who developed a direct and versatile method for creating hybrid catalytic capsules upon the assembly of enzyme–nanoparticle conjugates at the oil–water interface of emulsions (see Fig. S4 in ESI†).[29] Briefly, the positively charged gold nanoparticles associated with negatively charged enzymes (β-galactosidase) to produce reduced-charge amphiphilic conjugates in the water phase. The subsequent addition of oil and vigorous mechanical agitation produced stable capsules with a diameter of $40 \pm 15$ μm, which resulted from the entrapment of the enzyme–nanoparticle conjugates at the oil–water interface. The assembly of the enzyme and nanoparticles can both stabilize the emulsion and retain the surface availability of the enzymes for catalytic reactions. Besides, this method can be extended easily to fabricate other enzyme-based catalytic capsules and may be of great promise for biotechnological applications. The other work from Scherman and co-workers explored a simple one-step method of utilizing microfluidic droplets to generate porous hybrid capsules.[30] Specifically, microdroplets were first generated in a microfluidic device. The oil carrier phase was directed perpendicular to the aqueous dispersed phase, which consisted of three inlets for the aqueous solutions of cucurbit[8], methyl viologen (MV)–gold nanoparticles, and a naphthol-containing copolymer. Droplets were generated as the oil phase sheared off the aqueous phase, before passing through a winding channel designed for the thorough mixing of the three reagents. Under an appropriate flow rate ratio of oil to water, hybrid capsules were generated and exhibited a high level of monodispersity when collected on a microscope slide. In detail, during this process, cucurbit[8] was capable of simultaneously accommodating two guests to form a 1 : 1 : 1 ternary complex in water through multiple non-covalent interactions with MV (an electron-deficient first guest) and naphthol derivatives (an electron-rich second guest), subsequently forming amphiphilic conjugates in the water phase. The conjugates would be finally assembled at the interface of oil–water droplets, leading to the hybrid capsules. This method combined the advantages of microfluidic droplets and supramolecular host–guest chemistry, and the capsules comprised of a polymer–gold nanoparticle composite held together by cucurbit[8] uril ternary complexes can be produced from microdroplets in one step with a high frequency and monodispersity. A broad variety of cargoes can be quantitatively loaded during the capsule formation process and these kinds of capsules were amenable to on-demand encapsulant release.

For the latter case, that was the assembly process taking place at the interface between two phases, the general driving force for fabricating such hybrid capsules was the metal–organic coordination interaction between inorganic (metal) particles and polymers. Some representative works were conducted by Zhao and co-workers and a detailed illustration is shown as follows:[31,32] hydrophilic citrate-stabilized gold nanoparticles were firstly dispersed in water, and a hydrophobic polymer with a disulfide group at the midpoint and methacrylate groups on the repeating units were dissolved in toluene. An emulsion was acquired through the mixing of the two solutions under stirring. Amphiphilic reactive gold nanoparticles were obtained at the oil–water interface after a ligand exchange between the disulfide-containing polymer and citrate on the gold nanoparticles. This process was similar to the *in situ* production of compatibilizers at the polymer interface in reactive polymer blends. Capsules with gold nanoparticles on the surfaces were synthesized by interfacial cross-linking polymerization of methacrylate. Clearly, in this method, amphiphilic gold nanoparticles produced *in situ* at the liquid–liquid interface were used as surfactants, and oil droplets were used as templates.

**3.2.2 Assembly of polymers and inorganic precursors.** For the preparation of hybrid capsules that use polymers and inorganic nanoparticles as building-blocks, several accompanying problems, especially the separated preparation of inorganic nanoparticles prior to electrostatic adsorption, have limited its wider applications. To address these problems, Sukhorukov and co-workers synthesized hybrid capsules through conducting the precipitation of two salts within the wall of a pre-formed polyelectrolyte capsule.[15] These hybrid capsules have the merits of both inorganic materials (*i.e.*, high mechanical stability) and polyelectrolyte capsules (*i.e.*, controlled release/uptake properties of the capsule wall; detailed information can be found in Fig. S5 of the ESI†).[15] During the same period, some other methods based upon *in situ* sol–gel reaction of inorganic precursors on polymer-based templates have also been developed to synthesize hybrid capsules. For instance, upon polymer-coated spherical templates, Caruso and co-workers prepared several kinds of hybrid capsules (including polyelectrolyte/$LiNbO_3$ and polyelectrolytes/titania capsules) on the basis of the water-mediated sol–gel reaction of $LiNb(OC_2H_5)_6$ (for $LiNbO_3$) or titanium(IV) isopropoxide (for titania) (see Fig. S6 in ESI†).[33] They firstly coated the polyelectrolyte multilayers onto charged polystyrene colloids through the LbL deposition of PAH and poly(sodium 4-styrensulfonate). Then, the precursor ($LiNb(OC_2H_5)_6$ or titanium(IV) isopropoxide) was added to the polyelectrolyte-coated colloids in alcohol, which can infiltrate the polyelectrolyte coatings. Hydrolysis and condensation (sol–gel reaction) of the precursor occurred upon interaction with water adsorbed in the polyelectrolyte layers, leading to the formation of polyelectrolyte–inorganic hybrid coatings of defined thicknesses. Hybrid capsules were subsequently obtained by removing the colloid templates by treating them with tetrahydrofuran (THF). Alternatively, conducting the sol–gel reaction of inorganic precursors on polymeric micelles derived from amphiphilic block copolymers also creates rich opportunities to generate hybrid capsules in a facile way. To facilitate the sol–gel reaction near the surface of the micelles, silicon-containing groups (silanol groups, polyhedral oligomeric silsesquioxane groups, trimethoxysilylpropyl methacrylate groups, *etc.*) were often grafted onto amphiphilic block copolymers as the reactive points, where silica can be formed, thus forming hybrid capsules.[10,34–37] More specifically, the synthesis process usually involved the following three steps: (1) an amphiphilic block

 

