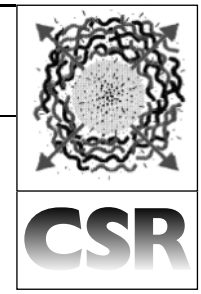
Polymer nanocapsules



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Hollow polymer particles with dimensions in the submicrometer region possess great potential for encapsulation of large quantities of and large sized guest molecules into their empty core domains. Conventional molecular chemistry requires costly synthetic procedures and only in special cases allows such particles to be prepared with exact control over their size and morphology. Therefore various self-assembly and templating approaches have been developed which will be briefly introduced in this article.

1 Introduction

In recent years materials with well-defined structures in the submicrometer region have attracted increasing interest. The idea is to tailor the composition, structure and function of materials with control at the nanometer level which may lead to new properties for well-known standard materials and hence to new applications. This concept has been to a large extent inspired by biomineralization, where a few inorganic minerals molded into an appropriate shape lead to a large variety of different materials properties.[1] As in Nature, one has to develop preparative procedures which allow precise control over the formation of structure and morphology. In this context over self-assembled superstructures of surfactants and/or polymers have proven to be valuable tools. They provide a compartmentalization on the nanometer scale which can be used as a structural template for the newly formed materials.[2]

In the following we will focus on hollow sphere structures with dimensions in the submicrometer region as a typical and synthetically especially demanding example. Such nanocapsules are of particular interest due to their potential for encapsulation of large quantities of guest molecules or large-sized guests within their empty core domain. These materials could be useful in applications in areas as diverse as biological chemistry, synthesis and catalysis. In fact, for polymeric nanocapsules a multitude of different applications have already been proposed, such as confined reaction vessels, drug carriers, protective shells for cells or enzymes, transfection vectors in gene therapy, carrier systems in heterogeneous catalysis, dye dispersants or as materials for removal of contaminated waste.

Similar and very effective nanometer sized containers, *viz.*, micelles and vesicular structures, are used by Nature in biological systems. However, due to the non-covalent interactions responsible for their formation these objects have only a limited stability and may undergo structural changes.[3,4] This leads, for example, to a rapid clearance of conventional lipid vesicles from the blood after their intravasal administration. Many applications (*e.g.*, in drug delivery) require, however, more stable particles.

Size- and shape-persistent nanocapsules can be prepared using a variety of different techniques, each of them having its special advantages (and of course also disadvantages).

The aim of this article is to give an overview of the current state of the art in the field of hollow polymer particles preparation. Both strengths and frailties of the respective preparative methods will be elucidated critically. For clarity the article is divided into four subsections according to the different approaches that are commonly used to attain the desired particle morphology. This division is clearly somewhat arbitrary, especially since there exists a certain overlap between the different methods: for example, the emulsion or suspension polymerization approach could be regarded as a special case of the self-assembly or the templating technique, depending on the respective point of view.

While in the first three basic approaches described, exclusively non-covalent interactions (*e.g.*, van der Waals, electrostatic or hydrophobic interactions) are used to imprint the characteristic shape on the resulting particles, the last section deals with single polymers that have by design an intrinsic hollow sphere morphology in the nanometer range. Although this approach *via* dendrimers is quite elegant, due to the tedious and costly preparation procedures it is mainly of academic interest.

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2 The self-assembly approach

Owing to their amphiphilic nature and molecular geometry, lipid molecules can aggregate in dilute aqueous solution into spherically closed bilayer structures, so-called vesicles or liposomes. It is quite reasonable that the hollow sphere morphology of these aggregates should render them suitable as precursors for the preparation of more stable nanocapsules. This can be realized using different concepts. Fig. 1[4] gives an overview of various methods. For example, lipids that are

functionalized with polymerizable groups can be polymerized within such vesicular structures.[4,5] As a result of the polymerization reaction the individual lipid molecules are interconnected *via* covalent bonds which of course stabilize the shell-forming membrane considerably. In some sense the polymerized lipids can be regarded as mimicking the role of the cytoskeleton or of the murein network, *i.e.* the polymer structures which Nature uses to stabilize biological cell membranes. In contrast to these natural polymer scaffolds that are simply attached to the lipid membrane *via* hydrophobic interactions, the polymerized lipids are, however, all covalently attached to a polymer chain within the membrane. It is obvious that this considerably obstructs their lateral mobility within the membrane.[4,5]

Interestingly, the polymerization of reactive lipids in bilayers formed from mixtures of different lipids may induce phase-separation phenomena within the membranes.[4,5] This can be exploited to produce labile domains in a controlled manner in the shell of the polymerized vesicles. These domains can be plugged or unplugged using external stimuli which renders such particles suitable for applications in the area of controlled or triggered release. Since the pioneering studies on polymerized vesicles derived from reactive lipids in the late 1970's and early 1980's this area has developed into a broad and active field of research. A detailed discussion of all its different aspects would be too much here, all the more since several recommendable reviews have already appeared on this topic to which the interested reader may refer (refs. 4 and 5 and references cited therein).

In an analogous fashion to the lipids, amphiphilic block copolymers can also aggregate in aqueous solution to vesicular structures.[6–8] Block copolymer vesicles may be significantly more stable than those formed from conventional lipids due to the larger size and the lower dynamics of the underlying polymer molecules.[8] Nevertheless, similarly to conventional lipids they are held together solely by non-covalent interactions. Hence they can disintegrate under certain conditions (*e.g.*, dilution or presence of surfactants) into individual block copolymer molecules. It is obvious that analogously to the reactive lipids block copolymer molecules could also be modified with polymerizable groups. A subsequent polymerization of the resulting 'macromonomers' interconnects them *via* covalent bonds which stabilize the whole particle. Such block copolymer based nanocapsules can be expected to possess great potential for encapsulation and controlled release from their interior. This is especially so, since the physical properties of their polymer shells can be controlled to a large extent by the block lengths, the block length ratio or the chemical constitution of the underlying polymer molecules.

