Chapter 3

Methods for synthesis of nanocontainers

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1 Introduction

Nanocontainers are a subject of great scientific and industrial interest with a wide range of applications, from inorganic and mesoporous nanomaterials to amphiphilic block copolymer nanosystems.

The literature is studded with various examples dealing with specific nanocontainers having particular composition, shape, and structure. Micelles, liposomes, polymersomes, solid nanoparticles, nanocapsules, nanotubes, nanogels, and dendrimers are just some of the many nanosystems found in the literature. Nanocontainers can have core-shell structure, and they can be nanospheres, nanotubes, nanobottles, nanofunnels, nanohorns, and nanofibers: they consist of inorganic oxide and hydroxide, inorganic salts, synthetic polymers, natural polymers, and hybrid composite.

Several different synthetic methodologies have been developed with the aim of getting such systems with void spaces allocating one or more different species through covalent or noncovalent forces (e.g., van der Waals, hydrogen bonding, and electrostatic) but precluding their direct contact with the adjacent environment.

In this chapter, we will present the main synthetic procedures of the various nanocontainers to cover as much as possible their emerging applications in biomedicine, plant biology, molecular biology, pharmaceutics, and materials science with particular attention to coating technology.

We will therefore deal with the layer-by-layer technique, self-assembly methods (comprehending dialysis and thin-film hydration), emulsion-based processes (comprehending miniemulsion polymerization, microemulsion, and microemulsion-mediated synthesis of silica-based nanomaterials), precipitation-based synthetic methods, ultrasonic techniques, and the divergent and convergent approach (Fig. 1).

2 Layer-by-layer technique

The layer-by-layer (LbL) technique was introduced by Decher and coworkers [1] in the early 1990s to fabricate ultrathin molecular films by the alternate electrostatic adsorption of oppositely charged polyelectrolytes from aqueous solution onto solid surfaces. Simple implementation, versatility, and feasibility with a broad range of charged species (polyelectrolytes, nanoparticles, proteins, etc.) make it attractive to be exploited as an efficient, robust, and reproducible procedure for nanoparticle engineering [2] allowing surface modification through uniform coating of controllable composition and thickness.

The LbL technique is applied to prepare multilayer shells on colloid particles such as classical polyelectrolyte, protein/polyelectrolyte, and nanoparticle/polyelectrolyte multilayers.

Caruso et al. [3] produced for the first time hollow inorganic silica and hybrid capsules using the LbL approach and extended it to a wide range of inorganic or organic materials such as polystyrene, zeolite, and multiwall carbon nanotube.

In 2006 Schuckin et al. [4] demonstrated first the self-healing effect of silica nanoparticles, incorporating benzotriazole (BZT), coated with poly(ethyleneimine)/poly(styrene sulfonate) (PEI/PSS) polyelectrolyte layers. He first carried out the adsorption of positive PEI on the negatively charged SiO_2 nanoparticles by a 15 wt% SiO_2 colloidal solution with PEI solution followed by 15 min of incubation and repeated washing. Then the authors performed the adsorption of the second negative layer using a PSS solution in a NaCl solution, while adsorption of BZT to give the third inhibitor layer was achieved from an acidic solution at pH = 3 since it is only slightly soluble in water at neutral pH. This step is repeated to increase the inhibitor loading in the LbL structure. The final nanoreservoirs have a SiO_2/PEI/PSS/benzotriazole/PSS/benzotriazole layer structure. Their work plays a crucial role in the field of anticorrosion materials since it has opened the route to a large variety of nanocontainers built up from different core materials via LbL deposition of different polyelectrolyte and corrosion inhibitor substances, able to release the active principle on demand.

Smart Nanocontainers. https://doi.org/10.1016/B978-0-12-816770-0.00003-4

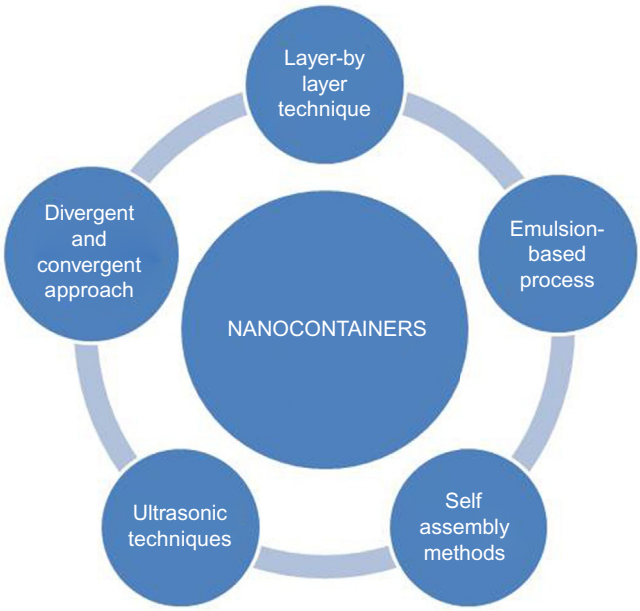


FIG. 1 Overview of the synthetic methods presented in the chapter.

Further development of the research consisted in using another silicon oxide-based species such as halloysite; first, BZT was embedded in halloysite, and then the surface of the nanotubes was modified by LbL deposition to avoid spontaneous leakage and uncontrolled release of the encapsulated BZT [5].

The nanocontainers cores mainly consist of inorganic materials: beside SiO_2 nanoparticles that have been largely used and halloysite [4–8], literature reports also other zinc-based systems (Zn oxide, zinc molybdate, magnesium and cerium zinc molybdate, and calcium zinc phosphate) [9–12], layered double hydroxide (LDH) [13], and iron oxides [14–18].

In particular, Fe_3O_4 has recently gained much attention: in 2018 Izadi et al. [15] prepared hydrothermally at 150°C Fe_3O_4 nanoparticles (NPs) by mixing $FeCl_3$ and $FeCl_2$ solutions in alkaline conditions. Next step was their functionalization with myristic acid (MA) to impart negative charges on surfaces via an ultrasound-assisted procedure at 60°C providing suitable condition for the deposition of positively charged polyaniline (PANI) layer. The adsorbed MA molecules create also the steric stabilization improving the suspension stability. PANI was deposited successively by dropwise addition of aniline at 4°C to a suspension of the functionalized NPs containing sodium dodecyl sulfate as stabilizer ($NaC_{12}H_{25}SO_4$) and ammonium persulfate [$(NH_4)_2S_2O_8$] as initiator in a reactor equipped with an ultrasound system. Final loading of the inhibitor was achieved by mean of ultrasound irradiation.

Polyaniline and polypyrrole are polyelectrolytes that in the LbL process have been mainly deposited via radical initiated polymerization of the monomer onto the nanocontainer core [10–12, 15–17]. The other polyelectrolytes commonly used in the field of anticorrosion self-healing are commercially available synthetic polymers such as polyethylene imine [4, 5], poly (diallyldimethylammonium) chloride [5, 18, 19], polyallylamine hydrochloride [5, 8, 13, 20, 21], poly(acrylic acid) (PAA) [11, 12, 14, 17, 18], and polystyrene sulfonate [4, 5, 7, 8, 13, 21], while only one paper reports the use of natural polymers and their derivatives such as chitosan and aspartic acid [22].

Synthetic polymers find wide application also in the field of biomedicine, pharmacology, theranostics, and biomaterials science [23–26]. However, to achieve biocompatible polymeric nanoparticles, natural polymers such as polylysine and chitosan have been largely used [27–29].

In particular, chitosan has unique biological properties, such as nontoxicity, biocompatibility, biodegradability, and mucoadhesivity. It is soluble in aqueous media of acidic pH due to the presence of amino groups, and the protonation form can act as a cationic polyelectrolyte.

We find it coupled to poly(acrylic acid) [30], to pectin [31], to hyaluronic acid [32], to DNA [33], to sodium alginate [34–36], to dialdehyde starch [37], to bovine serum albumin [28], and to polysaccharides carrageenan [38].

It is interesting to report also the cases where the simple polyelectrolytes assembly itself creates a nanocontainer: in 2003 Nicol et al. [39] produced multilayer structure loaded with small organic hydrophilic fluorophore molecules such as fluorescein, rhodamine B, and two coumarin-based dyes, combining strong polyelectrolytes of the polystyrene family

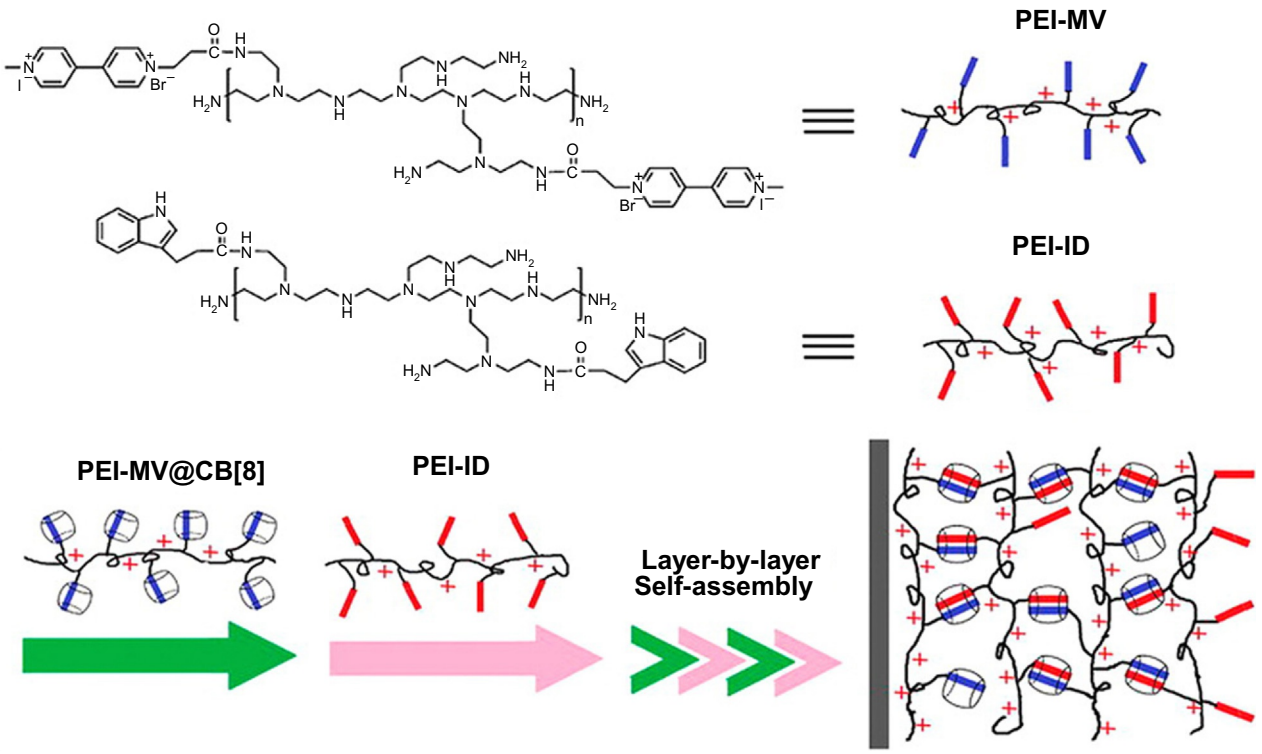


FIG. 2 Schematic representation of PEI-MV and PEI-ID molecules and preparation of the (PEI-MV@CB[8]/PEI-ID) ultrathin film. *(Source: Reprinted with permission from D.-D. Li, K.-F. Ren, H. Chang, H.-B. Wang, J.-L. Wang, C.-J. Chen, J. Ji, Cucurbit[8]uril supramolecular assembly for positively charged ultrathin films as nanocontainers, Langmuir 29 (46) (2013) 14101–14107. Copyright 2013 American Chemical Society.)*

(polyvinyl benzene chloride [PVBC] and PSS). They first prepared the films by alternated deposition of PVBC quaternized with *N*,*N*-dimethylethanolamine and PSS onto the substrates from water solutions and dipping them into the fluorophore solution, exploiting the enhanced interactions through the aromatic cycles between the polymers and polycyclic dyes.

Another very peculiar case where LbL formation of nanocontainer occurs via a supramolecular procedure is the LbL assembly of pure positively charged ultrathin films of two poly(ethylenimine) derivatives [40].

The assembly process of two modified poly(ethylenimine) with two different guests of cucurbit[8]uril (CB[8]) methyl viologen (MV) and indole (ID) onto a substrate in water, schematically shown in Fig. 2, is based on the host-guest interaction of the macrocycle CB[8] and not on the electrostatic ones that however are responsible of the successive loading of plasmid DNA as a negatively charged biological compound.