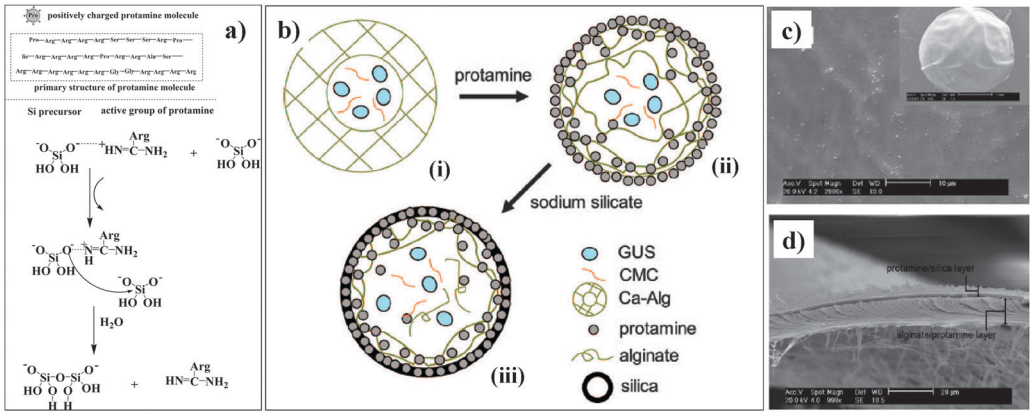


Fig. 9 (a) Tentative mechanism of silica formation induced by protamine molecules; (b) schematic representation of the formation process of the alginate–protamine–silica (APSi) capsule: (i) alginate capsule, (ii) alginate–protamine capsule, (iii) APSi capsule; (c) the surface morphologies of the APSi capsule (inset is the whole APSi capsule; bar = 1 mm); (d) cross section morphology of the APSi capsule. Reprinted with permission from ref. 41. Copyright 2008 American Chemistry Society.

copolymer that bore silicon-containing groups near the free end of the hydrophilic or hydrophobic block was synthesized; (2) the amphiphile was assembled into a micelle, with the silicon-containing groups situated at the innermost or outermost layer of the micelle; (3) the micelle was coated with a silica layer, which grew from the reactive points of the silicon-containing groups near the micelle surface through the adding of reactive silicate solutions under alkaline conditions. One of the pioneering studies was conducted by Fukuda and co-workers (see Fig. S7 in ESI†).[10] They precisely synthesized a silanol-functionalized amphiphilic block copolymer of the type PMMA-*b*-PPEGMA-*b*-poly(PEGMA-*r*-MOPS) by atom transfer radical polymerization (ATRP) and produced the silanol-carrying micelle of the polymeric amphiphile. The micelle was then mixed with reactive silicate solution, which produced a silica layer surrounding the micelle surface, thus forming an organic–inorganic hybrid capsule. The diameter of the capsule can be tailored through changing the molecular weight of the block copolymer. Obviously, this method avoided the utilization of pre-formed inorganic nanoparticles as assembly building blocks, and thus simplified the synthesis procedure. Nevertheless, during the synthesis process, biomolecules seemed to be unsuitable to be involved since most of the synthesis steps were organic solvent-mediated processes (mainly referring to polymer-coated spherical template) or the sol–gel reaction was initiated under alkaline conditions (mainly referring to polymeric micelles template), which may thus prevent this method to expend to biotechnological applications. Thanks to the ever-intensive research biomineralization/biomimetic mineralization, a green platform technology for hybrid materials synthesis in aqueous media, the fabrication of hybrid capsules beyond the assembly of polymers and inorganic nanoparticles moves ever closer.

With the deeper understanding of the biomineralization phenomenon and mechanisms, researchers have dedicated considerable efforts to fabricate hybrid capsules.[38–44] For example, Jiang and co-workers firstly utilized a natural positively-charged polypeptide, protamine, to induce and template silica formation at ambient temperature and near neutral pH conditions.[41] Meanwhile, a mechanism of protamine-induced silicification was also postulated (Fig. 9a): protamine molecules are positively charged at pH 7.0, and can adsorb and concentrate the negatively charged silicates *via* electrostatic and hydrogen bonding interactions. With an increase of silicate concentration around the protamine molecules, the silicic acid polycondensation reaction of second order is remarkably accelerated. At the same time, hydrogen bonding between $Si–O^-$ of silicate and $=NH_2^+$ of protamine inspires the nucleophilic substitution of a $Si–O^-$ oxygen atom on another adjacent silicon atom, making some additional contribution to the acceleration of polycondensation. Based upon the silicification mechanism, they performed this biomimetic silicification process on the outer surface of alginate capsules to synthesize alginate–protamine–silica (APSi) hybrid capsules. Specifically, alginate capsules with a liquid core–solid wall structure were first fabricated through a common extrusion technique, and then utilized to adsorb protamine through electrostatic interactions. Subsequently, the silicification process was conducted on the protamine-coated capsules to form APSi capsules with a compact and uniform hybrid wall (Fig. 9b and c). In short, this protamine-templated silicification resulted in the formation of APSi hybrid capsules with a two-layered wall encompassing an inner alginate–protamine layer and an outer protamine–silica layer (Fig. 9d). The rigid, porous silica wall dramatically inhibited the swelling of the capsule and effectively enhanced the mass transfer of small molecules.[41] This protamine-induced mineralization method was extended to synthesize titania and titania-based hierarchical structured materials by Jiang's groups (herein, the detailed synthesis mechanism of titania was similar to that of silica, which can be found in Fig. S8 of the ESI†). For example, they introduced biomimetic mineralization into LbL assembly process for the fabrication of protamine–titania hybrid capsules (see Fig. S9 in ESI†).[42] More specifically, these capsules were fabricated by alternative deposition of positively charged protamine layers and negatively charged titania layers on the

surface of $CaCO_3$ templates, followed by the dissolution of $CaCO_3$ through ethylene diamine tetraacetic acid disodium salt (EDTA) treatment. During the deposition process, the protamine layer induced the hydrolysis and condensation of a titania precursor (Ti-BALDH), to form the titania layer. Thereafter, the negatively charged titania layer allowed a new cycle of deposition step of the protamine layer, which ensured a continuous LbL process. The thickness as well as the mechanical stability of the capsule wall can be facilely tuned by tailoring the assembly number of the protamine–titania bilayers.

In comparison with the route by which the assembly of polymers and inorganic particles for the preparation of hybrid capsules proceeds, the advantages of this method can be summarized as follows: (i) the layer composed of inorganic nanoparticles could be *in situ* synthesized by the catalysis of the organic layer, therefore the individual preparation of nanoparticles can be avoided; (ii) the formation of hybrid multilayers could be performed from aqueous solutions under mild conditions in a facile way. Additionally, the size and shell thicknesses of these capsules could be easily controlled by the size of the templates as well as the number of deposited layers. This method opens a facile, general, and efficient way to prepare organic–inorganic hybrid materials with different compositions and shape, which can be used for the encapsulation of biomolecules and sensitive molecules, and consequently will find promising application in the realm of enzyme immobilization, drug delivery, and so on. To further expand this methodology based on the biomimetic mineralization and LbL assembly, hybrid double membrane capsules (HDMCs) with mitochondria-like structure were constructed through the synergy between biomimetic mineralization and LbL assembly using a double templating approach.[43] The organic inner membrane was acquired *via* a LbL assembly of oxidized alginate (o-alginate) and protamine on the $CaCO_3$ template. The silica template layer was then formed onto the inner membrane through the biomimetic silicification using protamine as the inducer and silicate as the inorganic precursor. The organic–inorganic hybrid outer membrane was acquired *via* biomimetic mineralization of the titanium precursor induced by adsorbed protamine. After the removal of $CaCO_3$ and silica templates subsequently, the HDMCs with microscale lumen and nanoscale intermembrane spaces were obtained. The diameter or thickness of all of the four compartments (*i.e.* lumen, inner membrane, intermembrane space, and outer membrane) can be easily tailored. Similar to single walled hybrid capsules, HDMCs also exhibited a high mechanical stability.