Up to now, however, only two papers dealing with such particles have appeared[9,10] In one of them the formation of vesicles from a poly(isoprene)-block-poly(2-cinnamoyl methacrylate) PI-PCEMA diblock copolymer in hexane–tetrahydrofuran mixtures has been exploited as a starting point.[9] Converting these vesicles into stable, water-soluble polymer nanocapsules required, however, a rather costly procedure. The PCEMA blocks were photocrosslinked and then in a second step the PI blocks had to be hydroxylated to make these hollow nanospheres water-soluble. The radii of the nanocapsules were about 50–60 nm and changed only very slightly during these conversions.

In a similar approach a rather simple one-step procedure has been used to prepare vesicular structures from poly(2-methyl-

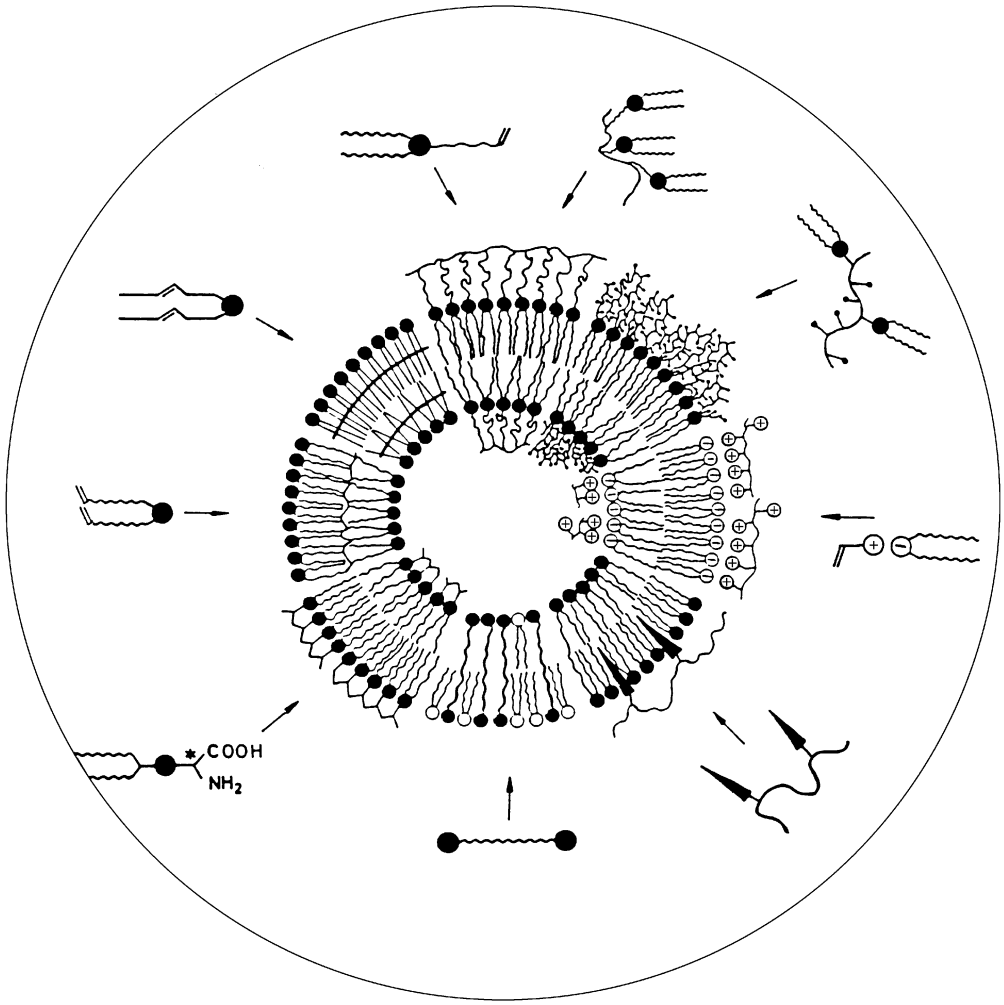

Fig. 1 Schematic representation of the different possibilities for stabilizing lipid vesicles. (Reproduced with permission from *Angew. Chem.*, 1988, **100**, 117.)

oxazoline)-block-poly(dimethylsiloxane)-block-poly(2-methyloxazoline) PMOXA-PDMS-PMOXA triblock copolymers directly in aqueous solution.[10] The size of the resulting vesicles could be controlled in the range from 50 to 500 nm. The underlying triblock copolymers were modified with polymerizable methacrylate end-groups without changing their aggregation behavior in water. These 'macromonomers' were polymerized within the vesicles using a UV-induced free radical polymerization. The polymerization did not lead to any measurable changes in size, size distribution or even molecular weight of the particles. Obviously the polymer chain reaction occurs mainly intravesicularly. Intervesicle reactions like intervesicular exchange of individual triblock copolymer molecules or a chain propagation reaction involving more than one vesicular aggregate play only a minor role in the time scale of the experiment.

In both cases the polymerization process led to the formation of covalently crosslinked polymer network structures. As a result the particles possess solid state properties like shape persistence. This allows them to maintain their morphological integrity even after their isolation from aqueous solution and redispersion in organic solvents like chloroform, tetrahydrofuran or ethanol. This is documented in Fig. 2 which shows

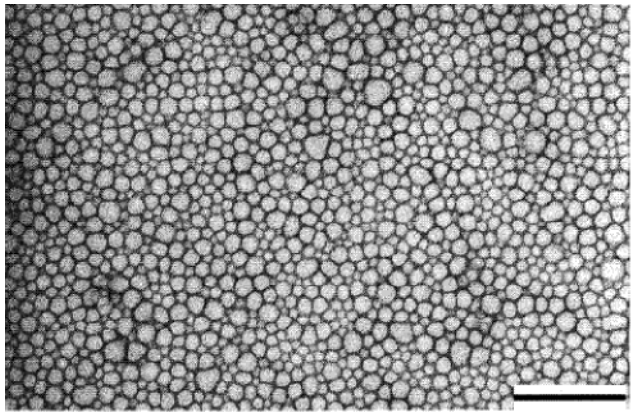

Fig. 2 Transmission electron micrograph of polymerized ABA-triblock copolymer vesicles. The length of the bar corresponds to 1 μm. (Reproduced with permission from *Langmuir*, 2000, **16**, 1035.)