Cucurbit[8]uril with its unique host-guest binding properties has been used as supramolecular linker also in other nanocontainer systems [41–43].

3 Self-assembly

Self-assembly provides an attractive means by which to prepare supramolecules and to synthesize new materials. At the molecular level, self-assembly involves competition between intermolecular (or thermodynamic) forces, and it takes advantage of the natural tendency of specific, local interactions among the components themselves. The forces include hydrogen bonding, electrostatic, and van der Waals interactions, which motivate agglomeration to minimize the free energy of the system, and electrostatic repulsion, which stabilizes NPs by repulsion of surrounding NPs. The balance of these forces stops agglomeration, and NPs are successfully self-assembled [44].

Self-assembly is therefore a technique suitable to prepare from amphiphilic block polymer (polymeric surfactants) polymeric aggregates consisting of ordered self-assembled species. Their structure, functionality, and morphology can be effectively controlled through appropriate molecular design and optimal preparation conditions.

In particular the the amphiphilic block copolymers (ABCs) are well established as building blocks for the preparation of micellar carriers. These structures have a unique chemical composition characterized by a hydrophilic block that is chemically tethered to a hydrophobic block.

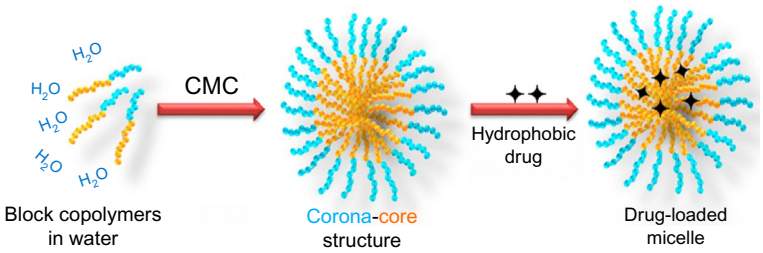


FIG. 3 Schematic representation of the self-assembly of amphiphilic block copolymers to polymeric micelles. *(Reprinted with permission from Y.H.A. Hussein, M. Youssry, Polymeric micelles of biodegradable diblock copolymers: enhanced encapsulation of hydrophobic drugs, Materials 11 (5) (2018) 688.*

In aqueous solution, polymeric micelles are formed via the association of ABCs into nanoscopic core/shell structures at or above the critical micelle concentration (CMC): the core of the micelles is formed by the hydrophobic segment of the polymer, while the hydrophilic segment forms the corona that provides compatibility of the micelles in the aqueous environment (Fig. 3), [45].

The hydrophobic core accommodates various hydrophobic molecules, such as therapeutics and imaging agents. This aspect is very important in the field of drug-delivery and pharmaceutical applications since it improves the solubility and stability in the biological system. The hydrophilic corona shields the core and protects the loaded drugs from interactions with the blood components [46].

These materials as drug-delivery systems are based on diblock (A-B), triblock (A-B-A), and graft copolymers generally composed of biocompatible, biodegradable hydrophobic polymer blocks such as polyesters or poly(amino acids) covalently bound to a biocompatible hydrophilic block, and some examples are reported in Table 1 [47–52].

Self-assembly can be achieved through direct dissolution, solvent evaporation, and dialysis methods [53]. In direct dissolution (also defined as bulk hydration), the simplest and more used synthetic procedure, the copolymers self-assemble in water at CMC or around it taking the hydrophobic drug in the core region of micelles: to increase the drug loading, the temperature can be conveniently raised.

An interesting example is offered by the study by Kadam et al. [54] in 2011 on micelles from poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) block copolymers having different polymers percentage as nanocontainers for solubilizing hydrochlorothiazide (HCT), a diuretic drug that is poorly water-soluble. PEO-PPO-PEO copolymers known as Pluronic® (BASF) P103 (EO17PO60PEO17), P123 (EO19PO69EO19), and F127 (EO100PO65EO100) form micelles that enable dissolution of HTC showing an increase in solubility of the drug in aqueous Pluronic® solutions with increase in copolymer concentration.

The enhanced solubility of drug can be attributed to the increased interaction between drug and copolymer molecules and more number of micelles formed at higher concentration.

In the entire concentration range studied, HCT showed higher solubility in P103 and P123 that are hydrophobic copolymers than in F127 that is hydrophilic.

TABLE 1 Common biocompatible and biodegradable block composing the amphiphilic block copolymer

Hydrophilic block	Hydrophobic block
Poly(ethylene oxide) (PEO), also referred to as poly(ethylene glycol) (PEG)	Poly(propylene oxide) (PPO)
Chitosan	Poly(L-lactide) (PLA)
Poly(N-vinyl pyrrolidone) (PVP)	Poly(lactide-co-glycolic acid) (PLGA)
Poly(N-isopropylacrylamide) (pNIPAAm)	Poly(β-aminoesters)
	Poly(L-histidine) (pHis)
	Poly(L-aspartic acid) (pAsp)
	Dioleoyl(phosphatidylethanolamine) (DOPE)
	Distearoyl(phosphatidylethanolamine) (DSPE)

Moreover, Kadam et al. investigated the micellization and solubilization behavior at different temperatures (28°C, 37°C, and 45°C) evidencing a little apparent increase in the solubility of HCT in water with an increase in temperature.

Another synthetic procedure for the drug-loaded micelles is the solvent evaporation method, also known as solution-casting technique. It consists of two steps: in the first one the drugs and block copolymers are dissolved in a volatile organic solvent, and in the second one the solvent evaporates giving a thin film of copolymer. Afterwards the resultant thin film of drug and copolymer is reconstituted with water, and drug-loaded micelles are obtained.

In particular, in 2014, Pippa et al. [55] designed and developed a suitable polymeric formulation based on the poly(isoprene-b-ethylene oxide) ABC (IEO) family incorporating amphotericin B (Ampho B) to overcome its water insolubility problem. They prepared two IEO block copolymers (IEO-a and IEO-b) and dissolved them with Ampho B in different molar ratios in dimethylsulfoxide (DMSO) and methanol; the removal of the solvent via evaporation and the vacuum dryness produced a thin film that was subsequently hydrated. Their work showed that the composition of the block copolymer itself, as well as the physicochemical characteristics of the drug and the copolymer/drug interactions and weight ratios, plays a key role in the self-assembly behavior of drug carriers and in the encapsulation efficiency.

More recently, in 2018, Mei et al. [56] prepared polymeric micelles with variable particle sizes, which consisted of 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-poly(ethylene glycol) (DSPE-PEG) derivatives (DSPE-PEG2000-N_3 and DSPE-PEG2000-Alk, Alk = propargyl) loaded with paclitaxel (PTX) by dissolving DSPE-PEG2000-N_3 (or DSPE-PEG2000-Alk) and PTX separately in chloroform/methanol (2:1) and mixing the corresponding solutions in a mass ratio of 1:50. After removal of the solvent, the obtained lipid film was hydrated in phosphates buffer solutions for 30 min under 50°C to form self-assembled micelles.

However, when the core-forming blocks are long and have increased hydrophobicity, the copolymers are able to incorporate increased amount of the hydrophobic drugs. With these materials the direct dilution (cosolvent method) with subsequent removal of the organic solvent by evaporation or extensive dialysis is the mostly used synthetic approach. The drug and copolymer are dissolved in organic solvent; then the solutions are placed in the dialysis bags that are then immersed in water to allow exchange of the solvent with water to give the drug-loaded micelles.

Such method was used to prepare micelles of PLGA-PEG-PLGA loaded with curcumin (CUR), which is characterized by an extremely low solubility in aqueous solution and poor bioavailability, by dissolving the copolymer and CUR in acetone and treating with ultrasonication for 5 min: the mixture was then dialyzed against distilled water at 4–8°C for 24 h using a dialysis membrane [57].

More recently, in 2016, Song et al. [58] prepared a novel polymeric block consisting of polyethylene glycol, poly-L-lysine, and poly-(lactic-co-glycolic acid) that was dissolved with edelfosine in DMSO and after stirring for 30 min underwent dialysis for 12 h to give spherical shape micelles.

Such methods can be extended to the preparation of various stimulus-responsive nanocontainers [43, 59–69] and in particular polymersomes (polymeric vesicles generally consisting of capsules with a bilayered membrane) [70–73]: such species have the advantages of being able of encapsulating also hydrophilic species in their aqueous interior and trapping hydrophobic moieties within the "membrane" [64].

Quite recently Sun et al. [74] prepared new photoresponsive and reduction-responsive polymersomes from amphiphilic PEO-b-PCSSMA where PCSSMA is a block polymer obtained by a coumarin-based disulfide-containing monomer (i.e., CSSMA), which self-assembled into polymersomes with hydrophilic PEO shielding coronas and hydrophobic bilayer membranes. The cosolvent method in which they used 1,4-dioxane to dissolve the amphiphilic monomers is successful in the formation of the polymersomes and encapsulation of DOX, a small-molecule therapeutics, and the hydrophilic Texas red-labeled dextran, a large-molecule therapeutics. Moreover, the presence of the coumarin-based disulfide blocks allows the sequential release of the payloads: actually the photoirradiation at 430 nm determined the cleavage of the coumarin moieties inducing the release of the encapsulated small-molecule payload while retaining the large ones. However, since the disulfide bond is sensitive to oxidants, incubation of the polymersomes with glutathione (GSH) caused the disassembly of the cross-linked vesicles and release of the large-molecule encapsulants.

4 Emulsion-based synthetic processes

Nanoparticles composed of polymeric or inorganic material can be generated via many different approaches. Practically, all the used processes, that is, the sol-gel process or the emulsion technique for the preparation of inorganic particles and mini-emulsion polymerization for the preparation of polymer particles, are based on kinetic control during preparation. The particles are built from the center to the surface, and the particle structure is governed by kinetic factors [75].

In particular, in this section, miniemulsion polymerization, microemulsion, and microemulsion-mediated synthesis of silica-based nanomaterials will be presented.

4.1 Miniemulsion polymerization

The miniemulsion polymerization is largely used for the synthesis of nanocontainers due to unique properties, such as ultralow interfacial tension, large interfacial area, thermodynamic stability, and the ability to solubilize otherwise immiscible liquids. It promises to be one of the versatile preparation methods that enable to control the particle properties such as mechanisms of particle size control, morphology, homogeneity, and surface area [76]. The miniemulsions are kinetically stabilized emulsions stable from days to months and with droplet sizes between 50 and 500 nm [77].

They are originated fundamentally by the right combination of four components: (i) hydrocarbons (aliphatic or aromatic), (ii) ionic surfactants, (iii) cosurfactants (generally 4–10 carbon chain aliphatic alcohol) and (iv) an aqueous phase.

The surfactant and cosurfactant, when properly selected, form a mixed film at the oil/water interface, resulting in an interfacial pressure exceeding the initial positive interfacial tension. Miniemulsions are isotropic, macroscopically homogeneous, and thermodynamically stable solutions containing at least three components, namely, a polar phase (usually water), a nonpolar phase (usually oil), and a surfactant. On a microscopic level the surfactant molecules form an interfacial film separating the polar and the nonpolar domains. This interfacial layer forms different nanostructures ranging from droplets of oil dispersed in a continuous water phase (O/W miniemulsion or direct miniemulsion) over a bicontinuous "sponge" phase to water droplets dispersed in a continuous oil phase (W/O miniemulsion or inverse miniemulsion). There are some factors that affect the stability of an emulsion and further affect the morphology and size distribution of produced particles. These factors include type and amount of surfactant and cosurfactant, the concentration of precursor solution, the kind of oil phase, and the water-to-oil ratio.

The surfactants establish the micellar system and stabilize the particles as well. The surface active agents or surfactant molecules are amphiphilic with a long hydrocarbon tail and a relatively small ionic or polar head group. Amphiphiles can be ionic (cationic or anionic), zwitterionic, or nonionic depending on the nature of their head groups. In several important applications, ionic surfactants are used in conjunction with a cosurfactant such as a medium-chain length alcohol. The cosurfactant is an uncharged entity, and its adsorption is not impeded by the electric field. It therefore provides the additional lowering of interfacial tension necessary for miniemulsion formation. Cosurfactants are usually alcohols or amines ranging from C4 to C10 and helps in the formation and stabilization of micelles/miniemulsions.

This includes cationic, anionic, nonionic, and amphiphilic surfactants. In concrete, cetyltrimethylammonium bromide (CTAB), sodium dodecyl sulfate (SDS), sodium 1,4-bis(2-ethylhexyl)-p-sulfosuccinate, or poly(ethylene glycol) ethers represent some of the most widely applied surfactants [78].