Little by little, researchers have realized that the mesopores in the walls of the capsules are of peculiar significance for many applications, which can provide accessible channels for the transportation of molecules between the capsule lumen and the outer environment. To prepare hybrid capsules comprising the capsule wall with a tailored pore size, high porosity, and large specific surface area, a facile method was developed by exploring the segregating and mineralization-inducing capacities of positively-charged hydrophilic polymers. Specifically, Jiang and co-workers used PAH as the model polymer, Ti-BALDH as the water-soluble titanium(IV) precursor to prepare capsules.[44] As shown in Fig. 10, PAH-segregated templates (P-$CaCO_3$ microspheres) were first prepared through a co-precipitation approach, which were then cross-linked by glutaraldehyde (named PG-$CaCO_3$). Subsequently, the PG-$CaCO_3$ were immersed in Ti-BALDH solution to implement biomimetic mineralization (named PGTi–$CaCO_3$), followed by the removal of the $CaCO_3$, and then the mesoporous hybrid capsules (named PGTi capsules) were obtained. These hybrid capsules exhibited extremely high mechanical strength, which even preserved the spherical structure in 40 wt% aqueous solution of sodium polystyrene sulfonate, while the mesoporous structures endowed the capsules with tunable mass transfer characteristics.

**3.2.3 Assembly of organic precursors and inorganic particles.** The organic phase polymerization of monomers is widely utilized for synthesizing pristine polymeric capsules. Incorporation of inorganic nanoparticles into such polymeric capsule is considered as an alternative way for synthesizing hybrid capsules. Depositing functional inorganic nanoparticles on these polymeric capsules is rather a simple method for generating multifunctional hybrid capsules.[45,46] For instance, Liu and co-workers firstly synthesized polyaniline capsules through conducting the polymerization of aniline on polystyrene nanospheres, followed by treatment with THF. Then, graphene-wrapped polyaniline hybrid capsules could be obtained by assembling graphene oxide (GO) onto the polyaniline capsules through electrostatic interaction, followed by the electrochemical reduction of GO (see Fig. S10 in ESI†).[45]

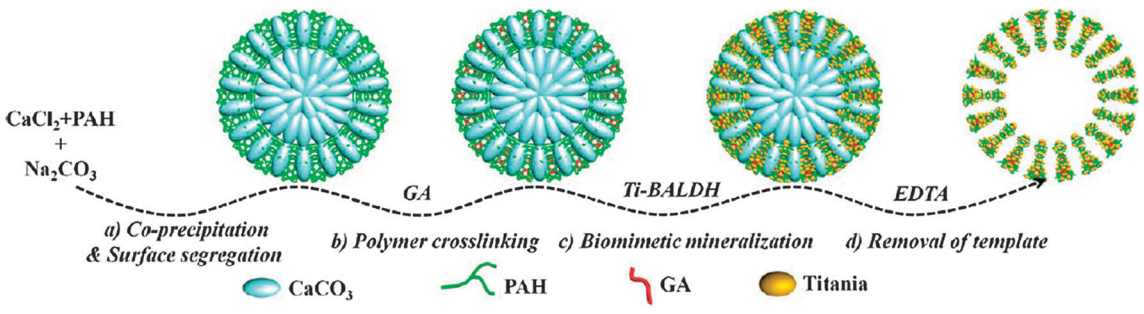


Fig. 10 Schematic preparation procedure of PGTi capsules: (a) formation of P-$CaCO_3$ microspheres through co-precipitation of PAH-containing $CaCl_2$ and $Na_2CO_3$ accompanied by the surface segregation of PAH; (b) formation of PG-$CaCO_3$ microspheres through the cross-linking of PAH *via* GA; (c) formation of PGTi–$CaCO_3$ microspheres through biomimetic mineralization induced by a cross-linked PAH network; and (d) formation of PGTi capsules after removing the $CaCO_3$ microsphere *via* EDTA treatment. Reprinted with permission from ref. 44. Copyright 2013 American Chemical Society.

 

The hollow structures of the resultant capsules greatly enhanced the specific surface areas, providing highly electroactive regions and short diffusion lengths. The embedded graphene can offer highly conductive pathways by bridging adjacent polyaniline capsules together, facilitating the kinetics for both charge transfer and ion transport throughout the electrodes. Nevertheless, the weak electrostatic interactions between reduced GO and polymeric capsules would lead to the detaching of such inorganic nanoparticles. Physical entrapment could constitute the ingenious solution. Pickering emulsion, the formation process of a kind of oil–water or water–oil emulsions stabilized by nanoparticles, may provide such an appropriate way for a physical entrapment method for generating hybrid capsules. Theoretically, inorganic nanoparticles with appropriately hydrophilic–hydrophobic properties can be adsorbed onto the oil (alkanes and polymerized monomers) droplets to form Pickering emulsions. Under specific conditions (often heating or UV irradiation), the monomers will polymerize into polymers and segregate onto the interface between the oil and water, locking the nanoparticles into the polymeric wall, and resulting in hybrid capsules. To date, several kinds of inorganic nanoparticle stabilizers including silica, titania, $Fe_3O_4$ and clay have been reported for preparing Pickering emulsions.[14,47,48] Several examples are extend to hybrid capsules. In 2007, Bon and co-workers provided the first example of titania–polymer hybrid capsules which were synthesized through the Pickering emulsion-assisted polymerization of styrene (Fig. 11a).[14] During this process, titania nanoparticles with appropriate hydrophilic–hydrophobic properties were firstly assembled at the interface of emulsion droplets. Styrene and divinylbenzene and an initiator necessarily enclosed in the oil droplets would be then polymerized into the cross-linked polystyrene network (see blue box in Fig. 11). Since the oil-phase (*n*-hexadecane) was a poor solvent for the cross-linked polystyrene network, which would lead to phase separation and precipitation at the interface, the titania nanoparticles can be then locked into the capsule surface, and finally this resulted in the titania–polymer hybrid capsules. The hybrid capsules had a size range of 20–50 μm, and coexisted with broken spheres (Fig. 11b). Meanwhile, an image of identical, perfect hybrid hollow spheres, which can be found in Fig. 11c, clearly showed the presence of the titania building blocks on the surface of the capsule wall. As illustrated in Fig. 11d, the thickness of the capsule wall was found to be *ca.* 1.5–2.5 μm. Through changing the organic precursor (or monomer) and species of nanoparticles, this method will be applicable for fabricating diverse inorganic–polymer hybrid capsules. On the basis of this method, Bradshaw and co-workers utilized MOF nanoparticles as stabilizers for preparing Pickering emulsions, and subsequently synthesized the first MOF–polymer hybrid capsules through the Pickering emulsion-assisted polymerization of styrene (see Fig. S11 in ESI†).[48] Since the surface hydrophilic–hydrophobic property of different species of MOF nanoparticles (ZIF-8, MIL-101, UiO-66) can be tailored by using facile ligand exchange approaches, this interfacial assembly method will be applicable for the preparation of different MOF–polymer hybrid capsules. Moreover, due to the several merits (including high surface area, high porosity, uniform pore size, *etc.*) of MOF nanoparticles, MOF-derived hybrid capsules may be conferred with multi-functionality and semi-permeability.