a transmission electron micrograph of polymerized triblock copolymer vesicles isolated from water and redispersed in ethanol. Ethanol is a good solvent for the whole underlying block copolymer molecule. Hence, non-polymerized vesicles would immediately disintegrate under such conditions into singly dissolved polymer molecules. One major problem in this context is, however, to isolate the nanocapsules quantitatively in an intact state. As reflected by the broad size distribution of the particles observed in Fig. 2, mechanical shear forces occurring during the isolation procedure may partially disrupt the particles and hence have to be carefully avoided.[10]

In one case the hollow nanospheres were loaded with Rhodamine B.[9] Interestingly, the dye could be quantitatively released in water and water–ethanol mixtures so that the Rhodamine B release rate could be tuned by the composition of the water–ethanol mixtures. Ethanol seems to be a good solvent for the underlying block copolymers. Hence a higher ethanol content in the solvent mixture increases the solvent quality and the crosslinked polymer shell of the particles swells increasingly. As a result shell permeability increases and the release of the dye becomes faster. This makes such systems attractive for applications, since prefabricated particles can be loaded effectively in an organic solvent and subsequently the encapsulated material slowly released in water.

A similar concept uses just the geometry of the vesicular aggregates as a template.[11–18] In this case it is not the amphiphilic molecules themselves that are polymerized to freeze in the whole superstructure of the supramolecular aggregate, they just provide a geometrically restricted environment for dissolving and polymerizing conventional monomers.

It is well-known that vesicles or liposomes are able to solubilize hydrophobic substances to a certain degree. Such compounds are usually dissolved in the hydrophobic part of the lipid bilayer. If such substances also carry polymerizable groups, their subsequent polymerization should lead to the formation of polymer chains entrapped in the interior of the membrane. In contrast to polymerizable lipids, the polymer chains are now simply dissolved within the alkane part of the bilayer forming lipids (see Fig. 3 for a schematic representation). Hence, they are of minor influence on the overall physical properties of the membranes.

One special feature of vesicular polymerization of conventional hydrophilic or hydrophobic monomers is that the different compartments provided by the self-assembly of the lipid molecules generally serve only as a template, which determines size and shape of the resulting polymers. Thus, it is possible to use nearly every natural or synthetic lipid, without any modification. Although in most reported studies on vesicular polymerization of conventional monomers, synthetic lipids like dioctadecyl dimethylammonium bromide (DODAB), chloride (DODAC), sodium di-2-ethylhexyl phosphate (SEHP) or even spontaneously formed vesicles prepared from mixtures of cationic and anionic surfactants,[11–17] have usually been used (perhaps primarily because of budget reasons), but any natural lipid would provide a suitable matrix. Moreover, a combination of polymerizable lipids and conventional monomers could be incorporated into the templating vesicles to yield hybrids with interesting new polymer structures.

Of course the incorporation of hydrophobic substances into lipid bilayers should not exceed a certain saturation concentration. Above this concentration the monomer is no longer homogeneously distributed within the bilayers. This has

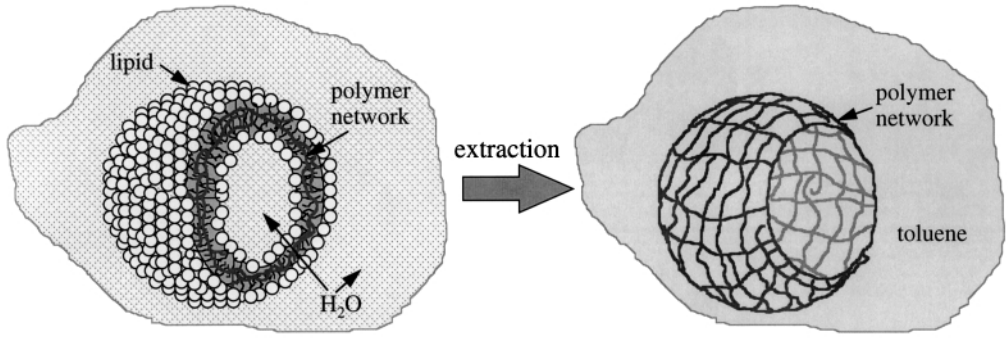

Fig. 3 Isolation of hydrophobic polymer hollow spheres formed by polymerization within monomer swollen lipid bilayers of vesicles. (Reproduced with permission from *Adv. Mater.*, 1998, **10**, 1387.)

recently been shown for toluene in phospholipid vesicles at concentrations above the saturation value.[19] Moreover, exceeding this saturation concentration may also disrupt the whole bilayer structure, thus converting the system into a conventional emulsion or even leading to the formation of a separate monomer phase in the presence of intact vesicles.

It is obvious that the overall thickness of the lipid membranes has to increase upon the solubilization of hydrophobic substances. The maximum swelling of the membrane leads typically to an increase from about 3 to about 5 nm.[20] This is, however, a negligible effect compared to the overall diameter of typical small unilamellar vesicles, which is about 100 nm. Therefore no dimensional changes of the underlying vesicles can usually be detected upon swelling the lipid bilayers of the vesicles[11–17] as long as the monomer concentration stays below the saturation value in the membranes.

It has been shown that the hydrophobic portion of lipid bilayers can be selectively swollen by a variety of hydrophobic monomers, like styrene,[11,12,14,15] alkyl (meth)acrylates[13,16,17] or even lipofullerenes carrying polymerizable octadecadiine side chains.[18] A crosslinking polymerization of such monomers leads to the formation of two-dimensional polymer networks in the interior of the membranes. Such networks can act as a polymeric scaffold that increases the mechanical stability of lipid membranes considerably without impeding the mobility of the lipid molecules within the aggregates (see Fig. 3).

The free radical polymerization of the hydrophobic monomers incorporated into the lipid membranes of vesicles can be initiated, similarly to the polymerization of reactive lipids, by UV irradiation or by thermal or redox chemical radical generation.