The use of the miniemulsion polymerization process offers the possibility to create stable capsules in a size range between 50 and 500 nm. The synthesis of nanocapsules can be accomplished by different methods using a variety of materials as "shells." One possibility to synthesize polymeric nanocapsules is based on the phase separation process. During the polymerization, the polymer and oil become insoluble, and the phase separation takes place within the miniemulsion droplets. Polymerization in miniemulsions is possible over a very broad range of monomers.

Actually, radical polymerization can be performed with many different monomers (e.g., styrene, acrylates, (meth)acrylates, fluoroacrylates, and acrylamides).

Copolymerizations between two hydrophobic monomers are also well suited to obtain homogeneous copolymer materials; the copolymerization of hydrophobic and hydrophilic monomers leads to amphiphilic polymer particles. The ABCs represent a class of functional polymers with a number of applications mainly ranging from the energetic and structural control of materials interfaces, to the sustained-release technologies, to gene delivery. ABCs are well established as building blocks for the preparation of micellar carriers. The development of new polymers will surely allow greater flexibility and potential to delivery systems based on ABCs. The use of ABCs is a feasible and attractive alternative to standard formulation techniques. In particular, entrapment in polymeric micelles may provide a viable approach for stabilizing substances during systemic circulation. The most common approaches to improve the effectiveness of ABC-based drug-delivery systems are the chemical modification of the block copolymer building blocks and the addition of auxiliary agents (e.g., metal nanoparticles).

The last decade has seen considerable progress in the development of synthetic strategies to prepare block copolymers of various architectures, solubility, and functionality. Architectures comprise diblock, triblock, and multiblock copolymers arranged linearly or as graft-, star-, or H-shaped blocks. Solubility varies from solvents with high cohesive energy densities such as water to media with very low cohesion energies such as silicon oil or fluorinated solvents.

Many of the classical synthetic routes to block copolymers like living anionic polymerization have long been known. In recent years, new methods such as living cationic and living radical polymerization have become available and have the advantage of yielding narrow molecular weight distributions with predetermined degrees of polymerization N. N is equal to the molar ratio of monomer (m) to initiator (i) concentration, $N = [m]/[i]$.

Reversible addition-fragmentation chain-transfer (RAFT) polymerization [79], atom-transfer radical polymerization (ATRP) [80], polyaddition [81], polycondensation [82], anionic polymerization [83], and even oxidative polymerization [84] can occur through both direct and inverse miniemulsions, depending on the used monomer and solvents. The possibilities of miniemulsion polymerization for the synthesis of an amazingly large list of polymers and copolymers have been extensively reviewed over the last two decades, and some examples are hereafter reported.

Anionic polymerization can be used to obtain polyamide in nonaqueous miniemulsions starting from ε-caprolactam, and in the aqueous phase, owing to the reactivity of cyanoacrylates, poly(butyl cyanoacrylate) nanoparticles can be synthesized [85]. It is recently used first to synthesize poly(methylethacrylate) (PMEA) in tetrahydrofuran, and through the sequential anionic polymerization techniques, successful diblock polymerization of polystyrene-block-PMEA (PS-PMEA) and poly(4-tert-butylstyrene)-block-PMEA (PtBS-PMEA) is achieved [86].

Polystyrene nanoparticles (150–175 nm) could be obtained via miniemulsion cationic polymerization of p-methoxystyrene using imidazolium-based ionic liquid as catalyst [87]. Polymeric nanocapsules (200 nm) are obtained by the cationic UV-activated polymerization of a vinyl monomer, namely, tri(ethylene glycol) divinyl ether, in water. The core-shell structure was obtained by confining the reaction at the interface between continuous and dispersed phase of an O/W miniemulsion [88].

The catalytic polymerization of monomer miniemulsions, where polymerization occurs in the miniemulsion droplets to afford polymer nanoparticles, has been reported for the following reactions: the copolymerization of terminal olefins in a miniemulsion to form polyolefins [89, 90], the copolymerization of terminal olefin miniemulsions to polyketones, and the step-growth acyclic diene metathesis (ADMET) polymerization of divinylbenzene in miniemulsions to give oligo (phenylene vinylene) particles [91].

Polyepoxide and polyurethane particles can be obtained via miniemulsions. In the case of the polyurethanes in an aqueous medium, the reaction with water has to be minimized, which can be achieved by the addition of a catalyst that allows polyurethanes to be formed with high molecular weight [92].

Condensation and polycondensation processes in the presence of water appear to be contradictory terms, as in bulk processes it is known that high temperatures have to be applied and water has to be removed. However, in the heterophase, a locally high hydrophobicity in the droplets allows water to be expelled from the reaction locus. In a miniemulsion, stable polyester nanoparticles with a high yield in the polymerization reaction could be synthesized [93].

Living radical polymerization is currently a very rapidly developing field in polymer chemistry. It has been successfully used to prepare block and graft copolymers of styrenes, (meth)acrylates, (meth)acrylonitrile, and dienes at temperatures ranging from 80°C to 130°C in the presence of catalytic amounts of transition-metal compounds (Cu, Fe, Ni, and Pd) [94].

In Table 2 a selected list of polymers and copolymers synthesized by miniemulsion polymerization is reported. The list does not exact to be exhaustive, but to give an idea of the versatility of the miniemulsion technique.

TABLE 2 Polymers and copolymers obtained by miniemulsion polymerization

Polyaddition	Polyurethane
	Polyepoxide
Polycondensation	Polyesters
	Polyurea
Anionic polymerization	Poly(methylethacrylate)
	Poly(ε-polycaprolactone)
Cationic polymerization	P-methoxystyrene
	(Triethylene glycol) divinyl ether
Catalytic polymerizations	Polyolefins
	Divinylbenzene
Living radical polymerizations	Styrenes
	(Meth)acrylates
	(Meth)acrylonitrile

The most commonly used hydrophilic block for polymeric micelle drug-delivery systems is poly(ethylene oxide)/poly (ethylene glycol), PEO/PEG. In the biomaterial literature, PEO is generally used in reference to polymers with a molecular weight >10,000 g/mol, whereas PEG is usually reserved for its lower molecular weight structural equivalent. One of the primary advantages of using PEO as a shell-forming material for polymeric micelles is low toxicity. In addition, PEO has long been recognized for its ability to minimize protein adsorption to surfaces. Attachment of PEO chains to hydrophobic surfaces is particularly effective against protein adsorption because of the hydrophilicity and unique solution properties of PEO, including minimal interfacial free energy with water, high aqueous solubility, high mobility, and large exclusion volume. Therefore PEO attachment is often used to improve the biocompatibility of foreign materials. In PEO-based polymeric micelle systems, the attached PEO brushes impart steric stability by physically blocking interparticle attraction between core regions and, possibly, hindering interactions between the core-forming blocks and blood components. In particular, high surface density and long PEO chain length minimize protein adsorption to hydrophobic surfaces [95].

As already mentioned, these ABC systems are also suited for generating polymer nanocapsules. The interfacial polymerization is one strategy to produce such structures, commonly in inverse systems. One of the most typical examples is the formation of polyurethane/polyurea by polyaddition or polycondensation of diisocyanates [96,97]. In addition to low-molecular diamines and diols, which are common reagents in such reactions, also biopolymers like cross-linked hydroxyethyl starch can be placed in the aqueous disperse phase as a water-soluble reagent [98].

Nanocapsules have the advantage of keeping their structural integrity compared to noncross-linked micelles that are subjected to unimer/micelle equilibrium. Miniemulsion droplets are typically used as templates for the preparation of nanocapsules either of organic or inorganic nature. Although the miniemulsion systems can be adapted to many different polymerization types, it is sometimes preferable to avoid reactions in the miniemulsion droplets because the product can be difficult to purify without damaging the structural integrity or reducing the stability of the colloids. Building the dispersed phase of a miniemulsion with a solution of polymer instead of a liquid monomer avoids possible degradation of the nanoparticles structure upon their purification when the solvent in the dispersed phase can be subsequently evaporated after the preparation of the nanodroplets. Thus it was possible to fabricate unconventional polymer dispersions with semiconducting [99], polyamide [100], syndiotactic or isotactic polystyrene [101], and polystyrene-block-poly(methyl methacrylate) nanoparticles [102].

A valuable redox-responsive nanoobject such as a nanocapsule should also allow the triggered diffusion of substances encapsulated in its core upon a redox stimulus. This represents one the most challenging tasks in colloid science when the triggered release must be coupled with the maintenance of the structural integrity and colloidal stability of the nanocontainers. One promising answer to overcome this issue is the preparation of patchy nanocapsules with responsive patches located in the nanocapsule shell. Indeed, patches in the capsule shells can act as channels for the diffusion of substances present in the core while keeping the structural integrity of the shell [103].

Whereas patchy nanocapsules from block copolymers were reported in the literature, they presented neither functionality nor responsive behavior. In particular, patchy nanocapsules were prepared from redox-responsive poly(vinyl ferrocene)-block-poly(methyl methacrylate) (PVFc-b-PMMA) block copolymers, and the release of guest-encapsulated substances from their cores upon selective oxidation of the nanopatches was monitored [104].

Nanocapsules composed of a PVFc-b-PMMA shell and a hydrophobic liquid core were prepared in water. The nanocapsule shells display a patchy structure with poly(vinyl ferrocene) patches with sizes of 25 nm surrounded by poly(methyl methacrylate), as shown in Fig. 4.

The functional nanopatches can be selectively oxidized, thereby influencing the colloidal morphology and introducing polar domains in the nanocapsule shell. The hydrophobic-to-hydrophilic transition in the redox-responsive nanopatches can be advantageously used to release a hydrophobic payload encapsulated in the core by an oxidation reaction.

Under properly chosen reaction conditions, a polymeric shell around a liquid core can be formed. Another possibility is the precipitation of the polymer onto stable nanodroplets in an inverse miniemulsion. In particular, in this way, poly(methyl methacrylate) nanocapsules with an antiseptic agent inside were produced. An efficient formation of nanocapsules could be achieved using different interfacial cross-linking or polymerization reactions. dsDNA molecules were successfully encapsulated into polybutylcyanoacrylate (PBCA) nanocapsules by anionic polymerization performed at the miniemulsion droplet's interface [105]. The formation of nanocapsules in the inverse water-in-oil miniemulsion system was successfully applied for the encapsulation of silver salts with their subsequent reduction to silver particles within the capsules and for the encapsulation of hydrophilic contrast agents, that is, for magnetic resonance imaging using polyurethane, polyurea, and cross-linked dextran shells. Furthermore, it was also shown that the nanocapsules can be functionalized and taken up by the cells efficiently.

The application of synthetic polymers for drug delivery often requires tremendous efforts to ensure biocompatibility and degradation. The use of biomaterials (i.e., protein and lignin) can help to overcome these problems. As an example,