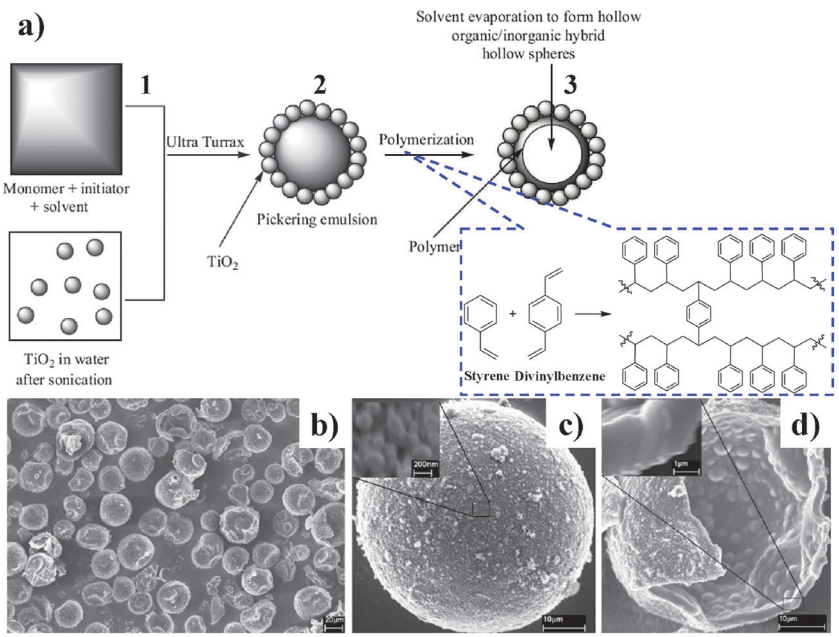


Fig. 11 (a) Schematic illustration of the fabrication of organic–inorganic hybrid hollow spheres using titania nanoparticles-stabilized Pickering emulsion polymerization: (1) the monomer and initiator are dissolved in *n*-hexadecane, titania nanoparticles is dispersed in water by using sonication, (2) a titania-stabilized Pickering emulsion is formed by using an Ultra Turrax instrument to apply a shear force, (3) polymerization is carried out overnight (polymerization mechanism is shown in the blue box), and organic–inorganic hybrid capsules with a liquid core are obtained; (b) SEM images of hybrid hollow spheres (styrene/DVB/hexadecane = 1.0 : 1.5 : 1.5 g); (c) magnification of an identical perfect hybrid hollow spheres; (d) magnification of an identical broken hybrid hollow sphere. Reprinted with permission from ref. 14. Copyright 2007 Wiley-VCH.

**3.2.4 Assembly of organic precursors and inorganic precursors.** As illustrated above (Section 3.2.1 to 3.2.3), at least one moiety (either "polymers" or "inorganic particles") in the capsule wall is pre-prepared and utilized for the synthesis of nano-hybrid capsules. If we suppose that if the capsules can be synthesized from both two precursors of organic and inorganic moieties (that is, the whole synthesis process includes the polymerization of organic precursors as well as the generation of inorganic particles from inorganic precursors), the structure or property of the capsules will be tailored in a more facile and free way. One of the pioneering exploitations of this idea was conducted by Jiang and co-workers. Based upon the phenomenon and principle of bioadhesion and biomineralization, they have fabricated novel polymer–inorganic hybrid capsules through combining biomimetic mineralization and bioadhesion (Fig. 12).[49] During this preparation process, positively-charged protamine was firstly adsorbed on the surface of $CaCO_3$ microspheres, which were denoted as protamine-adsorbed $CaCO_3$ microspheres. Since the surfaces of the protamine-bearing $CaCO_3$ microspheres were positively charged, and had the mineralization-inducing capacity, they were utilized as templates for inducing the polymerization of an inorganic precursor to form inorganic (silica or titania) layer. Then, dopamine (an organic precursor) was polymerized on the surface of the inorganic layer. After removal of the sacrificial templates, hybrid capsules were obtained. Owing to the formation of hydrogen bonding (or coordination bonding) between the catechol groups in the polydopamine layer and Si–OH groups (or Ti atom) in the inorganic layer, the capsules showed a much enhanced mechanical stability in comparison to pristine polydopamine capsules. Besides, during the whole synthesis process, the polymerization of dopamine was in charge of forming the organic moiety in the hybrid capsule wall. The polymerization mechanism could be clarified as follows: as shown in Fig. S12 (ESI†), dopamine is firstly converted into 5,6-dihydroxyindole (DHI) through a series of oxidation and nucleophilic reaction. Partial DHI is covalently oxidatively polymerized into dopamine–DHI–DHI trimeric conjugates, whereas the other is physical self-assembled into $(dopamine)_2$–DHI physical trimer. Finally, polydopamine would be acquired through the complexation of the two typical intermediates. Recently, Cheng and co-workers also made a progressive contribution to the design and synthesis of hybrid capsules derived from organic and inorganic precursors.[50] In short, through a sol–gel process (tetraethoxysilane to silica) and photo-induced polymerization method (monomers to polymeric hydrogel), they fabricated multifunctional hybrid microcapsules with the advantages of mesoporosity, luminescence, and temperature responses (detailed information can be found in Fig. S13 of the ESI†).

# 4. Biotechnological applications

Generally, hybrid capsules are a kind of unique scaffold with a capsular structure in morphology and organic–inorganic moieties in composition. A capsular structure means diverse cargoes can be loaded within the inner hollow core, whereas the versatile functionalities can be conferred to the outer semi-permeable wall; a hybrid composition means many more interactions can be manipulated to create hierarchical structures and multiple functionalities. Consequently, hybrid capsules will display a great significance in chemical/biological conversions, drug delivery, *etc.* In this section, several great application examples of hybrid capsules in the biotechnological field are presented and a short comment is given.