The polymerization process itself seems, however, to be rather sensitive towards the composition of the system, *i.e.*, the chemical constitution of the monomer and the lipid and the concentration of the monomers in the bilayers which, of course, limits its possible applications. While polymerization of alkyl methacrylates in dimethyldioctadecylammonium chloride vesicles[16,17] or the polymerization of reactive lipofullerenes in dipalmitoylphosphatidylcholine vesicles[18] clearly leads to the formation of polymer hollow spheres, in the case of styrene/divinylbenzene in dioctadecyldimethylammonium bromide an intravesicular phase separation occurs during polymerization, thus leading to the formation of so-called parachute-like structures.[15]

An interesting aspect of the formation of crosslinked polymer particles in vesicular dispersions arises from the fact that, in contrast to linear polymers, they should be able to retain their structure even after their isolation from the lipid matrix. This has recently been shown for crosslinked poly(alkyl methacrylates) by confocal laser scanning microscopy (CLSM), scanning electron microscopy and light scattering investigations.[19] Fig. 4 shows a typical CLSM micrograph of a hollow polymer particle isolated from a giant lipid vesicle. Note that despite the diameter of more than 150 μm the thickness of the polymer shell of this particle is below 1 μm. Although the particles contract considerably after their isolation from the lipid membrane they preserve their spherical shape. Their dimensions always remain, however, directly proportional to those of the underlying vesicles. This is not surprising since the polymer chains can be expected to be forced into a nearly two-dimensional conformation in the interior of the lipid membrane. After their liberation from the membrane the polymer chains can gain entropy by adopting a three-dimensional conformation. To do this, such spherically closed polymer shells have to shrink and the thickness of their shells increases. Up to now it has, however, not been fully clarified why the polymers retain their spherical shape (without collapsing) even in the dry state.

The extent of the observed contraction of the particles depends sensitively on the crosslinking density of the polymer network structure. The contraction increases with increasing crosslinking density, thereby showing the same scaling behavior as branched polymers upon variation of their number of branches. For the highest crosslinking densities the particles contract to about 1/10 of the original size of the templating vesicles.

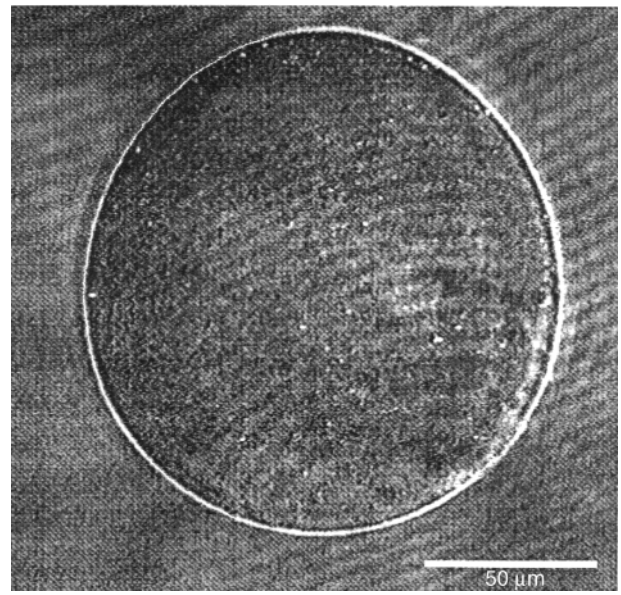

Fig. 4 Confocal laser scanning micrograph of a giant crosslinked poly(butyl methacrylate) hollow sphere prepared by vesicular polymerization. The scale bar corresponds to 50 μm. (Reproduced with permission from *Langmuir*, 1998, **14**, 1031.)

In the context of possible applications it would be of great interest to have detailed information about the permeability of these polymer hollow spheres. It has to be expected that besides the chemical constitution of the polymer backbone, the mesh-size, *i.e.*, the crosslinking density of the polymer network structure, also plays an important role. Only molecules that are smaller than this mesh-size should be able to diffuse across the polymer shell. Molecules which are larger cannot pass the polymer membrane of the hollow spheres for geometrical reasons.

Whereas the size and shape of the resulting polymer particles are directly determined by the templating vesicles, the polymer scaffold can be modified rather easily using conventional chemical reactions. This allows, for example, the conversion of poly(*tert*-butyl acrylate) hollow spheres into poly(acrylic acid) hollow spheres. The resulting polyelectrolyte nanocapsules can swell as a response to changes in the pH of their environment. This pH-dependent transition influences considerably the permeability of such polyelectrolyte shells and can be used to selectively entrap and release water-soluble polymers.

Although such a vesicular polymerization represents a rather elegant approach to producing polymeric nanocapsules its technical application is expected to be rather limited. The reason for this lies in the low economical efficiency of this method. Apart from the often energy consuming vesicle preparation procedure, the synthesis of one gram of pure polymer nanocapsules already requires approximately 1.5–2 times their weight of lipid, a reaction volume of about 300–400 milliliters of water and additionally several liters of organic solvents (for purification).

Not only vesicular aggregates but also micelles can be used for the controlled formation of nanocapsules; this again, however, requires a rather costly synthetic procedure.

It is, for example, well-known that block copolymers may assemble to polymeric micelles with diameters in the 10 to 100 nm range. These block copolymers can be modified so that either the interior or the exterior blocks within the micelles contain polymerizable groups. For example poly(isoprene)-

block-poly(acrylic acid) (PI-PAA) diblock copolymers form micelles in aqueous solution with a PI core and a PAA shell. It has been shown that the PAA shell can be crosslinked with α,ω-diamino-poly(ethylene glycol)[21] (see Fig. 5). Similarly, a poly(isoprene)-block-poly(2-cinnamoylethyl methacrylate)-block-poly(*tert*-butyl acrylate) (PI-PCEMA-PTBA) triblock copolymer forms micelles with a PTBA corona, PCEMA shell and a PI core in THF–methanol mixtures.[22] In this case the micellar structure could be locked in by UV-crosslinking of the PCEMA within the micelles. Subsequently the PI cores of both the crosslinked PI-PAA and the PI-PCEMA-PTBA micelles could be degraded by ozonolysis into small fragments that could diffuse into solution and leave nanospheres with a central cavity. A schematic representation of the whole process is given in Fig. 5.[21]

The potential of such systems for encapsulation of smaller molecules has been demonstrated by loading the crosslinked PCEMA-PTBA capsules with Rhodamine B.[22] The incorporation of the dye into the central cavity of the particles could directly be visualized by TEM.