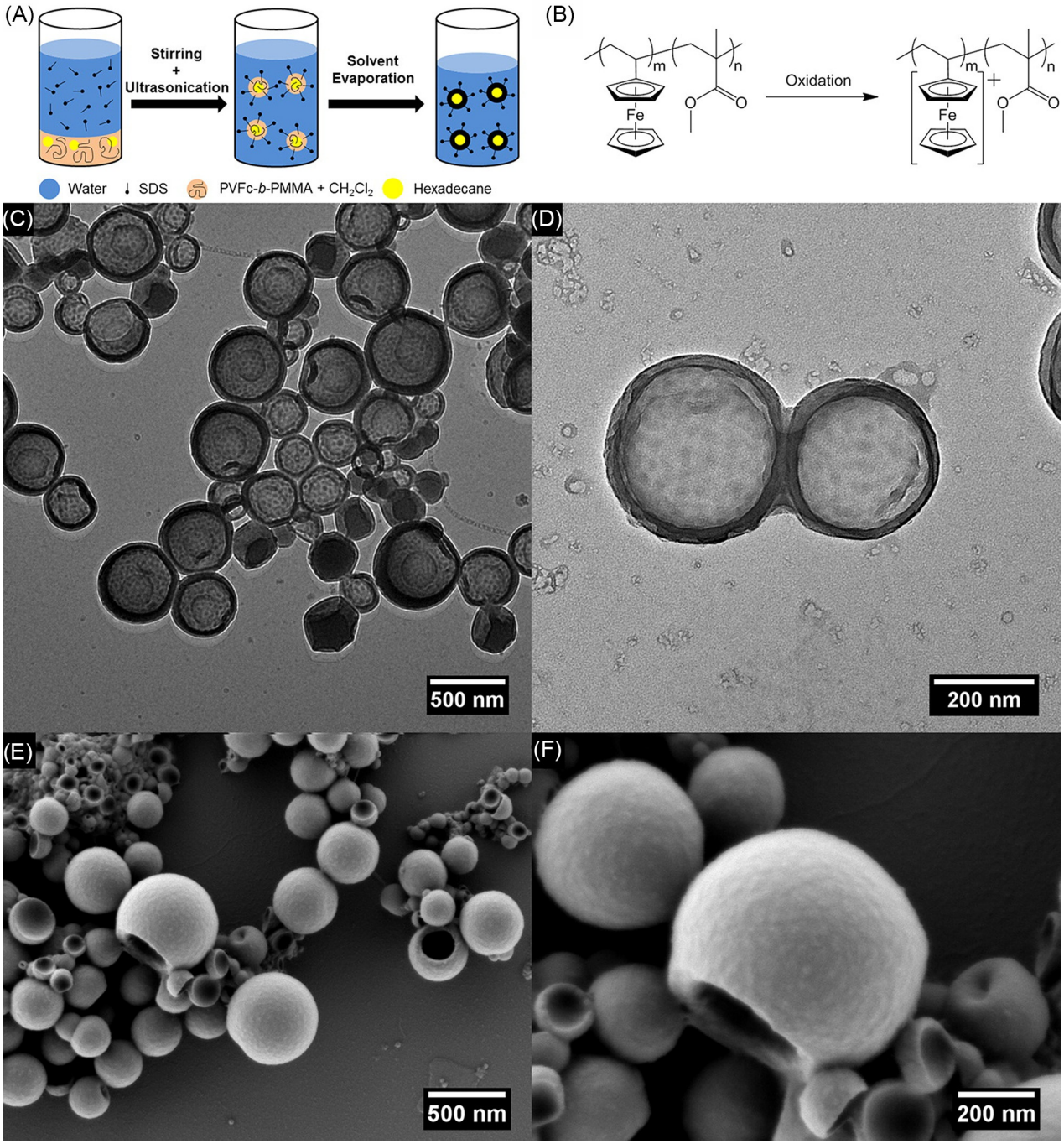


FIG. 4 Schematics for the preparation of the nanocapsules (A) with PVFc-b-PMMA, a polymer that can be subsequently oxidized (B). TEM micrographs (C, D) and SEM micrographs (E, F) of the dialyzed nanocapsules. In TEM, the microphase separation is evidenced by the presence of dark domains (PVFc block) in the PMMA surrounding matrix. *(Reprinted with permission from R.H. Staff, M. Gallei, M. Mazurowski, M. Rehahn, R. Berger, K. Landfester, D. Crespy, Patchy nanocapsules of poly(vinylferrocene)-based block copolymers for redox-responsive release, ACS Nano 6 (10) (2012) 9042–9049. Copyright (2012) American Chemical Society.)*

nanocontainers entirely composed of albumin proteins were first synthesized [106]. These protein nanocontainers (PNCs) were loaded with hydrophilic compounds, and release of the payload is triggered through natural lysis in vitro in human monocyte-derived dendritic cells (moDCs). No aggregation of PNCs in human blood plasma was observed, indicating stability for blood circulation. As the PNCs were readily taken up by moDCs, they are considered as a promising delivery platform for vaccination strategies and could minimize the risk of side effects caused by foreign carrier substances.

Kang et al. [107] reported the development of a biocompatible and degradable nanocarrier platform based on hydroxyethyl starch (HES). HES is a derivative of starch and possesses both high biocompatibility and improved stability against enzymatic degradation; it is used to prepare nanocapsules via the polyaddition reaction at the interface of water nanodroplets dispersed in an organic miniemulsion. The synthesized hollow nanocapsules can be loaded with hydrophilic guests in its aqueous core, tuned in size, chemically functionalized in various pathways, and show high shelf life stability. The surface of the HES nanocapsules is further functionalized with poly(ethylene glycol), which increases blood half-life time.

The abundant biomaterial lignin was used to prepare hollow nanocapsules by interfacial polyaddition in inverse miniemulsions. These cross-linked lignin nanocontainers can be loaded with hydrophilic substances that can be released by an enzymatic trigger from natural plant extracts revealing them as potential nanocontainers for agricultural applications. In an inverse miniemulsion the cross-linking polymerization of lignin was tailored to take place only at the interface of stable aqueous nanodroplets (acting as capsule templates) dispersed in an organic solvent. Enzyme-responsive, cleavable cross-linked lignin nanocontainers were thus generated by selective polyaddition at the oil-water interface.

Yamsawas et al. [108] chose the reaction of toluene diisocyanate (TDI) with the lignin hydroxyl groups to generate a cross-linked shell surrounding a liquid aqueous core. The reaction setup allows the efficient encapsulation of hydrophilic substances (drugs, fertilizers, and pesticides) that was proved by the hydrophilic model compound (SR101). The obtained lignin nanocontainers showed diameters in the range of 150–200 nm and were stable in organic or aqueous dispersion over a period of several weeks or months. Lignin nanocarriers were realized with different morphologies (solid nanoparticles, core-shell structures, and porous nanoparticles), using Kraft lignin modified through esterification of its hydroxyl groups with (meth)acrylic anhydride. Then, lignin nanocarriers were produced by a combination of miniemulsion polymerization and a solvent evaporation process. As phase separation occurred during the solvent evaporation, solid nanoparticles, core-shell structures with a liquid core (hexadecane and plant oils) and a solid lignin shell, or highly porous lignin nano- and microparticles have been prepared. All the systems were loaded with hydrophilic substances.

4.2 Microemulsion

The microemulsion-based approach recently came into focus as an alternative strategy to form nanoscale hollow spheres. Hollow spheres are highly promising shuttle systems for drug transport and drug release in medical application. Such hollow spheres are a specific class of nanomaterials exhibiting a core-shell structure comprising an inner cavity that can be loaded with all kinds of active agents. A wide variety of nanoscale hollow spheres can be obtained via a microemulsion approach. This includes oxides (e.g., ZnO, TiO_2, SnO_2, AlO(OH), and $La(OH)_3$), sulfides (e.g., Cu_2S and CuS), and elemental metals (e.g., Ag and Au) [109–111]. All hollow spheres are realized with outer diameters of 10–60 nm, an inner cavity size of 2–30 nm, and a wall thickness of 2–15 nm. The microemulsion approach allows the modification of the composition of the hollow spheres, fine-tuning their diameter, and encapsulation of various ingredients inside the resulting nanocontainers. Hollow spheres (diameter 50 nm up to ~2–3 μm) are typically prepared by the so-called hard-template approach [112]. As a two-step process, the hard-template approach requires coating of nanoparticles serving as hard templates in a first step. In the second step the hard template needs to be removed with the shell remaining as a hollow sphere. Although widely applied, hard-template processing has several disadvantages. Due to the size of the nanoparticle template, the resulting hollow spheres are as large as the template and typically exceed the nano range. Another restriction is related to the necessity to remove the template without destroying the hollow sphere wall.

In view of the applied materials, hollow spheres for drug delivery and drug release most often are composed of organic polymers and polyelectrolytes [113] with diameters $\geq$100 nm, which are prepared by different synthetic strategies from those of inorganic hollow spheres. Inorganic hollow nanospheres for drug transport and release are most often constituted of SiO_2, Fe_2O_3/Fe_3O_4, or Au as sphere materials [114].

The microemulsion approach aims to get rid of hard templates in particular and to allow for high flexibility in synthesis and materials selection. In general the approach has several beneficial aspects.

The microemulsion approach can be widely modified by adjusting the type and amount of polar/nonpolar phase and surfactants. This allows for fine-tuning the micelle diameter and as an immediate consequence controlling the diameter of the resulting hollow spheres. The possibility to establish W/O and O/W microemulsions increases the experimental flexibility of the approach. A wide variety of nanoscale hollow sphere compositions are accessible, ranging from elemental metals to metal oxides, metal sulfides, or organic-inorganic hybrids. While establishing the sphere wall of the hollow spheres, all compounds dissolved inside the micelle are encapsulated. Accordingly the use of microemulsions gives direct access to container-type functionalities.

For the synthesis of nanoscale hollow spheres, most often, inverse microemulsions that consist of CTAB as the surfactant and *n*-hexanol as the cosurfactant are used. The polar dispersant phase is water or 1:1 mixtures of water and

TABLE 3 Suitable starting materials for hollow sphere synthesis

Type of hollow sphere	Starting material for nonpolar oil phase	Starting material for polar water phase
Au	$C_{12}H_{25}SH$	$KAuCl_4$
Ag	$[Ag(PPh3)]_4NO_3$	$NaBH_4$
ZnO	$Zn(Cp^*)_2$	H_2O
TiO_2	$TiCl_4$	H_2O
SnO_2	$Sn(i\text{-}OC_3H_7)_4$	H_2O
AlO(OH)	Al(t-OC4H9)$_3$	H_2O
$La(OH)_3$	$La(Cp)_3$	0.1 M KF
Cu_2S	$[Cu(PPh_3)_2]Cl$	$(NH_2)_2CS$
CuS	$Cu(C_9H_{17}COO)_2$	$(NH_2)_2CS$

methanol; *n*-hexane, *n*-dodecane, or toluene constitutes the nonpolar oil phase. As a general procedure, a first reactant is dissolved in the water-containing micelle [112]. The formation of an equilibrated and stable W/O microemulsion is indicated by its optical transmittance. Then the second reactant is slowly added to the nonpolar dispersant phases, as reported in Table 3.

To separate the nanoparticles from the micellar system, most often destabilization upon addition of a polar, aprotic solvent (e.g., acetone) or diethylene glycol to the micellar system is applied [112].

The container-type functionality of nanoscale hollow spheres is first validated depending on the encapsulation of typical inorganic salts, biomolecules/bioactive molecules (e.g., phenylalanine, quercetin, and nicotinic acid), and fluorescent dyes (e.g., rhodamine and riboflavin) [115, 116].

Recently, gadolinium carbonate $Gd_2(CO_3)_3$ hollow nanospheres are prepared via a microemulsion-based synthesis using tris(tetramethylcyclopentadienyl)gadolinium(III), $Gd(Cp^t)_3$, and CO_2 as the starting materials [117]. CO_2 was just purged over the microemulsion system: due to the much higher solubility of CO_2 in alkaline water (as compared with the nonpolar dispersant phase), the reaction proceeded with slow hydrolysis of $Gd(Cp^t)_3$ at the liquid-to-liquid phase boundary of the microemulsion where the freshly formed Gd^{3+} directly reacts in the presence of CO_2 to produce $Gd_2(CO_3)_3$.

Nanoscale ZnO hollow spheres, prepared via a microemulsion approach with bis(pentamethylcyclopentadienyl)zinc(ii) as a starting material, are used to instantaneously encapsulate thiourea. The prepared hollow spheres exhibit an outer diameter of 7 nm, a wall thickness of about 2 nm, and an inner cavity of 3 nm [118].

The study of Carretti et al. [119] showed that the microemulsions can be used to solubilize hydrophobic polymers. The authors solubilized an acrylic and vinyl polymers, usually employed in works of art/architecture conservation, respectively, in O/W microemulsions where the oil phase was constituted of p-xylene or in a mixture with a nitro-diluent and in SDS micellar solutions containing propylene carbonate and 1-pentanol (1-PeOH). These systems enhanced the effectiveness of polymer removal from surfaces and, in particular, from porous frameworks typical of works of art. Three O/W microemulsions and different micellar solutions were selected (among over 100 potential systems) to test their efficiency in solubilizing acrylic and vinyl polymers: Tween 20/EG/p-xylene/water, SDS/1-PeOH/p-xylene/water, and SDS/1-PeOH/p-xylene/ND/ water and PC/SDS/water and PC/SDS/water/1-PeOH.

4.3 Microemulsion mediated synthesis of silica-based nanomaterials

By applying a pathway very similar to the one used to produce polymer nanocapsules by interfacial miniemulsion polymerization, inorganic capsules can be obtained by sol-gel processes taking place at the interface. Sol-gel template synthesis is the prevailing method for producing mesoporous silica nanoparticles (MSNPs) [120]. It consists in the hydrolysis and polycondensation of organosilanes in aqueous or water-alcohol media in the presence of surfactant micelles as organic templates. As a rule, micellar templates are inert, and after the synthesis is completed, they are removed by high-temperature treatment (calcination) or etching of particles in alcohol solutions of HCl or NH_4NO_3 at 40–60°C. As a result, pores are formed in the particle volume, with the diameter being determined by the template size. Wu et al. [121] reported the preparation of silica capsules from oil-in-water nanoemulsions containing the precursor tetraethyl orthosilicate (TEOS)

in octane as a disperse phase and an aqueous solution of surfactant as a continuous phase. TEOS is hydrolyzed at the liquid-liquid interface, which leads to the formation of hollow silica spheres that trap inside the hydrophobic core.