## 4.1 Biocatalysis

Natural cells play key roles in maintaining the balance of substance and energy through regulating the reaction processes *in vivo*. The chemical/biological reactions are mainly conducted either in capsule lumen or in the capsule wall by using enzymes as the efficient catalysts, which give us a great inspiration in the utilisation of capsules as ideal model systems for immobilizing enzymes and subsequently conducting chemical/biological conversions.

For a hybrid capsule, there are at least two compartments for enzyme immobilization: the capsule lumen and capsule wall. Many more efforts have been devoted to the former aspect: encapsulating

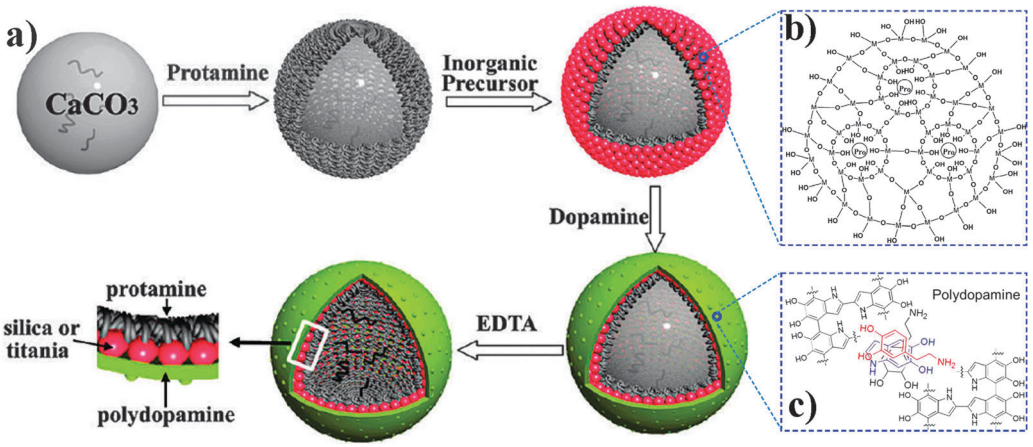


Fig. 12 (a) Schematic representation of the formation process of the protamine/titania (or protamine/silica)–polydopamine capsules; and molecular structures of (b) the inorganic (M refers to Ti atom or Si atom) and (c) organic (polydopamine) moieties. The schematic polymerization mechanism of dopamine to polydopamine is illustrated in Fig. S12 of the ESI.† Reprinted with permission from ref. 49. Copyright 2011 American Chemical Society.

 

enzymes in the capsule lumen. Correspondingly, the desirable mechanical stability and appropriate pore size of the hybrid capsule wall will confer the resultant immobilized enzymes with low enzyme leaching and high reusability or recyclability. Jiang and co-workers have made relatively systematic investigations on constructing enzyme catalytic systems on various hybrid capsules. One of the excellent examples was coating protamine–silica hybrid wall on an alginate capsule to construct β-glucuronidase-containing APSi hybrid capsules for catalytic conversion of baicalin.[41] The biosilica capsule wall dramatically prevented the swelling of the capsule, inhibited the leaching of the enzymes, and effectively enhanced the mass transfer of the substrate(s)/product(s). Meanwhile, the biocompatible polysaccharide liquid core created a benign microenvironment and well preserved the three-dimensional structure of β-glucuronidase. The stability of the encapsulated β-glucuronidase was significantly enhanced after biosilicification, and no loss of activity was found after 10 reaction cycles. Moreover, the relative activity of β-glucuronidase encapsulated in the APSi capsules reached 125%, not only exceeding that encapsulated in alginate capsules but also being higher than that of the free enzyme. Additionally, other enzymes (such as yeast alcohol dehydrogenase) were also encapsulated in protamine–titania hybrid capsules, and the encapsulated enzymes displayed enhanced recycling stability.[42]

Entrapping enzymes on the capsule wall will offer an alternative way to construct enzyme catalytic systems. Since the enzymes mainly act as a part of the capsule wall, the resultant capsules are often called as catalytic capsules. One of the excellent instances was developed by Rotello and co-workers (Fig. 13).[29] They demonstrated the successful integration of hybrid enzyme–nanoparticle conjugates with capsule structures. The utilization of the enzyme–nanoparticle capsules as catalysts was demonstrated in an enzyme activity assay. The β-galactosidase on the capsule surface retained catalytic activity for the hydrolysis of chlorophenol red β-D-galactopyranoside (CPRG) substrate. Compared to free β-galactosidase, 76% of the enzymatic activity was retained for β-galactosidase in the enzyme–nanoparticle capsules, which was similar to that observed for the monophasic activity of enzyme–nanoparticle conjugates (84%). Collectively, till now, the hybrid capsules are primarily utilized for immobilizing single enzymes in the biocatalysis field.

In recent years, multi-enzymatic catalysis, which is recognized as the next generation of biocatalysis, is particularly appealing since the multi-enzymatic catalysis processes have some intrinsic advantages in comparison to single enzyme catalysis processes: (1) the demand of time, cost and chemicals for product recovery could be reduced and (2) the concentration of harmful or unstable compounds could be decreased to a minimum. It has been proven that the spatial organization of multienzymes in a single support could lead to an enhanced productivity. Fortunately, hybrid capsules with hierarchal structures could offer appropriate positions for immobilizing different enzymes to construct spatially-separated multienzyme systems owing to the multi-compartmental structures.[43,44] As one of the few examples,[43] a spatially separated multienzyme system was constructed through arranging multienzymes on different positions on hierarchically-structured hybrid capsules, HDMCs. In detail, two enzymes, *i.e.* formaldehyde dehydrogenase and formate dehydrogenase, were encapsulated in the capsule lumen and the intermembrane space of the HDMCs, respectively. A cascade reaction, that was converting carbon dioxide to formaldehyde through two consecutive reductions, was conducted and compared to a system with co-immobilized and free enzymes. It was found that the formaldehyde yield was the highest for the spatially separated multienzyme system, followed by co-immobilized enzymes enabled by single-compartment capsules (SCCs), and that the yield of formaldehyde for the free enzymes in the bulk solution was the lowest. This phenomenon was attributed to the close proximity and the relative positions of the enzymes in the capsules. Meanwhile, this spatially separated multienzyme system also exhibited high recyclability as a result of the superior mechanical stability of the HDMCs.

### 4.2 Drug delivery

Once a kind of material structure is applied to the drug delivery area, two primary factors should be taken into consideration: the loading capacity and release properties, which are governed by a variety of factors, especially the porosity and surface functionality.