The degradation of the shell crosslinked PI-PAA micelles leads to water-soluble crosslinked poly(acrylamide) hollow spheres which considerably increase the hydrodynamic diameter of their shells after removal of the core.[21] The increase of D_h from 27 to 133 nm has been explained by the fact that the crosslinked poly(acrylamide) shells can be regarded as a hydrogel that swells when the core domain fills with water after removal of the poly(isoprene). The diameter of the hollow-sphere products depends sensitively on both the degree of polymerization of the block copolymers originally used to form the micelle and the nature of the crosslinking diamine used to prepare the shell crosslinked micelles.

3 The template approach

Another possibility for generating polymer hollow spheres is to form a polymer shell around a preformed template particle that can subsequently be removed, thus leaving an empty polymeric shell. There are several methods of realizing such a template synthesis of hollow polymer particles.

A convenient way is to exploit the well-known polyelectrolyte self-assembly at charged surfaces. This chemistry uses a series of layer-by-layer deposition steps of oppositely charged polyelectrolytes.[23] One starts with colloidal particles carrying surface charges (*e.g.*, a negative surface charge). Polyelectrolyte molecules having the opposite charge (*i.e.*, polycations) are readily adsorbed to such a surface due to electrostatic interactions. Not all of the ionic groups of the adsorbed polyelectrolyte are consumed by the electrostatic interactions with the surface. As a result the original surface charge is usually overcompensated by the adsorbed polymer. Hence, the surface charge of the coated particle changes its sign and is now available for the adsorption of a polyelectrolyte of again opposite charge (*i.e.*, a polyanion). As sketched in Fig. 6 such sequential deposition produces ordered polyelectrolyte multilayers, the thickness of which can be exactly controlled by the number of deposition steps.[23] To avoid, however, a polyelectrolyte-induced particle flocculation one has to work at rather low particle concentrations and excess polyelectrolyte not adsorbed to the surface has to be removed carefully after each step.

As template particles, weakly crosslinked melamine–formaldehyde particles have been used. Exposure of the coated particles to an acidic solution of pH < 1.6 dissolves the melamine–formaldehyde core without affecting the layered polyelectrolyte shells. As can be seen in the transmission electron micrograph of Fig. 7, the resulting polyelectrolyte shells are shape persistent and clearly preserve their hollow sphere morphology after removal of the template. Nevertheless it has to be expected that their long-term stability depends sensitively on the surrounding environment of the particles. Especially in biological fluids (*e.g.*, in blood plasma), or in media of high ionic strength which may screen the ionic interactions responsible for maintaining their integrity, the long-term stability of such polyelectrolyte shells may be rather limited.

It has been shown that small dye molecules can readily permeate such layered polyelectrolyte shells while larger sized polymers with molecular weight larger than 4000 Da obviously do not.[24] For these investigations, however, a polyelectrolyte (*i.e.*, poly(allylamine hydrochloride)) has been used as a

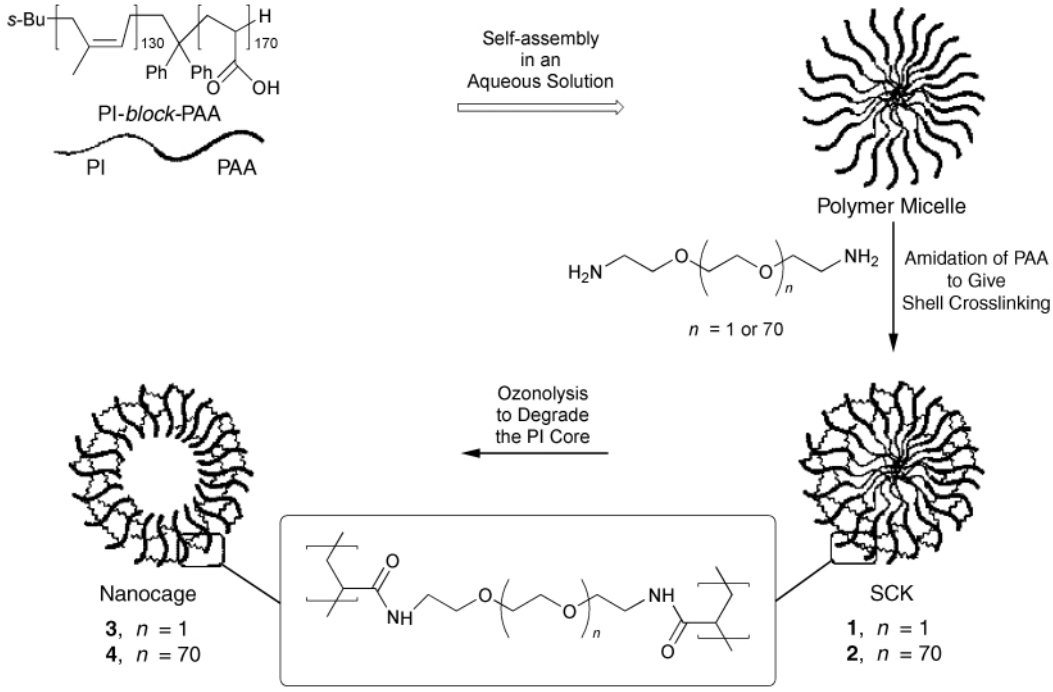

Fig. 5 Procedure for the preparation of nanocapsules from amphiphilic diblock copolymers. The shell of the final nanocapsules consists of crosslinked poly(acrylamide). (Reproduced with permission from *J. Am. Chem. Soc.*, 1999, **121**, 3805.)