The ability to trap and release molecules from MSNPs holds promise in sensor, drug-delivery applications, self-healing anticorrosion materials, and antifouling systems. Silica particles can be used with different functions: (i) as surface that can be functionalized, (ii) as scaffold for the adsorption of active compounds (e.g., inhibitors, drugs, and biocide), and (iii) as containers for the encapsulation of active compounds.

The great diversity in surface functionalization of mesoporous silica offers a unique advantage in the construction of nanogates responsive to different stimuli. Various types of nanoparticles, organic molecules, and biomolecules have been used as capping agents to block molecule transport from a silica mesopore and to unlock the entrance for triggered release under specific external stimuli. A combination of mesoporous silica with functional polymers generates a novel type of hybrid nanoswitch that takes advantage of the unique features of polymers and porous materials. Liu et al. [122] proposed mesoporous silica coated with pH-responsive polymer poly(4-vinyl pyridine) obtained through the facile "grafting to" method. The grafted polymer nanoshell can work as a pH-sensitive barrier to control the release of trapped molecules from mesoporous silica.

Rim et al. [123] synthesized a natural pore blocker calcium phosphate (CaP) to cover MSNPs. This type of nanocarrier allows the facilitated release of entrapped drugs within acidifying intracellular compartments such as endosomes and lysosomes.

In the drug-delivery applications, it is fundamental that the nanoreservoirs are pH-responsive to release the guest molecules in function of the pH value of the media. Hu et al. [124] presented a straightforward synthesis of pH-responsive chitosan-capped MSNPs MCM-41 (Mobil Composition of Matter No. 41) type to accommodate guest molecules. Subsequently, (3-glycidyloxypropyl)trimethoxysilane was grafted onto the surface of the nanoparticles, which served as a bridge to link MSNPs to chitosan. Owing to the pH-responsive and biocompatible features of chitosan, the loading and release of an anticancer drug, DOX, were carried out in vitro, in which the composite chitosan-capped nanoparticles (CS-MSNPs) showed excellent environmental response.

In the literature, silica nanoparticles (SiNPs) were usually first prepared using NH_4OH as the catalyst, and then active compounds were absorbed into the pores. For some functional molecules, in situ encapsulation into SiNPs can be carried out by using ammonia (NH_4OH) catalyzed hydrolysis of silane precursors in an inverse microemulsion. Encapsulation of DOX in SiNPs using this strategy is a challenge because of its instability in NH_4OH.

The synthesis of the SiNPs and the loading of doxorubicin were carried out by He et al. [125] in a one-pot synthesis by using sodium fluoride-catalyzed hydrolysis of silane precursor (TEOS) via an inverse microemulsion. Through further surface chemical modification using silicon coating procedures, carboxyl-terminated DOX/SiNPs (COOH-DOX/SiNPs) COOHDOX/SiNPs, exhibiting high drug entrapment efficiency, strong fluorescence, and long sustained release, were developed.

The template synthesis of mesostructured pH-sensitive SiO_2 nanocontainers was studied by Dement'eva et al. [126]. In this approach the targeted functional substance and CTAB are loaded during the synthesis procedure. The structure, capacity, and regularities of the desorption (release) of a templating functional substance from the mesostructured nanocontainers (MSNCs) change at different pH values of an aqueous medium under static and quasidynamic conditions. The reported data suggest that the use of micelles of a functional substance as a template makes possible to combine the stages of the synthesis of nanocontainers and their loading with this substance.

Dement'eva et al. [127] realized a novel type of MSNP-based container particle in which template micelles are formed by molecules (in particular, biologically active molecules) that could both act as the structure-forming agents and subsequently perform different desired functions. In this case the subsequent dissolution of a formed SiO_2 matrix caused a gradual release of the functional compound molecules. Such containers are of significant interest for solving practical problems like the development of agents for anticorrosion protection and targeted delivery of prolonged action drugs.

The addition of stimulus-responsive nanocontainers encapsulating corrosion inhibitors to passive coating is a good way to protect the substrates. The study of stimulus-responsive nanocontainers finds application not only in the biomedical fields but also in the development of new self-healing anticorrosion systems for metal substrates. Such smart nanocontainers can control the release of encapsulated corrosion inhibitors under the stimulation of environmental changes, such as pH, temperature, light, redox, and aggressive ionic strength.

Chen et al. [128] reported a novel and facile light-triggered release system for an anticorrosion coating based on implanting azobenzene moieties into the nanopores of hollow mesoporous silica nanocontainers (HMSNCs). The nanocontainers not only possess a high loading capacity but also can control the entrance and release of trapped active molecules based on the dynamic motion of azobenzene molecules. The azobenzene-HMSNCs were prepared according to a combined strategy of bifunctional modification and selective etching process. Azobenzene-modified hollow mesoporous

nanocontainers with reversible and light-responsive release properties have successfully incorporated onto aluminum substrates. The composite coating can automatically repair the corrosion area upon UV irradiation when scratched, due to the light- and pH-stimulated release of corrosion inhibitors during the corrosion process.

Wang et al. [129] proposed a new efficient hybrid container for anticorrosion coating based on PANI-modified mesoporous silica sphere, prepared via in situ polymerization and surface-protected etching. The PANI-modified containers do not only show higher concentration of loaded inhibitor than silica sphere but also show greater anticorrosion efficiency thanks to the presence of PANI. The functionalized silica spheres are loaded with biocide placing into a saturated solution of 1H-benzotriazole (BTA) in acetone under vacuum. The coating with BTA loaded containers shows significant anticorrosion property because of the release of BTA from containers.

The corrosion inhibitor can be loaded at the stage of the sol-gel synthesis of silica containers, using as micellar template the inhibitor molecules as reported by Dement'eva et al. [130] who proposed the use of catamine AB as micellar template.

Zhao et al. [131] presented the synthesis of corrosion inhibitor (BTA)-loaded hollow silica nanocapsules with magnesium hydroxide precipitated in the shells (HSNs-M/BTA) through inverse microemulsion (W/O) polymerization. There are three main steps in this process: (i) formation of W/O emulsion, (ii) TEOS hydrolysis, and (iii) condensation of hydrolysis products at oil-water interface.

Specifically, oil-soluble molecules of TEOS were diffused onto the oil-water interface and hydrolyzed under the effects of a basic catalyst (dodecylamine). Hydrolyzed silicon hydroxyl of TEOS can be adsorbed, and condensation polymerization mainly occurred at the oil-water interface due to electrostatic interactions between silicon hydroxyl and cationic emulsifier (CTAB). At the same time, magnesium hydroxide precipitation occurred at the oil-water interface resulting from the precipitation reaction between magnesium ions in aqueous solution and hydroxide ions (see Fig. 5).

Then the novel hollow silica nanocapsules were embedded into hybrid silica-zirconia coatings to obtain an effective anticorrosive layer for aluminum protection.

In the antifouling applications a good approach is the encapsulation/entrapment of biocides in nanocapsules to control the release of bioactive species in time and to reduce the amount of biocide. Beyond commercial products such as 2-mercaptobenzothiazole, environmentally friendly antifoulants with natural origin as zosteric sodium salt were encapsulated [132]. Silica nanocapsules were obtained at basic conditions from the hydrolysis and polycondensation of the silica precursor TEOS at the interface of pore-templating surfactant micelles containing diethyl ether, acting as cosolvent of the oil/

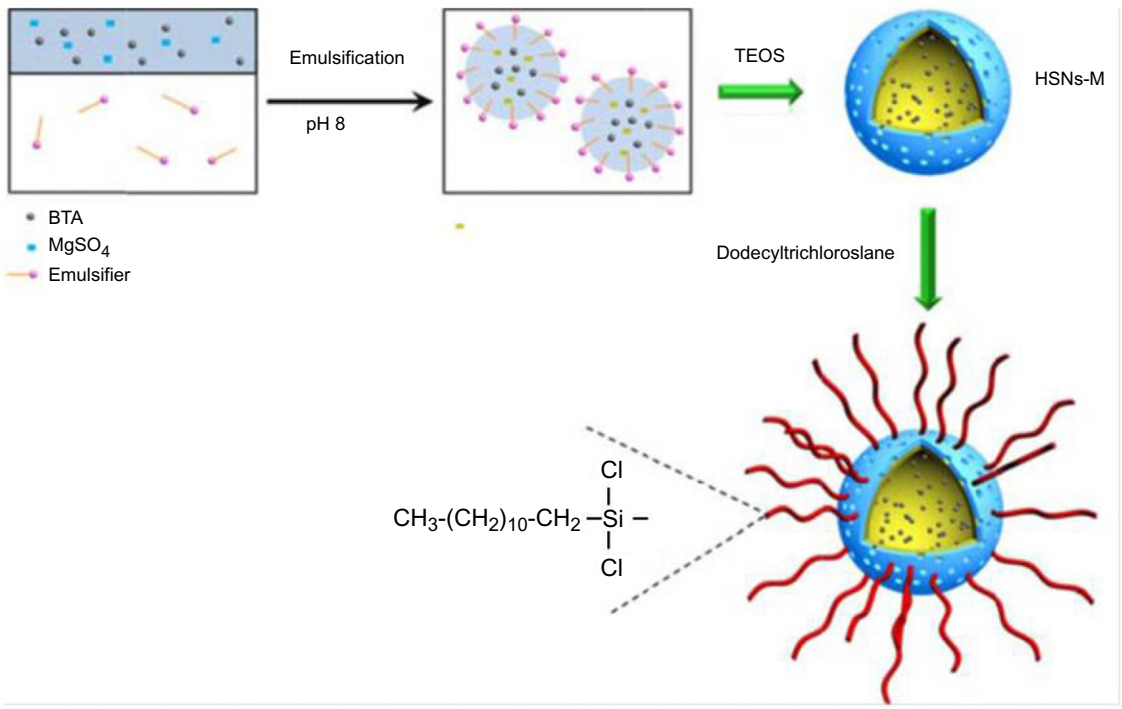


FIG. 5 Schematic illustrations for the preparation and hydrophobic modification of HSNs-M/BTA. *(Reprinted with permission from D. Zhao, D. Liu, Z. Hu, A smart anticorrosion coating based on hollow silica nanocapsules with inorganic salt in shells, J. Coat. Technol. Res. 14 (1) (2017) 85–94. Copyright 2016 Springer Nature.)*

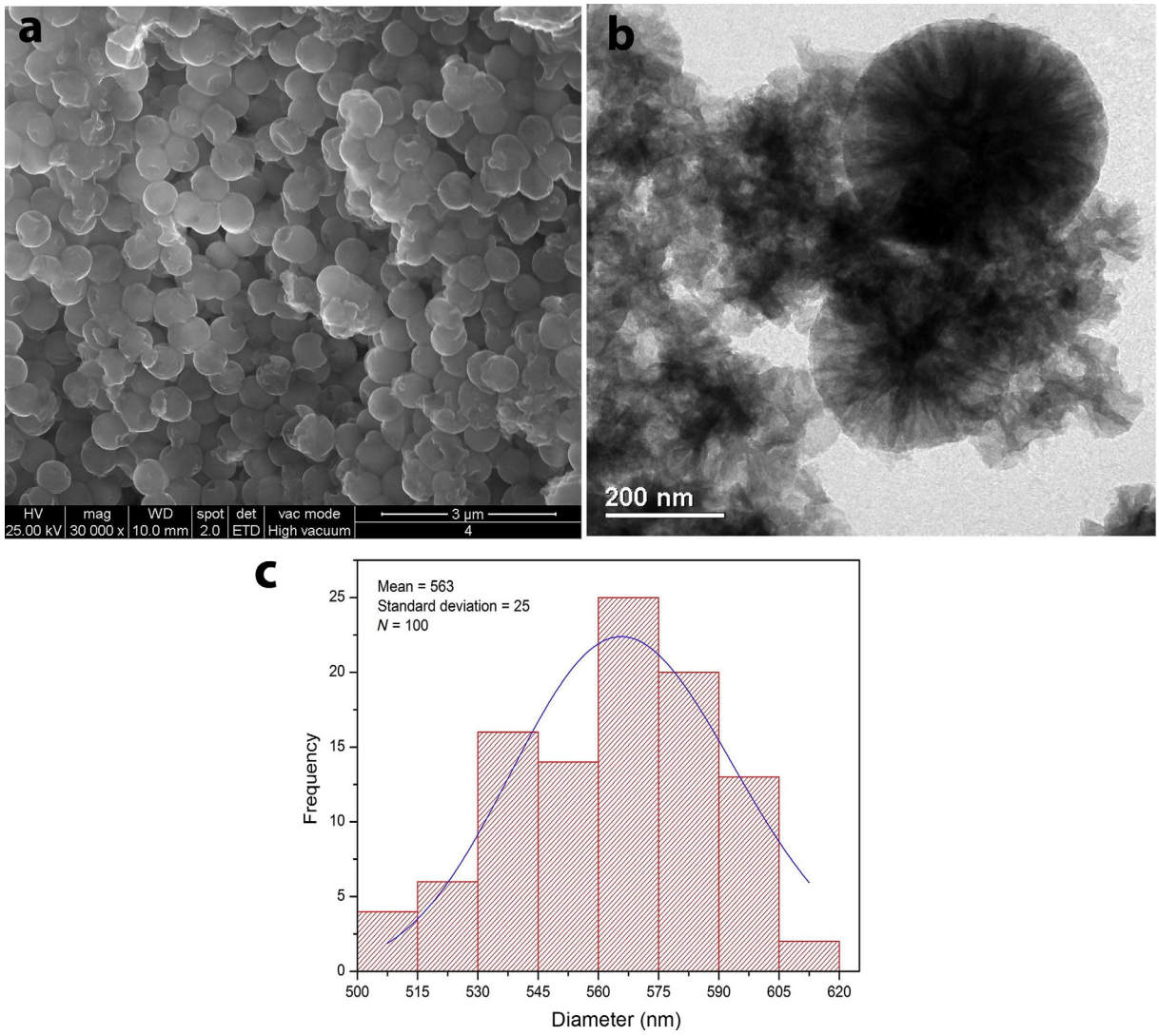


FIG. 6 (A) SEM and (B) TEM micrographs of the silica nanocapsules loaded with the zosteric sodium salt and (C) histograms with size distribution determined with ImageJ [132]. *(Reprinted with permission from L. Ruggiero, L. Crociani, E. Zendri, N. El Habra, P. Guerriero, Incorporation of the zosteric sodium salt in silica nanocapsules: synthesis and characterization of new fillers for antifouling coatings, Appl. Surf. Sci. 439 (2018) 705–711. Copyright 2018 Elsevier.)*