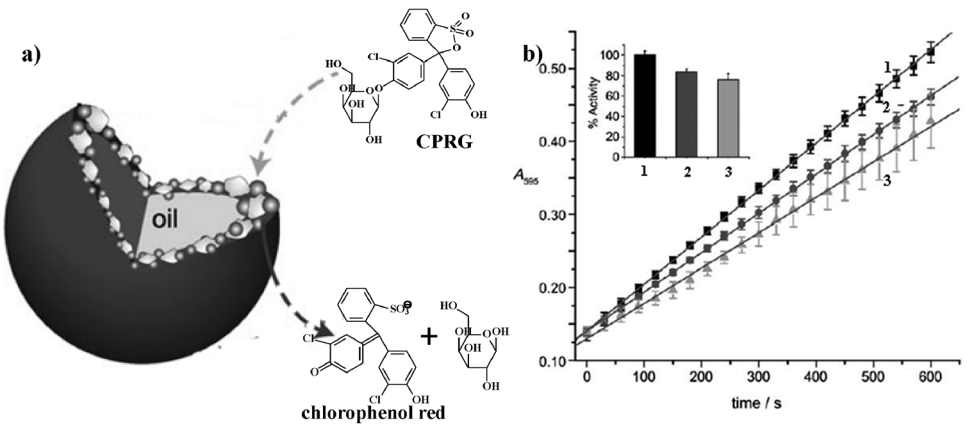


Fig. 13 (a) Enzymatic cleavage of yellow CPRG on the capsule shell by β-glucuronidase to produce chlorophenol red; (b) activity assay of β-glucuronidase in a phosphate buffer: (1) free enzyme, (2) enzyme–nanoparticle conjugate, (3) enzyme–nanoparticle conjugate stabilized hybrid capsules. The inset shows the relative activity (free enzyme solution = 100%). Reprinted with permission from ref. 33. Copyright 2009 Wiley-VCH.

Hybrid capsules just well fit the standard of such hosts for drug loading and controlled release, since the lumen provides a huge space for drug encapsulation, and the organic–inorganic hybrid composition of the capsule wall offers multifunctional properties for controlled drug delivery. Initially, research was mainly focused on the construction of robust drug carriers using hybrid capsules, and magnetic particles were incorporated during the synthesis process to confer the system target delivery property *in vivo*. For instance, Zhang and co-workers synthesized magnetic polymer enhanced hybrid capsules (MPEHCs), which were composed of double walls.[47] The modified silica nanoparticles were attached onto the surface of the MPEHCs to form an outer wall and the hydrophobic $Fe_3O_4$ nanoparticles were dispersed into the inner polymer wall. Ibuprofen release behaviours from MPEHCs were investigated in phosphate buffer solution (pH 7.4, 37 °C, Fig. 14a). It was demonstrated that *ca.* 38.6 wt% of ibuprofen was released in the first 10 min, while the residual ibuprofen was dissolved out slowly. It took a time of 6720 min to release 80.7 wt% of ibuprofen into the bulk solution. The release behaviour revealed that the ibuprofen loaded in the outer nanoparticle layer was released quickly because ibuprofen could dissolve easily into the release medium. However, the release rate of ibuprofen entrapped in polymer network and inner core of MPEHCs was constrained. The slower release rate of ibuprofen can be ascribed to the fact that the capsule wall enhances resistance to medium penetration and ibuprofen diffusion across the interstices in the double shells. The polymer–silica hybrid wall only conferred the MPEHCs with a high mechanical stability, whereas $Fe_3O_4$ nanoparticles can contribute to the target delivery of the drug *in vivo*. These systems are usually faced with two problems for the drug carrier, the lack of stimuli-responsiveness as well as the bad degradation. To address these two issues, several novel scaffolds have been prepared and showed high performance in the drug delivery area. In 2011, Katagiri and co-workers prepared magneto-responsive hybrid capsules through a colloid-templating method, which comprised three layers (*i.e.* polyelectrolyte multilayers, $Fe_3O_4$ nanoparticle layer and amphiphile bilayers).[22] Heating the $Fe_3O_4$ nanoparticles by irradiation with an alternating magnetic field would cause changes in the permeability of amphiphile bilayer membrane by a phase transition behaviour. These differences in heat generation could be utilized for varying the magnetically-induced release function of drugs through the hybrid capsules. Meanwhile, it was also found that the release rate of dyes (as a model alternative of drug) through the hybrid capsules could be controlled through tailoring the deposition amount of $Fe_3O_4$ nanoparticles on the capsules. As described above, this work addressed the issue of stimuli-responsiveness for a drug delivery system. However, difficulties in biodegradation also existed, which seemed to be a generic problem for hybrid capsules. Owing to the properties of good biocompatibility and biodegradation, alginate has been used popularly to encapsulate cargoes for constructing delivery systems. Coradin and co-workers developed a microgel method for the synthesis of silica–poly(lysine)–alginate hybrid capsules and studied their possible degradation by living cells using fibroblasts as model organisms (Fig. 14b–e).[40] They cultured the fibroblast cells without (Fig. 14b) and with (Fig. 14c) the capsules and found that the fibroblasts cultured with the capsules showed a good preservation of the cellular organization. The capsules can be detected in the cytoplasm and appeared to be localized in specific compartments. Compared to extracellular particles in Fig. 14d, the internalized capsules exhibited a fragmented, highly porous interior (Fig. 14e), which indicated that the capsules can be partially digested by the cells. All these results suggested that fibroblast cells can internalize and degrade these kinds of capsules and the capsules showed some potential as carriers for drug delivery. However, to the best of our knowledge, the hybrid capsules, which were utilized in drug delivery cases, did not exhibit good stimuli-responsiveness and excellent biodegrading property simultaneously. Fortunately, some recently developed hybrid capsules may become promising candidates for drug delivery vehicles. Typically, the Fe(III)–TA capsule developed

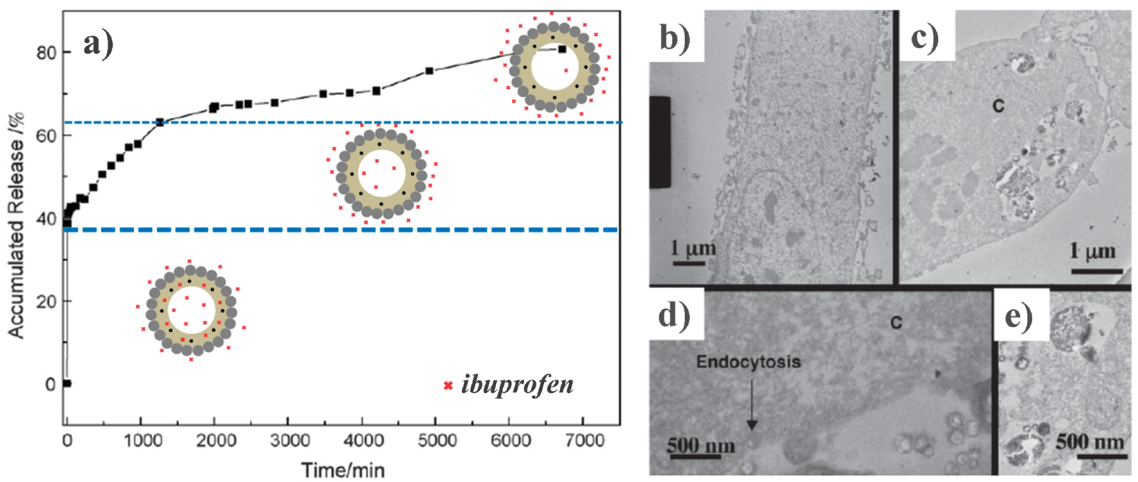


Fig. 14 (a) Release profile of ibuprofen loaded in MPEHCs. Reprinted with permission from ref. 47. Copyright 2009 Elsevier. Transmission electron microscopy (TEM) images of fibroblast cells cultured in the absence (b) and presence (c–e) of silica–poly(lysine)–alginate capsules. Reproduced from ref. 40. Copyright 2006 the Royal of Social Chemistry.