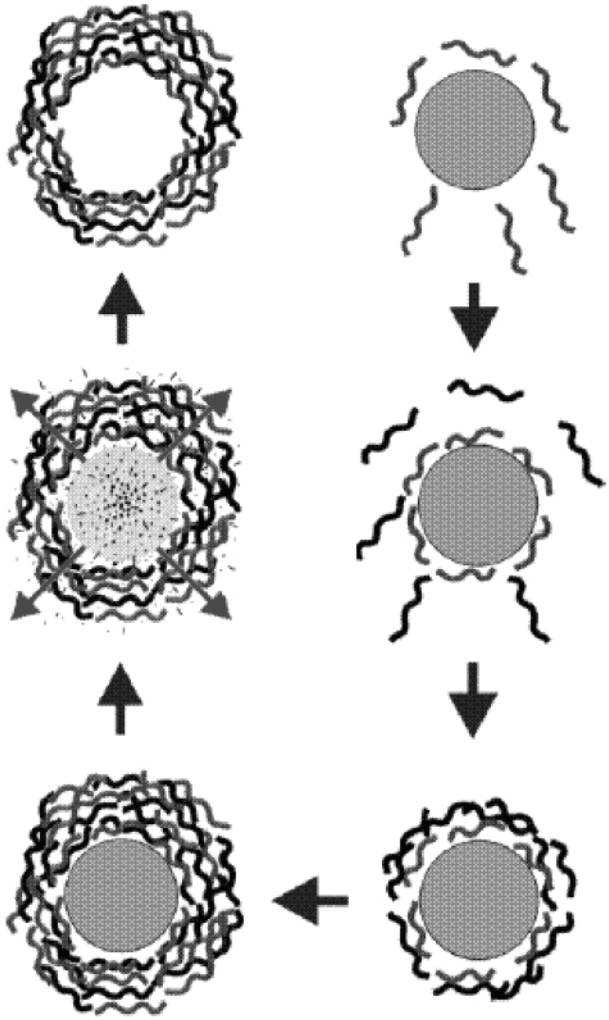

Fig. 6 Illustration of the procedure for preparing hollow spheres using layer-by-layer deposition of oppositely charged polyelectrolytes on colloidal particles (Reproduced with permission from *Chem. Mater.*, 1999, **11**, 1048.)

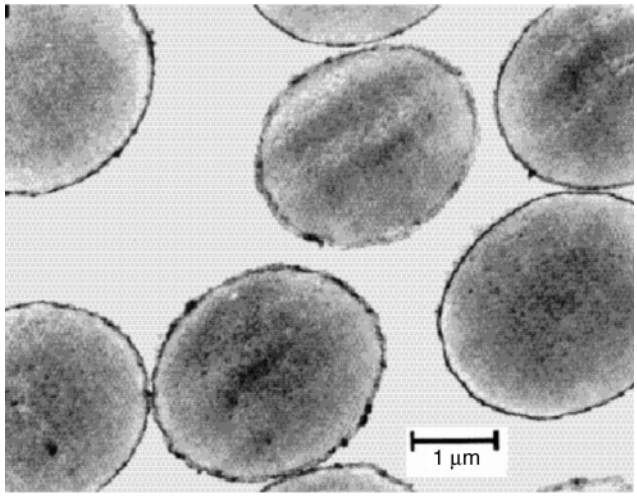

Fig. 7 Transmission electron micrograph of polyelectrolyte hollow spheres. The shell of the particles consists of 9 layers ((poly(styrene sulfonate)poly-(allylamine hydrochloride))$_4$/poly(styrene sulfonate)). (Reproduced with permission from *Chem. Mater.*, 1999, **11**, 1048.)

molecular probe. Therefore, it is unfortunately not possible to discern whether this screening effect is due solely to the increased size of the polymer probe or if electrostatic interactions between the layered polyelectrolyte shell of the capsules and the positively charged polymer also play a role. Eventually the situation may be different for neutral polymer probe molecules of similar size which cannot undergo such interactions.

Interestingly, the capsules could be filled with oils by sequential exchange of the solvent.[24] These oil-filled capsules could be dispersed in water due to their amphiphilic nature, thus leading to a stable, surfactant-free oil-in-water emulsion.

Functionalized polystyrene latex particles carrying surface charges are also suitable substrates for the polyelectrolyte self-assembly technique. In one case inorganic particles were incorporated into the adsorbed shells by a sequential adsorption of nanometer-sized SiO_2 particles with negative surface charge and cationic poly(diallyldimethylammonium chloride) (PDADMAC).[25] Layers with a thickness ranging from tens to hundreds of nanometers could be prepared by this procedure. Removing the polystyrene core leaves SiO_2/PDADMAC nanocomposite shells and after calcinating even pure SiO_2 hollow spheres.[25] Both the composite and the purely inorganic capsules can be expected to show interesting physical properties such as enhanced mechanical stability or exceptional permeability behavior.

Similarly poly(*N*-vinylpyrrolidone)-stabilized polystyrene latex particles were coated with thin overlayers of poly(aniline) to produce electrically conductive core–shell particles.[26] In contrast to the layer-by-layer deposition method where preformed polymers are adsorbed to a surface, here the polymer is formed *in situ* by oxidative coupling of monomers at the particle surface. The poly(aniline) layer in the reported case had, however, a rather non-uniform and inhomogeneous morphology. Therefore extraction of the polystyrene core left poly(aniline) shells that displayed a so-called 'broken egg-shell morphology', *i.e.*, they were largely disrupted.

Also gold nanoparticles have successfully been used as templates for nucleation and growth of surrounding poly(pyrrole) and poly(*N*-methylpyrrole) shells.[27] Etching the gold with, for example, $KCN–K_3[Fe(CN)_6]$ solution leaves structurally intact hollow polymer nanocapsules with a shell thickness governed by the polymerization time. Their shell thickness could be controlled in the range from 5 to more than 100 nm. The gold particles are not only useful as template material but can also be used to deliver guest molecules into the capsule core. For example, ligands attached to the gold surface prior to polymerization remained trapped inside the hollow capsule after gold etching which demonstrates their potential as protective shells for sensitive compounds like enzymes.

Obviously the ions of the gold etchant were able to diffuse through the polymer shell, the permeability of which could even be tuned by the oxidation state of the polymer. However, even rather small organic guest molecules like Rhodamine B were not released again from the interior of the particles, even over a period of three weeks.[27] That means that there is only very restricted access to enclosed substances in the interior of the shells, which limits their applications.