water miniemulsions [133]; the active compound zosteric sodium salt has been loaded, during the synthesis, after dissolution in MeOH. The effective encapsulation was realized to sufficiently control the release over time creating innovative filler for antifouling coatings (see Fig. 6).

5 The precipitation-based synthetic methods

Precipitation-based synthetic methodologies, that is, coprecipitation, nanoprecipitation comprehending flash and microfluidic nanoprecipitation too, and polymer precipitation, are largely used to produce both inorganic materials and biodegradable systems for drug delivery.

The coprecipitation method [134–137] is particularly used in the preparation of a class of inorganic host materials known as LDHs [138–148], also called hydrotalcite-like compounds, that could be described by the general formula $[M^{2+}_{1-x}M^{3+}_{x}(OH)_2]^{x+}[A^{n-}_{x/n}]\cdot mH_2O$, where M^{2+} and M^{3+} represent divalent and trivalent metal ions, respectively, and A^{n-} is the guest anion (Fig. 7, [143]): LDHs comprise positively charged layers and intercalated anions to keep the materials electroneutrality.

Such materials find application in the field of protective coatings since they could play double roles in releasing inorganic and organic inhibitors and entrapping corrosive agents (Cl^- and SO_4^{2-}).

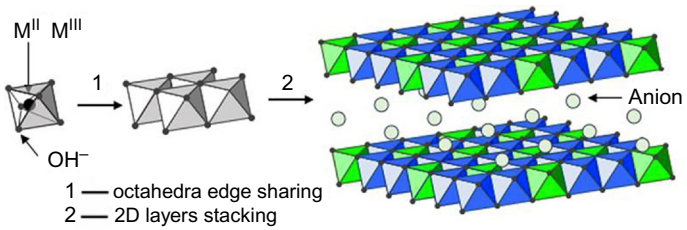


FIG. 7 Schematic representation of the layered double hydroxide structure. *(Reprinted with permission from V.R. Cunha, R.B. de Souza, A.M.C. da Fonseca Martins, I.H.J. Koh, V.R. Constantino Accessing the biocompatibility of layered double hydroxide by intramuscular implantation: histological and microcirculation evaluation, Sci. Rep. 6 (2016) 30547. Licensed under a Creative Commons Attribution (CC BY 4.0) license. Attribution 4.0 International (CC BY 4.0).)*

The synthesis is based on mixing salt solutions at controlled pH: Stimpfling et al. [141] have introduced several different organic inhibitors (aniline and benzene derivatives) in Zn_2Al LDHs and more recently [142] also the amino acids cysteine (L-Cys), phenylaniline (L-Phe) and arginine (L-Arg) in Mg_2Al, MgZnAl, and Zn_2Al LDHs starting from aluminum and magnesium nitrate salts, magnesium/zinc nitrate salts, and Al nitrate to produce Mg_2Al-Cys LDH, MgZnAl-Cys LDH, and Zn_2Al-Phe hybrid LDH, respectively. The corresponding amino acids were introduced as the anionic form in a fourfold molar excess: reaction was carried under a nitrogen flow to avoid carbonation.

Analogously, Alibakhshi et al. [148] prepared Zn-Al-NO_3^- LDH from $Zn(NO_3)_2$, $Al(NO_3)_3$, and $NaNO_3$ at pH at 9.8 ± 0.3 via simultaneous addition of NaOH solution (0.2 M): this is also the starting material to get the phosphate derivative Zn-Al-PO_4^{3-} LDH from an ion exchange method by adding the nitrate system to a $Na_3PO_412H_2O$ solution.

Whereas it is usually not possible to obtain in a straightforward synthesis the desired LDH product, the ion exchange method in which a specific ion was substituted into the starting material offers a valid approach to obtain LDHs starting from the coprecipitation method [138, 149–156].

This last method allows also the encapsulation of bioactive compounds in LDHs [155]; actually, it is well known that LDHs represent promising inorganic nanocarriers that have several attractive features for their uses in the delivery of negatively charged drugs [158, 159].

Beyond LDHs, other drug nanocarrier systems can be achieved by means of other precipitation-based methods like nanoprecipitation, flash and microfluidic nanoprecipitation.

Nanoprecipitation, also named solvent displacement or interfacial deposition, was developed by Fessi et al. [160] and allows the encapsulation of drugs (mainly hydrophobic) in either nanocapsules or nanospheres starting from preformed polymers.

Its advantages are the simplicity, the ease of scalability, the good reproducibility, the low amounts of toxic solvents, the narrow particles size distribution, and the low energy input [161]. Nanoprecipitation is a one-step process where the polymer and the drug are dissolved in a proper solvent that must be miscible to a second solvent that is however a nonsolvent for the polymer and drug. Therefore, when the polymer solution is added to such nonsolvent, nanoprecipitation occurs by a rapid desolvation of the polymer. Indeed, as soon as the polymer-containing solvent has diffused into the dispersing medium, the polymer precipitates, involving immediate drug entrapment [162].

In the manufacturing of drug delivery, FDA-approved polymers were chosen because of good hydrolizability, biocompatibility, and drug release properties: the aliphatic polyesters such as poly(caprolactone) (PCL), polylactic acid, and poly (lactic-co-glycolic acid) have been extensively and routinely used [163–172], as well as copolymer derivatives [173–180].

Among the several examples, it is interesting to report the preparation of insulin-loaded PLGA-PEG (Ins-NPs) nanoparticles by Chopra et al [177]. In this study the authors evaluated the role of key process steps and the conditions, such as pH and washing procedures, in the synthesis of the Ins-NPs formed by nanoprecipitation. This simple method enhanced the insulin loading of PLGA-PEG NPs maintaining sub-100 nm NP size and extended the applicability to other protein drug-delivery systems that are subject to limited loading. They prepared Ins-NPs by dissolving PLGA-PEG first and insulin in DMSO, an organic solvent that is miscible in the aqueous phase, and then adding the solution dropwise to a stirred aqueous solution (water or buffer solution) to form NPs. Here, DMSO is the solvent, and water is the antisolvent. Once in contact with water, PLGA-PEG and insulin self-assemble to form spherical NPs fairly monodisperse with diameters less than 100 nm. The use of buffer rather than pure water influences the insulin loading. Moreover, insulin loading can be affected by incorporating chelating ions like Zn(II) ions that were added to insulin solution at the very beginning.

The nanoprecipitation method is considered the straightforward technique accounting for more than 50% of the NPs reported for drug-delivery systems allowing hydrophilic and hydrophobic compounds to be entrapped [181]: it can be achieved in bulk synthesis and also using flow focusing in microfluidic channels [182]. Nanoprecipitation by microfluidic

mixing has been used to synthesize a variety of nanoparticles, such as drug nanosuspensions, polymer nanoparticles and micelles, liposomes, and lipid nanoparticles [183]. The development of microfluidics-assisted nanoprecipitation is tended to the enhancement of the controllability and reproducibility in physicochemical properties of nanoparticles compared with bulk synthesis methods [184]. In fact, flow processes are considerably more reproducible, as the geometry of mixing is fixed and the flow regime is more controlled [185]. The use of microfluidic devices has enabled screening of a variety of reaction conditions by systematically varying flow rates, temperature, and reactant concentrations to optimize the quality of the resulting products using very small amounts of reagents [186]. In fact the control of fluid dynamics is critical to achieve homogeneous (e.g., narrow size distribution) products in a reproducible fashion: the flow regime (turbulent/transition/laminar) or the lateral mixing between polymer solution and nonsolvent strongly affects the kinetics of phase separation, of particle nucleation and growth, and potentially aggregation [185].

Recent comparison of the manufacturing of poly(lactic-co-glycolic acid) copolymer nanoparticles encapsulating the hydrophilic N-acetylcysteine (N-Ac), via microfluidics-assisted and conventional nanoprecipitation technique, has been made by Chiesa et al. [181]. They used a novel microfluidics-based device, a staggered herringbone micromixer (SHM), (Fig. 8) characterized by a Y-shaped architecture incorporating staggered herringbone ridges, and operated design of experiment-assisted evaluation of critical process such as total flow rate and flow rate ratio and formulation (polymer concentration and structure and drug-polymer ratio).

They produced N-Ac-loaded PLGA NPs that yielded NPs of tunable sizes in a wide range of mean sizes (about 100–900 nm), uniform in size (polydispersity index around 0.2) without particular workup after precipitation with respect to the conventional nanoprecipitation method and in a shorter time than with the conventional nanoprecipitation method.

A further development of the nanoprecipitation technique was done by Johnson and Prud'homme [188] who adopted a confined impinging jets (CIG) mixer to induce a rapid mixing between a stream containing a molecularly dissolved solute and stabilizing molecule and an opposing stream containing a miscible solvent, which acts as a nonsolvent for the solute and stabilizer; fundamental is that such mixing time is shorter than the formation time for a nanoparticle. Fig. 9 reports different developed CIG mixer geometries [189].

This new process is called flash nanoprecipitation (FNP): rapid mixing, on the order of milliseconds, occurring in the turbulent regime in a confined volume is required to affect homogenous conditions for the creation of uniform local high supersaturation. This leads to precipitation of any solute or molecule existing above its saturation level, regardless of its chemical nature [189].

Flash nanoprecipitation has emerged in the last decade as a simple, powerful, and scalable process for forming multicomponent NPs, specifically core-shell NPs with a hydrophobic core and polymer-stabilizing corona for therapeutic and imaging applications [190–194]. This copolymer-directed assembly process can produce nanometer-sized particles with an active species partitioned into the core in a substantially amorphous state [195].