 

by Caruso and co-workers was just a pH responsive, biodegraded and biocompatible hybrid capsule.[11] The pH stimuli-responsiveness of the coordination between Fe(III) and TA resulted in a pH-dependent disassembly of the hybrid capsules. The disassembly behaviour can be tailored by changing the pH values (2.0, 4.0, 5.0, 7.0), which may lead to a changeable delivery of the encapsulated cargoes. In addition, the cytotoxicity of the Fe(III)–TA capsules could be ignored. Coupled with their pH-sensitive disassembly property, the Fe(III)–TA capsules will have great potential applications in the drug delivery area due to the varying pH in different parts of the body (*e.g.*, blood (pH 7.4), stomach (pH 1.0 to 3.0), duodenum (pH 4.8 to 8.2), *etc.*).

### 4.3 Other biotechnological applications

Besides biocatalysis and drug delivery, hybrid capsules also emerge potentials in other biotechnological areas. In the bio-separation area, Jiang and co-workers fabricated thermo-responsive hybrid capsules through a colloid-templating method, which was made up of the crosslinked polymersomes of amphiphilic thiol-containing polyhedral oligomeric silsesquioxane (PTPS).[36] Such hybrid capsules were amphiphilic because the wall was comprised of the hydrophobic TMPTA and reactive surfactant PTPS containing polyethylene oxide (PEO) chains. The hydrophilic PEO chains as the corona of hybrid capsules led to the high loading of hydrophilic molecules and the stable dispersion of capsules in water. Meanwhile, POSS as one part of the capsule wall made the capsule wall tough rather than rigid and resulted in a certain loading capacity of capsules with hydrophobic molecules. Besides, when heated to a high temperature, the hydrogen bonds between hydrophilic PEO chains and water molecules were destroyed, resulting in less hydrophilicity of the capsule wall and, consequently, leading to the shrinkage and aggregation of capsules in water. Correspondingly, the encapsulated molecules could be separated from the bulk solution. In the bioanalysis area, such as magnetic resonance imaging (MRI) (a routinely used medical imaging technology that uses magnetic moment of protons (from water, lipids, *etc.*) in the body to form images), Wong and co-workers utilized $GdDOTP^{5-}$ (contrast agents) as the basis for the formation of polymer–silica-walled NACs, facilitating the incorporation of MRI contrast media into the NAC core.[27] Several advantages could be found for this MRI system: (1) the incorporation of $GdDOTP^{5-}$ within the NAC core restricted the molecular rotation of the contrast agent leading to a relaxivity enhancement; (2) the polymer–silica hybrid capsule wall was not only tolerated *in vivo* but also permeable to water, allowing the $GdDOTP^{5-}$ to function in its role as a $T_1$-shortening agent (herein, $T_1$ means the longitudinal relaxation time of per $Gd^{3+}$ in each NAC. The shorter $T_1$ is, the better the contrast presents); (3) the size and properties of the NAC can be finely controlled during the synthesis by an appropriate selection of the positively-charged polymer, the solvent system, and the total charge ratio. Besides, by encapsulating $Gd^{3+}$ within the NAC, this system cannot only increase the relaxivity of each individual $Gd^{3+}$ ion but also construct an agent in which large quantities of high relaxivity $Gd^{3+}$ are delivered. This has implications for the field of targeted MRI in which iron oxide based nanoparticles are often used to generate large changes in the MR signal from low concentrations of agents. Besides MRI, contrast-enhanced ultrasound imaging is also proven as an effective technique for identifying the location and size of lesions.[23,26] For instance, gold-nanoshelled hybrid capsules enclosed with PLA and PVA, which were synthesized by Dai and co-workers, was successfully utilized as theranostic agents for ultrasound contrast imaging and photothermal therapy.[26] In this case, PLA was in charge of enhancing the contrast for the ultrasound imaging, whereas the gold nanoshell was responsible for killing the cancer cell through the near-infrared (NIR) irradiated photothermal therapy. As another example in the field of bioanalysis, surface-enhanced Raman spectroscopy (SERS) has also attracted some attention. Scherman, Abell, and co-workers developed an innovate hybrid capsule, which comprised a polymer–gold nanoparticle composite held together by cucurbit[8] uril ternary complexes.[30] The incorporation of gold nanoparticles allowed these capsules to be used as substrates for surface-enhanced Raman spectroscopy (SERS). The authors investigated the influence of particle size on the intensity of SERS signals by using the modular supramolecular approach. Two capsules were prepared, one containing 5 nm-diameter (1a) and a second with 20 nm-diameter (1b) gold nanoparticles. When the samples were excited with a 633 nm laser, characteristic SERS signals for cucurbit[8] and $MV^{2+}$ were observed. The signal strength derived from the capsules containing 1b was much greater than those containing 1a. To investigate the feasibility of detecting encapsulated materials by SERS, fluorescein isothiocyanate (FITC)-labelled dextran was loaded into the capsules. Significant Raman enhancement of the FITC signals was observed in addition to those from cucurbit[8] and MV. A similar dependence on the size of the gold nanoparticles for the degree of enhancement was also observed, demonstrating the potential of the porous capsule wall as a SERS substrate for the detection of encapsulated cargoes. Additionally, it is worth mentioning that incorporating new materials into the hybrid capsules could confer multi-functional properties, which may exhibit high performances in biotechnological applications. MOFs are an example of such amazing materials, and two typical MOF-derived hybrid capsules have been synthesized as described before and show size-dependent permeability and stimuli-responsiveness. One example was the $[Cu_3(BTC)_2]$ hybrid capsules developed by De Vos and co-workers.[20] Given that the capsules form an enclosed space and that all the micropores in the MOF crystal lattice have exactly the same dimensions, the integrity and permeability of the MOF membrane that forms the capsule wall can be probed by including molecules of different sizes in the inner phase during synthesis. Experiments have proven that molecules (*i.e.* ethylene glycol) smaller than the micropores in the $[Cu_3(BTC)_2]$ crystal lattice are able to diffuse freely through the MOF membrane, whereas molecules (*i.e.* Rose Bengal) larger than the micropores of the $[Cu_3(BTC)_2]$ crystal lattice have been successfully retained within the capsule. The size-selective permeability displayed by such capsules, together with the mild synthesis and activation conditions that allow encapsulation of functional species during synthesis, makes these hollow structures interesting candidates for application as microreactors. The other example is the