4 The emulsion/suspension polymerization approach

Hollow polymer particles can also be prepared applying suspension and emulsion polymerization techniques.[28–31] Although in most cases these methods have been shown to lead to particles with diameters of several micrometers, nanometer-sized polymer hollow spheres are also accessible.

For example the polymerization of divinylbenzene in toluene/divinylbenzene swollen polystyrene latex particles or in polystyrene containing toluene droplets leads to the formation of hollow PDVB particles.[28] This is the result of a microphase separation limited compatibility of the chemically different polymers in solution, which leads to the formation of a PDVB

shell around a toluene–poly(styrene) core. After evaporation of the toluene a cavity remains in the center of the particles.

Another rather convenient method leading to hollow polymer particles proceeds *via* emulsion polymerization.[29–31] Usually a two-stage process *via* seeded latexes with physical or time separation between the two steps is applied. In a first step the core particles are synthesized *via* conventional emulsion polymerization. Then in a second step a different monomer is added and a crosslinked shell is polymerized around the core particle. The synthesis of such core–shell latexes is quite simple in concept but rather difficult in practice. This holds particularly if one is interested in well-defined and homogeneous particle morphologies which are a basic requirement for the preparation of hollow polymer particles. It has been demonstrated that both thermodynamic and kinetic factors are of crucial importance here. Additionally, to end up with a hollow polymer sphere one has finally to remove the core of the particles. Since core and shell are, however, frequently chemically rather similar this is another critical step of the preparation procedure. Usually rather aggressive reaction conditions, like a prolonged alkali and acid treatment at high temperature, are required to degrade the particle core.[29,30] Although clearly hollow polymer particles are formed using such methods, the question remains to what extent the polymer shells survive intact under these conditions.

A rather elegant approach to remove the core under very mild conditions has recently been demonstrated.[31] The authors report the synthesis and characterization of nanometer sized hollow organosilicon particles. The synthesis followed a two-step procedure similar to that described above. The core of the particles was formed by a rather low molecular weight poly(dimethylsiloxane) (PDMS) around which a crosslinked organosilicon shell was formed in a second step. The PDMS from the interior of the particles could be removed quantitatively by ultrafiltration. The preparation procedure is summarized in Fig. 8. The remaining organosilicon nanoboxes were

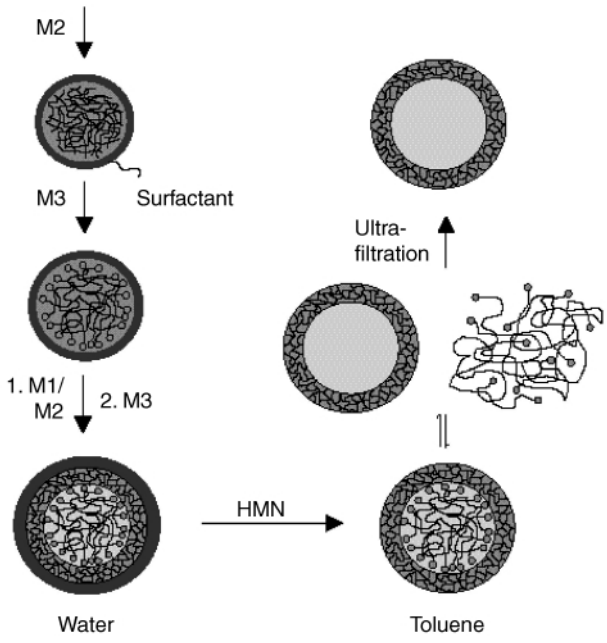

Fig. 8 Preparation of organosilicon nanocapsules. M1: $MeSi(OMe)_3$, M2: $Me_2Si(OMe)_2$, M3: Me_3SiOMe, HMN: hexamethyldisilazane. (Reproduced with permission from *Adv. Mater.*, 1999, **11**, 1299.)

characterized by gel permeation chromatography, dynamic light scattering, X-ray scattering and atomic force microscopy. The nanocapsules had typical diameters of 50 nm and a shell thickness of about 6 nm. Interestingly, they could be refilled with poly(dimethylsiloxane) chains with a molecular weight of about 6000 Da, *i.e.*, rather large molecules, which reflects an obviously rather high porosity of the polymer shells. Hence, typical low molecular weight substances are expected to be released very fast from such particles. Nevertheless, these organosilicon capsules represent a very promising system for applications in various areas.

5 The dendrimer approach

Dendrimers are highly branched cascade molecules that emanate from a central core through a step-wise repetitive reaction sequence. By design such a molecule consists of three topologically different regions: a small initiator core of low density and multiple branching units, the density of which increases with increasing separation from the core, thus eventually leading to a rather densely packed shell. Hence, at some stage in the synthesis of such a dendrimer the space available for construction of the next generation is not sufficient to accommodate all of the atoms required for complete conversion. Extending this principle in a more general fashion, dendrimers that have internal 'cavities' with a dense outer shell may be synthesized by controlling the chemistry of the last step. This has been demonstrated by the preparation of the fifth generation poly(propylene imine) dendrimer[32] shown in Fig. 9.

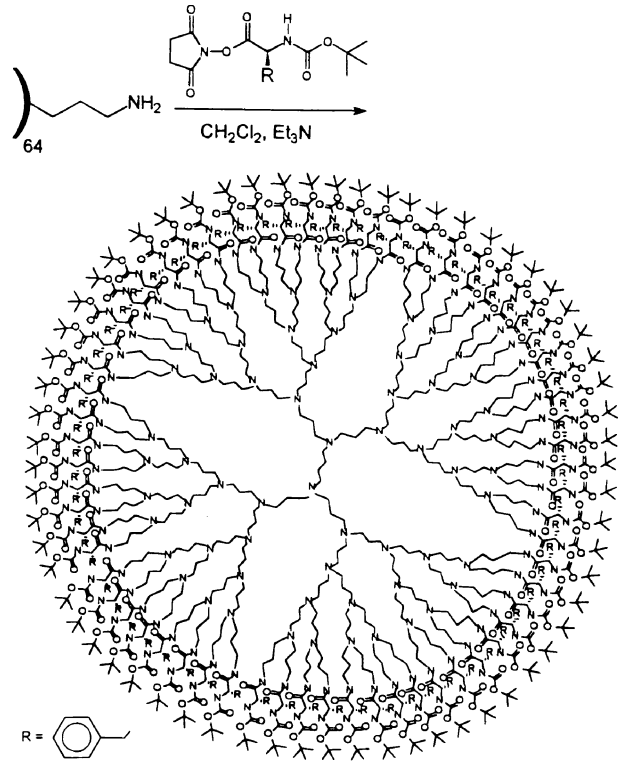

Fig. 9 A dendritic box capable of encapsulating small guest molecules during construction. (Reproduced with permission from *J. Am. Chem. Soc.*, 1995, **117**, 4417.)