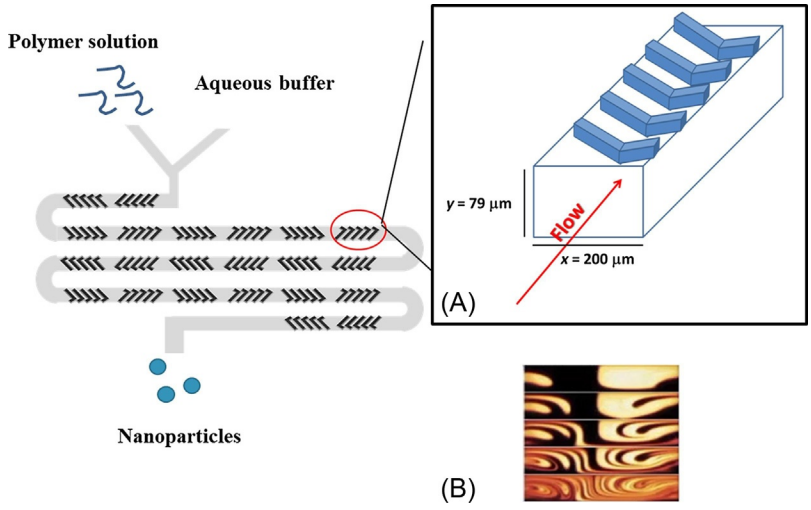


FIG. 8 Schematic representation of the staggered herringbone micromixer (SHM) with sequential regions of asymmetric ridges. Focus on (A) microchannel (200 × 79 µm) with herringbone structure (ridges, 31 × 50 µm); (B) confocal micrographs show organic and aqueous streams evolution through the cross section of the SHM microchannel (Mixer design by Stroock et al [187]). *(Reprinted with permission from E. Chiesa, R. Dorati, T. Modena, B. Conti, I. Genta, Multivariate analysis for the optimization of microfluidics-assisted nanoprecipitation method intended for the loading of small hydrophilic drugs into PLGA nanoparticles, Int. J. Pharm. 536 (1) (2018) 165–177. Copyright 2018 Elsevier.)*

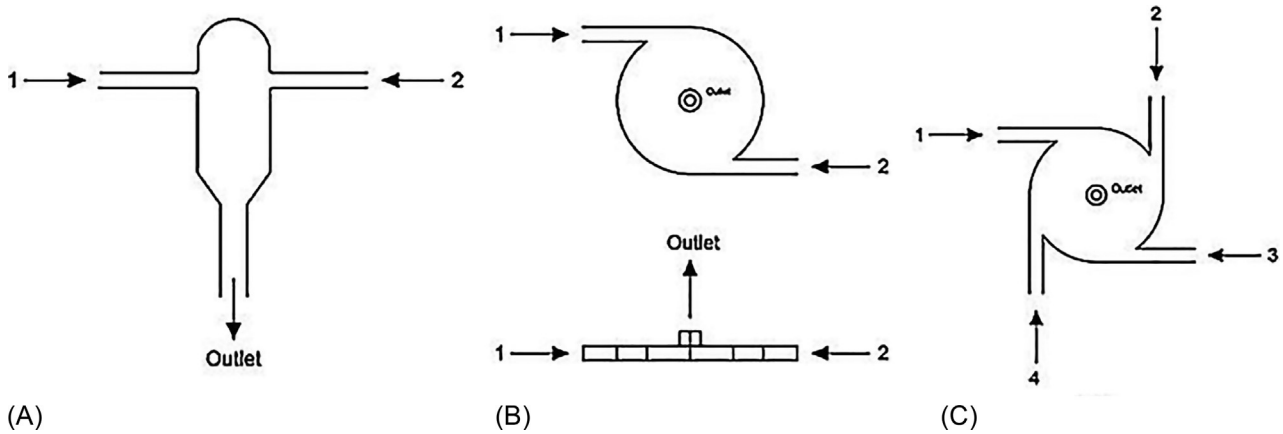


FIG. 9 Various mixer geometries: (A) CIJ mixer, (B) two-inlet multiple inlet vortex mixer (MIVM) top and side views, and (C) four-inlet MIVM. *(Reprinted with permission from W.S. Saad, R.K. Prud' homme, Principles of nanoparticle formation by flash nanoprecipitation, Nano Today 11 (2) (2016) 212–227. Copyright 2016 Elsevier.)*

The encapsulating agent used in FNP is typically an amphiphilic block copolymer, such as poly(ethylene glycol)-b-poly (lactic-co-glycolic acid) (PEG-b-PLGA), [polystyrene-block-poly-(ethylene glycol) (PS-b-PEG), polycaprolactone-block-poly-(ethylene glycol) (PCL-b-PEG), polylactide-block-poly-(ethylene glycol) (PLA-b-PEG), GRAS zein, and poly(ethylene glycol)-block-poly(propylene sulfide) (PEG-bl-PPS) [195–207].

In a very recent work by Bobbal et al. [207], hydrophobic and hydrophilic molecules were effectively loaded into polymeric bicontinuous nanospheres (BCNs) via FNP: such a lyotropic soft nanoarchitecture of PEG-bl-PPS is obtained by impinging THF solution of the oxidation responsive diblock copolymer against water or phosphate buffer solution in a CIJ mixer. The hydrophilic molecules calcein, Texas Reddextran (10 kDa), tetramethylrhodamine dextran (70 kDa), and Texas Red-ovalbumin were added separately to water before impingement, while the hydrophobic molecules ethyl eosin and lipophilic dye DiD were added to THF before impingement. Loading efficiencies of larger hydrophilic macromolecules ovalbumin and 70-kDa dextran (33%, each) were higher than that for smaller hydrophilic molecules calcein and 10-kDa dextran (5.3% and 9.46%, respectively). Hydrophobic molecules ethyl eosin and DiD demonstrated loading efficiencies $>70\%$. These results evidence the ability of FNP to efficiently load diverse payloads into BCNs.

Last nanocontainer synthesis method based on precipitation is the precipitation polymerization; precipitation polymerization is known to be used for the fabrication of complex core-shell hybrid particles and hollow structures [208], and it is characterized by easy preparation, good yield and the absence of additives (such as stabilizer and surfactant) [209]. To perform precipitation polymerization, the choice of solvent is fundamental since the monomers that must be initially soluble produce then oligomers that precipitate in the reaction medium [210]. This method has been used to prepare stimulus-responsive polymers and molecularly imprinted polymers (MIPs).

In the case of stimulus-responsive polymers, we have examples of nanocontainers prepared first by polymerization precipitation using Fe_3O_4 or $Fe_3O_4@SiO_2$ template nanoparticles followed by drug loading [211–214]. MIPs nanocontainers are obtained also in one-pot reaction by mixing the drug and the monomers at once [209, 214]. In particular, Kempe et al. [209] prepared erythromycin (ERY)-imprinted poly(methacrylic acid-co-trimethylolpropane trimethacrylate)s by free-radical precipitation polymerization, mixing (meth)acrylic acid (MAA), trimethylolpropane trimethacrylate, and (−)-erythromycin hydrate in different ratios in acetonitrile and heating at 60°C for 8 h, followed by extraction with suitable solvents.

Kempe et al. used ERY as a template during the polymerization to create recognition sites for the drug in the polymer network of the resulting nanocarriers. MAA, which is one of the most commonly used functional monomers for the preparation of MIPs and has been applied to the imprinting of a broad range of templates, is assumed to presumably interact with ERY via hydrogen bonds. The presence of ERY during the polymerization has an influence on both the morphology of the particles formed and their binding capacity of ERY.

6 Ultrasonic techniques

Ultrasonication based on acoustic waves with frequencies and power in the range of 16–100 kHz and 10–1000 Wcm^{-2}, respectively, is a promising tool for the synthesis of nanosized materials with narrow particle size distribution thanks to controlled nucleation and growth rate of the nanoparticles: it may offer an appropriate alternative for laboratory-scale productions due to its rapid nature and the relatively low cost of required apparatus [215].

The use of ultrasound in a liquid medium determines special physical and chemical effects associated to cavitation: this phenomenon consists in the formation of bubbles because of the pressure variations in the liquid induced by the acoustic waves, their growth, and implosive collapse. High temperature and pressure pulse and intense turbulence associated with liquid circulation currents are generated providing possibly new routes for chemical reactions that are difficult or impossible to achieve under conventional conditions or enhance reaction rate.

Therefore the ultrasonic technique has been successfully applied to prepare various types of nanocontainers such as inorganic oxides [12, 216, 217] and nanostructural delivery carriers for drug [218–224].

In particular, because of the advantage of obtaining smaller droplet size, high energy efficiency, whereas an emulsion with desired diameter is needed and a lower amount of surfactant is required, nanocontainer/nanocarrier preparation has been carried out through ultrasound-assisted emulsification processes [224–227].

For example, such methods are used to synthesize nanostructured lipid nanocarriers [228–229], and different nanoemulsion formulations [230, 231] can be achieved.

A recent and very interesting study by Dehvari et al. [232] reports the transformation of oleylamine-coated Fe_3O_4 nanoparticles, prepared through a thermal decomposition route into an aqueous phase using hyaluronic acid (HA) via an ultrasonic-assisted emulsion approach as an intermediate step for the preparation of fluorescence-guided magnetic nanocarriers.

The emulsion obtained by adding HA solution containing 2-morpholinoethanesulfonic acid (MES) buffer to the NP suspension formed by dispersing Fe_3O_4 powder and oleic acid (OA) in chloroform under sonication was implemented by using an ultrasonic probe into the suspension until a cloudy phase appeared.

In their process, ultrasound waves were employed as external energy for the collapse of the cavitation bubbles that disrupt the boundary between the immiscible phases of water and chloroform. The process led to the association of OA with the primary combination of OA and oleylamine (OAm) surfactant layer on the particle surface to form a quasibilayer structure. Taking advantage of the intercalation of OA and OAm long chains in combination with hydrogen bonding between the head groups, microemulsion droplets were formed within the aqueous phase whereby the other end of the OA molecules, that is the carboxylic group, promotes NP solubility in water and HA attachment. Such a micelle-like structure provides an interface between the core and the surrounding environment acting as an extra barrier between the NP core and the oxidizing environment and protecting and stabilizing the magnetic core owing to OAm and OA hydrophobic coating on the surface of Fe_3O_4 NPs. Facile HA attachment enhances Fe_3O_4 stability in the aqueous solution and allows coupling to Chlorin e6 through *e*thyl(dimethylaminopropyl)carbodiimide/N-hydroxysuccinimide coupling chemistry, enabling the construction of a targeted-imaging probe.

7 Convergent and divergent approach

Dendrimers, which are an important class of hyperbranched molecules, are considered ideal carriers in biomedical applications such as imaging, drug delivery, and gene and cancer therapy because they are characterized by a high level of control over their architecture, size, shape, branching length, density, and surface functionality [233].

The two major synthetic strategies used for the synthesis of dendrimers are the divergent approach and convergent approach whose choice depends mainly on the kind of monomer employed and the target polymer structure, possessing both synthetic strategies relative advantages and disadvantages.

In the divergent approach, developed by Tomalia et al. [234, 235] and Newkome et al. [236], the monomer unit constituting the core undergoes a multiple coupling (branching) with the complementary reactive group (unprotected) of other monomers. This is the coupling step that adds one layer (or generation) to the structure.

To get a controlled growth, the other reactive groups on the monomers are protected, but they can be chemically activated by conversion to a reactive chemical group, for coupling to a second set of molecules to produce the next-generation dendrimer. This step is the activation step.

The overall process can be repeated with an appropriate choice of coupling and activation steps to produce a dendrimer with a well-defined generation.

As an example, we report the synthesis of tetrafunctional poly(amidoamine) (PAMAM) dendrimers (Fig. 10) [237].

This divergent approach has the advantage that it can lead to a large-scale preparation of dendrimers, as the quantity of the dendrimer sample essentially doubles with each added generation.

However, structural defects are likely to be since incomplete functionalization or additional side reactions, which grow exponentially with each generation, can occur.

Many families of dendrimers can be produced using this technique such as polyamines poly(amido amine), poly(propylene imine), and poly(ethylene imine), poly-L-lysine, melamine, poly(etherhydroxylamine), poly(esteramine), and polyglycerol [238].

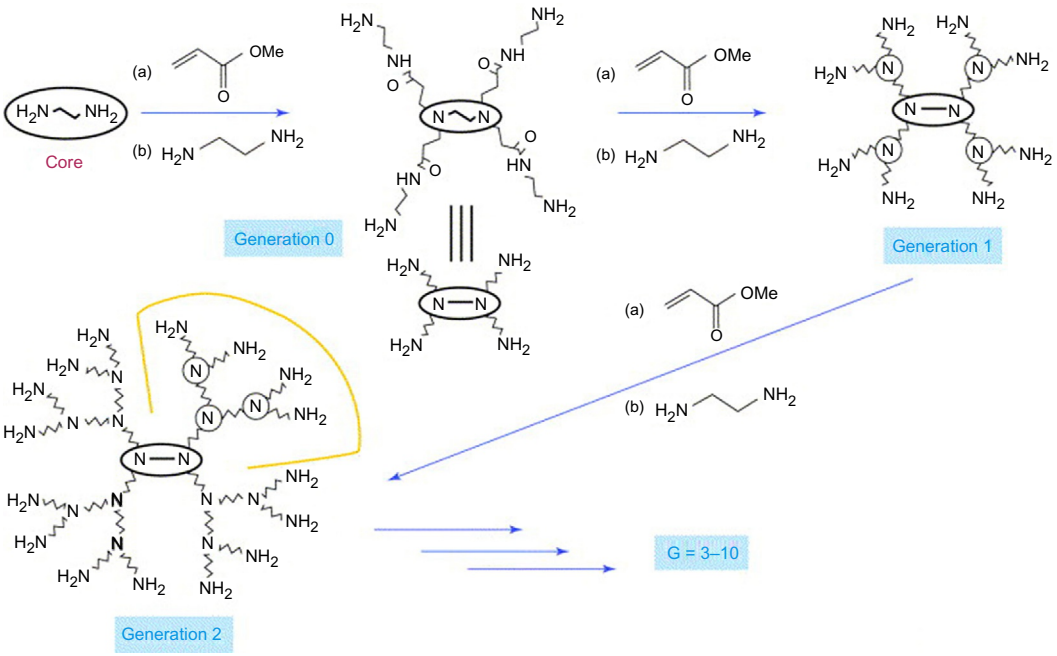


FIG. 10 Synthesis of tetrafunctional poly(amidoamine) (PAMAM) dendrimers. Step a: exhaustive Michael addition of amino groups with methyl acrylate. Step b: amidation of the resulting esters with ethylenediamine. *(Reprinted with permission from R. Esfand, D.A. Tomalia, Poly(amidoamine) (PAMAM) dendrimers: from biomimicry to drug delivery and biomedical applications, Drug Discov. Today 6 (8) (2001) 427–436. Copyright 2001 Elsevier.)*

Differently from the divergent approach in which the synthesis starts from the core of the dendrimer and the arms are attached by adding building blocks in an exhaustive and step-wise manner, in the convergent approach, introduced by Fréchet and coworkers [239], the synthesis starts from the exterior, beginning with the molecular structure that ultimately becomes the outermost arm of the final dendrimer. In this strategy, the final generation number is predetermined, necessitating the synthesis of branches of a variety of requisite sizes beforehand for each generation.