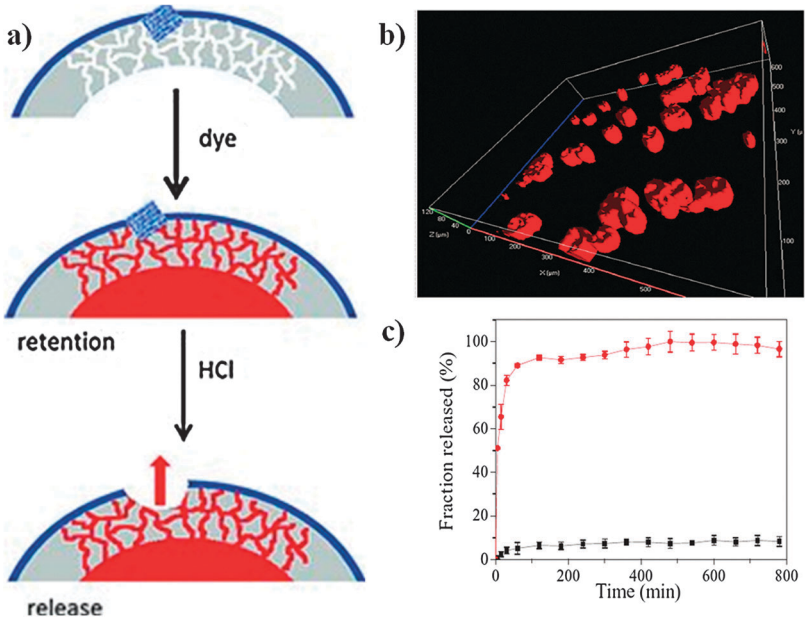


Fig. 15 (a) Schematic of the pH-triggered release of encapsulated dyes in the MOF–polymer hybrid capsules; (b) reconstructed *z*-stack of CLSM images of MOF–polymer hybrid capsules loaded with dyes indicating the dye is distributed throughout the capsule interior; (c) time *vs.* release curves of dyes from MOF–polymer (black squares) and pristine polymer capsules after acid dissolution of the MOF (red circles) determined by monitoring the characteristic dye absorption at 518 nm. Reprinted with permission from ref. 48. Copyright 2013 Wiley-VCH.

MOF–polymer hybrid capsules synthesized through immobilising MOF nanoparticles assembled at the interface of emulsion droplets into a polystyrene layer, which was developed by Bradshaw and co-workers (Fig. 15).[48] These hybrid capsules showed excellent retention of dye molecules owing to the dense polymer matrix and the micro-sized pores of the MOF crystal lattices. After dissolving the MOF nanoparticles treated with acid solution, dye release was extremely rapid. This pH-triggered molecule release property rendered these MOF–polymer hybrid capsules potential applications in drug delivery.

## 5. Summary and perspectives

Till now, numerous hybrid capsules have been designed and synthesized inspired by the structure, composition and formation processes of biological cells and some other natural materials. In this *tutorial review*, the common synthesis methods and biotechnological applications of the hybrid capsules have been highlighted. The hybrid capsule wall not only offers a controlled and selective passage property for the cargoes, but also endows the capsules with desirable application performances in biocatalysis, drug delivery, bioseparation, bioanalysis, *etc.*

In spite of these great achievements over the past decades, the following aspects, along with others, should be paid more attention in the future research and development of hybrid capsules. (1) Although many methods for hybrid capsule synthesis have been reported and some of which (like LbL assembly of polymers and nanoparticle developed by Caruso, polyamine–salt assembly induced assembly of nanoparticles developed by Wong, supramolecular host–guest assembly upon microdroplet platform developed by Scherman and Abell) are universal and exhibit high efficiency in encapsulating cargoes, novel methods and approaches should be always pursued to obtain hybrid capsules with controllable hierarchical structures, compositions and novel properties. Furthermore, the majority of the reported methods are only validated and implemented at small scales partially due to the high cost or difficult/complicated synthesis procedure of the raw assembling blocks. Therefore, more convenient, economical, and scalable methods are highly anticipated. (2) In nature, the unique compartmentalized structures of biological cells enable them to co-encapsulate diverse biomolecules spatially and precisely regulate hundreds of enzymatic reactions. Inspired by this architecture, the construction of novel hybrid capsules with multicompartmental structures is a crucial requirement for the development of carriers for multi-cargoes (*i.e.* multienzymes for enzymatic cascade reactions, multidrugs for controlled simultaneous and/or subsequent release) co-encapsulation. Although prominent examples of multicompartmentalized assemblies based on liposomes and polymersomes have been extensively investigated by Caruso and co-workers, the multicompartment systems based on organic–inorganic hybrid capsules have not been reported except in Jiang's work. Thus, future research should focus on the exploitation and applications of multicompartmental hybrid capsules. (3) The pore size and accessible surface area (porosity) of the hybrid capsule wall, which can greatly influence the application performance of capsules, such as their catalytic or therapeutic efficiency, have rarely been considered in previous studies. Constructing hybrid capsule walls with ordered and tunable pore structures and high porosity as well as high surface area becomes an urgent task. Drawing inspiration from

 

the pore formation approaches in inorganic capsule walls may become a feasible shortcut. Moreover, more comprehensive explorations should be carried out into the pores' formation mechanism and processes, which may help to precisely control and tailor the architecture of the pores to impart novel and unique functionalities. (4) From fundamental and practical viewpoints, the relationships between the structure, composition, properties and applications of capsules should be investigated in-depth. For example, in the drug delivery area, the *in vivo* tests of hybrid capsules should be conducted and systematic studies of their *in vivo* behaviour including therapeutic efficiency, biodegradation, biocompatibility and toxicity are still required. The qualitative and quantitative establishment and understanding of the relationships will promote the rational design and preparation of intelligent/smart capsules for specific applications.

Altogether, the incorporation of organic and inorganic components into one scaffold ensures various properties (hierarchical structures, multiple functionalities) can be introduced into the hybrid capsules. Hopefully, this general introduction of synthesis methods, structure properties, as well as the potential applications of hybrid capsules can offer the readers some inspiration for the design and preparation of hybrid capsules and other relevant functional materials. Furthermore, with the rapid advancement in chemistry, materials science, physics, biology, medicine, pharmaceutics and engineering, cutting-edge research and the development of hybrid capsules will witness a booming period.

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