Due to their dense outer shell these molecules can be regarded as dendritic boxes that are capable of retaining guest molecules trapped during synthesis. Subsequent guest diffusion out of the box was slow since the dendrimer shell is close packed due to the bulky H-bonded surface groups. If the tertiary butyl groups were removed guest molecules could diffuse out of the boxes, but only if they were sufficiently small. Thus Rose Bengal remained in the containers while *p*-nitrobenzoic acid leaked out.[32]

Closely related to such dendritic boxes are amphiphilic dendrimers[33] or hyperbranched polymers[34] consisting of a hydrophobic (hydrophilic) core and a hydrophilic (hydrophobic) shell. Due to their amphiphilic nature these systems are

also selectively able selectively to solubilize guest molecules within their core domain.

This permeability of the outer shell for small molecules and ions could, for example, be exploited for a controlled synthesis of inorganic nanoparticles in the core region of a poly-(amidoamine) starburst dendrimer.[35] While small Cu^{2+} ions could diffuse into the interior of the dendritic boxes the *ca.* 2 nm diameter Cu-nanoparticles formed upon reduction were too bulky to leak out again.

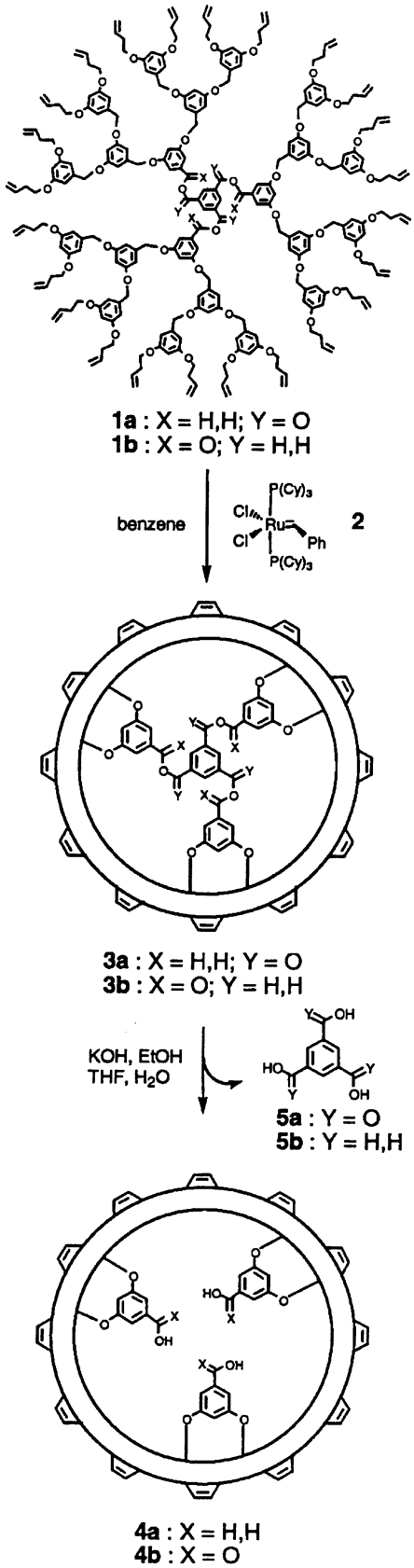

Fig. 10 Preparation of a cored dendrimer. (Reproduced with permission from *J. Am. Chem. Soc.*, 1999, **121**, 1389.)

Dendrimers are, however, generally not real hollow polymer particle systems due to their core that covalently links the 'dendritic wedges' of the molecule. It is obvious that this core part is of crucial importance for the integrity of the whole molecule. Hence, removing the core requires another connection between the outer zones of the molecule. Indeed, applying similar concepts as shown in the approaches of Wooley[21] and Liu,[22] it is also possible to produce real hollow structures from dendrimers. This has recently been demonstrated using a polyether dendrimer with a trimesic acid ester core.[36] This polymer contains three cleavable ester bonds at its core and robust ether bonds throughout the rest of the molecule. As shown schematically in Fig. 10 the hollow particles were formed by selective crosslinking of homoallyl ether groups at their periphery and subsequent degradation of the core region by hydrolysis. An interesting possibility offered by this method is that the remaining functional groups in the interior of the container system could serve as 'endo-receptors' available for molecular recognition. This approach allows a high control over the size and geometry of the formed nanocapsules. However, the preparation of the particles requires a rather costly and tedious procedure which clearly presents a limiting factor for possible applications.

6 Conclusions

In recent years several promising approaches for the preparation of hollow polymer particles have been developed. The required exact control over the particle morphology on a nanometer scale can often be achieved using self-assembly and templating techniques. This has been accomplished for several model systems, although it is usually quite difficult and requires rather sophisticated analytical methods to decide whether a certain procedure leads in fact to well-defined and homogeneous nanocapsules. The current state of the art therefore provides a reasonable basis for developing such systems further towards applications. However, although various applications of these new materials, *e.g.*, for encapsulation of drugs, enzymes or fragrances, are currently discussed they are yet to be realized. Since the majority of the proposed applications are located in the life science area most of the model polymers described up to now are not well-suited and nanocapsules composed of biocompatible materials are required. Generally, many of the described approaches are rather ineffective (*e.g.*, they require very low concentrations) and hence a further challenge will be to scale up the production of the nanocapsules.

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