The convergent method involves two stages: first, wedge-shaped dendritic fragments called "dendrons" are produced through a reiterative coupling of protected/deprotected branch, and second, dendrons are anchored to a core to produce various multidendron dendrimers. An example reported the synthesis of poly(benzyl ether) from 3,5-dihydroxybenzyl alcohol as showed in Fig. 11. [240].

Such method offers the advantage of a precise control over molecular weight and a greater structural control, as each growth step requires a relatively low number of coupling reactions. Another advantage is the ability to produce dendrimers having functionalities in precise positions and number.

However, when compared with the divergent approach, such process is less readily scalable [241, 242]. This method produces the Fréchet-type polyether dendrimer family (poly-aryl type, PAE) and Janus-type dendrimers with multiple topologies [243]. However, researchers use alternatively the divergent and convergent approach at different stages to get the proper dendrimer macromolecule [244].

It is interesting to evidence the unique structure of dendrimers that provides special opportunities for host-guest chemistry (Fig. 12) and is especially well equipped to engage in multivalent interactions making dendrimers suitable to be used as nanocontainers.

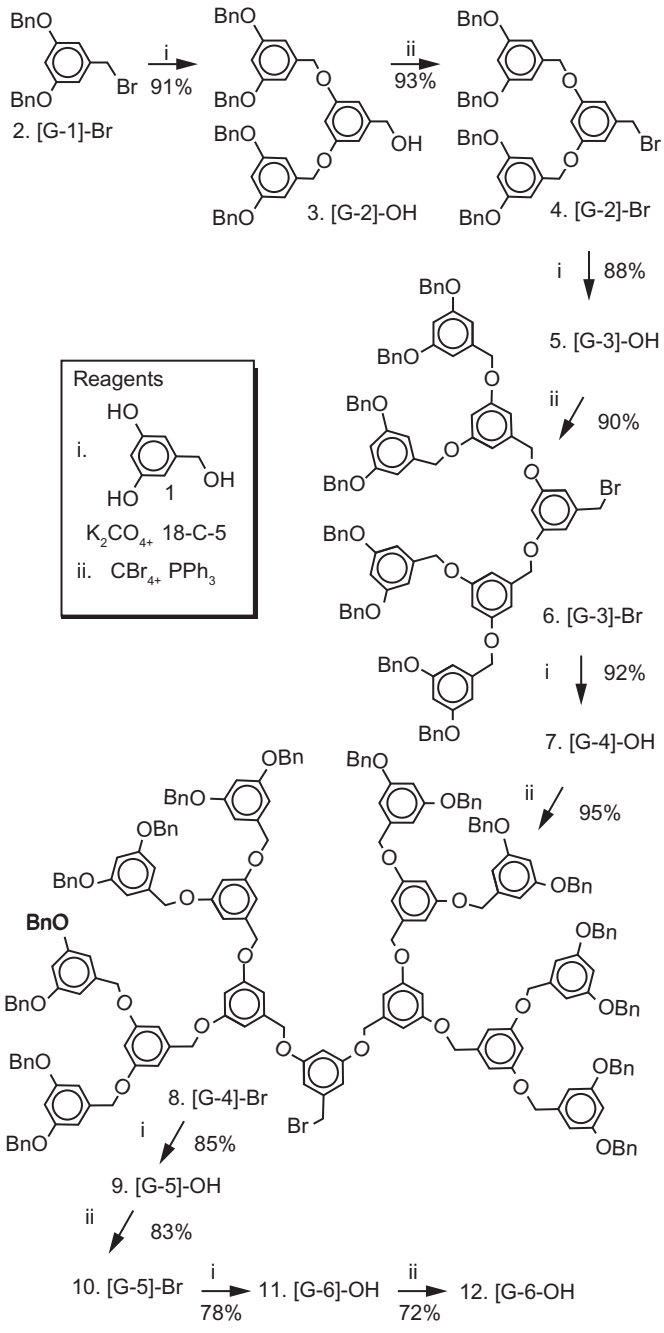
Dendrimers can encapsulate active species by an effective combination of physicochemical interactions such as electrostatic forces, hydrophobicity, π-π stacking, hydrogen bonds, and the effects of physical steric immobilization. The interaction, determined by the chemical structure of the dendritic skeleton and the active principles, does not lead to the formation of covalent bonds with the active principles [245] but to the formation of drug-dendrimer "complexes" as the community of dendrimers scientists refer to [246].

Small drug molecules are encapsulated most of the time in the dendrimer interior, whereas large molecules preferably adsorb near the surface: dendrimers complexes help in solubilizing in water or otherwise water-insoluble drugs.

In alternative, to avoid drug release before reaching the targeted system, the dendrimer termini can be bound covalently to the drug so that drug-dendrimer "conjugates" are produced.

FIG. 11 Synthesis of poly(benzyl ether) from 3,5-dihydroxybenzyl alcohol. Step i: coupling of the monomer phenolic groups to the bromide derivative. Step ii: alcohol activation by conversion to the bromine derivative. *(Reprinted with permission from S.M. Grayson, J.M.J. Fréchet, Convergent dendrons and dendrimers: from synthesis to applications, Chem. Rev. 101 (12) (2001) 3819–3867. Copyright (2001) American Chemical Society.)*

Scheme 1



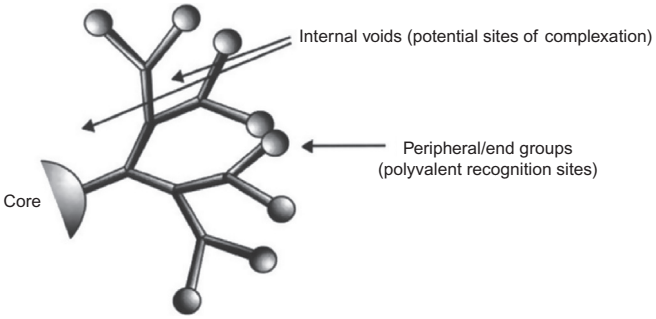


FIG. 12 Three main parts of a dendrimer: the core, end groups, and subunits linking the two molecules. *(Reprinted with permission from E. Abbasi, S.F. Aval, A. Akbarzadeh, M. Milani, H.T. Nasrabadi, S.W. Joo, Y. Hanifehpour, K. Nejati-Koshki, R. Pashaei-Asl, Dendrimers: synthesis, applications, and properties, Nanoscale Res. Lett. 9 (1) (2014) 247. Licensed under a Creative Commons Attribution (CC BY 4.0) license. Attribution 4.0 International (CC BY 4.0).)*

Conjugation allows a higher drug payload and dendrimer-drug conjugates turn out to be superior to drug-dendrimer complexes and superior to the free drug because the drug can be specifically targeted. However, conjugation may be accomplished with a longer and more complicated synthetic procedure time and materials consuming [247].

A final overview of drug-dendrimer complexes and drug-dendrimer conjugates and their potential applications is reported in Fig. 13 [248].

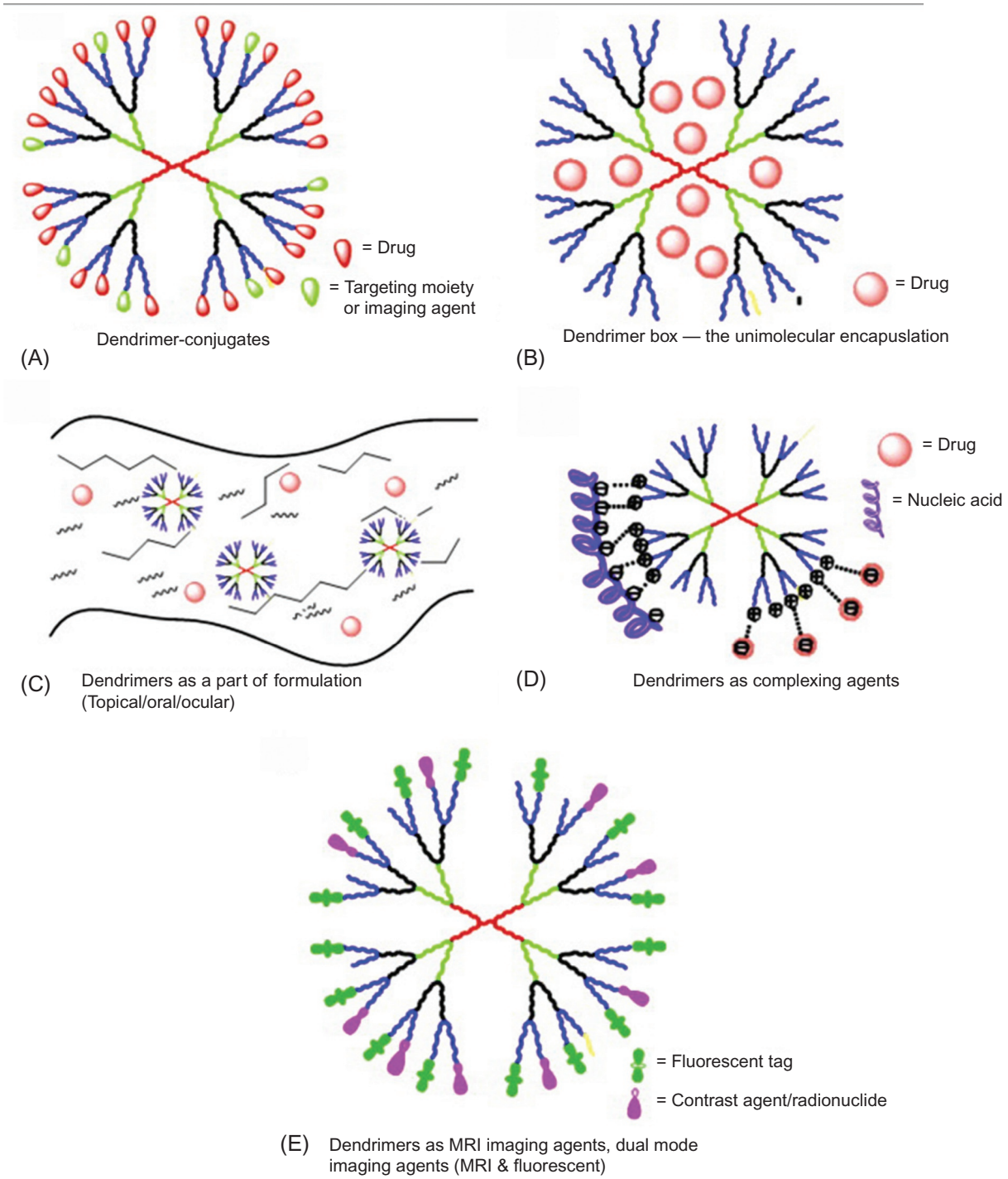


FIG. 13 Potential applications of dendrimers. (A) Dendrimer-drug conjugates, dendrimers linked to targeting moieties, and imaging agents. (B) Encapsulation of the drugs in the dendritic interiors. (C) Dendrimers incorporated into various delivery systems for enhancing permeation, solubility, and so on. (D) Dendrimers as complexing agents. (E) Dendrimers as carriers for MRI and fluorescent imaging. *(Reprinted with permission from A.R. Menjoge, R.M. Kannan, D.A. Tomalia, Dendrimer-based drug and imaging conjugates: design considerations for nanomedical applications, Drug Discov. Today 15 (5–6) (2010) 171–185. Copyright 2010 Elsevier.)*

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