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REVIEW

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Amphiphilic micro- and nanogels: Combining properties from internal hydrogel networks, solid particles, and micellar aggregates

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Abstract

Polymeric micro- and nanogels are defined by their water-swollen hydrophilic networks that can often impart outstanding biocompatibility and high-colloidal stability. Unfortunately, this highly hydrophilic nature limits their potential in areas where hydrophobic or amphiphilic interactions are required, for example, the delivery of hydrophobic cargoes or tailored interactions with amphipathic (bio-)surfaces. To overcome this limitation, amphiphilic micro−/nanogels are emerging as new colloidal materials that combine properties from hydrogel networks with hydrophobic segments, known from solid hydrophobic polymer particles or micellar cores. The ability to accurately adjust the balance of hydrophobic and hydrophilic components in such amphiphilic colloidal systems enables new tailored properties. This opens up new applications ranging from the controlled and sustained delivery of hydrophobic drugs, over carriers for catalytic moieties, to their assembly at hydrophilic/hydrophobic interfaces, for example, as advanced stabilizers in Pickering emulsions. While promising, the synthetic realization of such amphiphilic materials remains challenging since hydrophobic and hydrophilic moieties need to be combined in a single colloidal system. As a result, adjusting the micro−/nanogel amphiphilicity often changes the colloidal features too. To overcome these limitations, various strategies have been reported. The aim of this review is to give a brief overview of important synthetic tools, considering both advantages and disadvantages, thus critically evaluating their potential in different research fields.

KEYWORDS

amphiphilicity, coatings, crosslinking, drug delivery, microgels, nanogels, Pickering emulsions

1 | INTRODUCTION

Micro- and nanogels are crosslinked polymer particles that show unique properties due to their combination of colloidal size, structural stability (no critical micelle concentration), colloidal stability (no surfactants needed), and internal networks that can be swollen by suitable solvents.[1–3] In aqueous systems, colloidal particles with hydrophilic polymer networks lead to highly swollen hydrogel micro−/nanoparticles that are the focus of this article. Tuning the properties of such networks through molecular design of the polymeric building blocks can be used to control (dynamic) features such as (bio-) degradability, biocompatibility, swelling behavior, as well as mechanical and diffusion properties.[4–8] Especially the utilization of external stimuli such as temperature, pH, light, enzymes, magnetic field, etc., in aqueous environments is of high interest to control either the interaction between network polymer and aqueous environment or by cleaving/forming crosslinking points.[9–11] A triggered change in network mesh size enables various advanced applications ranging from drug delivery vehicles[12–15] and switchable catalytic carriers[16–18] to responsive soft colloidal crystals[19–21] and ordered assemblies at liquid interfaces,[22,23] for example, colloidal stabilizers for Pickering emulsions.[24] In addition, they can be combined with inorganic nanoparticles such as silica, gold, silver, and magnetic nanoparticles resulting in hybrids systems that share the properties of the organic and inorganic parts. This leads to potential applications in coatings, removal of heavy metals from water, antibacterial films, catalysis, theranostics, biosensors, and so forth.[25–27] Nevertheless, since micro−/nanogels are mainly governed by their highly hydrophilic nature, this prominent feature also restricts their areas of applications. For example, a main challenge for conventional hydrophilic micro−/nanogels is their limited ability to encapsulate hydrophobic compounds, for example, hydrophobic or lipophilic drugs. In addition, they are restricted in their interaction with amphiphilic (bio-) materials and interfaces.

In direct contrast to such hydrogel particles, solid polymer particles are long established for applications where hydrophobic colloids are needed (e.g., hydrophobic coatings, oil–water separation).[28,29] Due to their hydrophobic nature, these nanoparticles are not swollen in aqueous solution, leading to hard and rigid materials with very limited ability to tailor their mechanical and diffusion properties in this specific environment. Thus, additional strategies are needed to impart, at least, partial hydrophilicity on the particle surface. For example, covalent PEGylation or additional surfactants are often used to tailor interactions with biological systems and/or improve colloidal stability.[30–32]

As alternatives to the two extremes of either truly hydrophilic or purely hydrophobic nanoparticles, amphiphilic colloidal materials are promising since they combine hydrophobic and hydrophilic segments in one system. Polymeric materials that use this design are mostly realized by the assembly of amphiphilic (block) copolymers. This can be achieved by phase separation of block copolymers (BCP) in the confinement of emulsion droplets[33–35] or by self-assembly in aqueous surrounding. Depending on the architecture of the polymeric building blocks, different colloidal structures are obtained, that is, liposomes/polymersomes,[36–39] polymer cubosomes,[40,41] or micellar aggregates.[42–45] Using well-defined BCP with separate hydrophilic and hydrophobic blocks leads to clearly distinguished hydrophobic cores and hydrophilic shells (micelles) or lamellar membranes (polymersomes).[46–48] In contrast, random amphiphilic copolymers are characterized generally by a non-ordered distribution of hydrophilic and hydrophobic groups along the backbone.[49,50] As a result, the distinction between core and shell is not as sharp in the assembled structures. Moreover, these systems can be used to fabricate single-chain nanoparticles (SCNP) as new important class of materials.[51–53] Most importantly, the random copolymer structure can easily be realized for natural biopolymers through hydrophobic modification (e.g., polysaccharides).[54–56] Thus, amphiphilic micelles can also be obtained for such polymers that are otherwise restricted in their ability to form well-defined BCP.

Even though such self-assembled structures can overcome certain limitations of purely hydrophilic micro−/

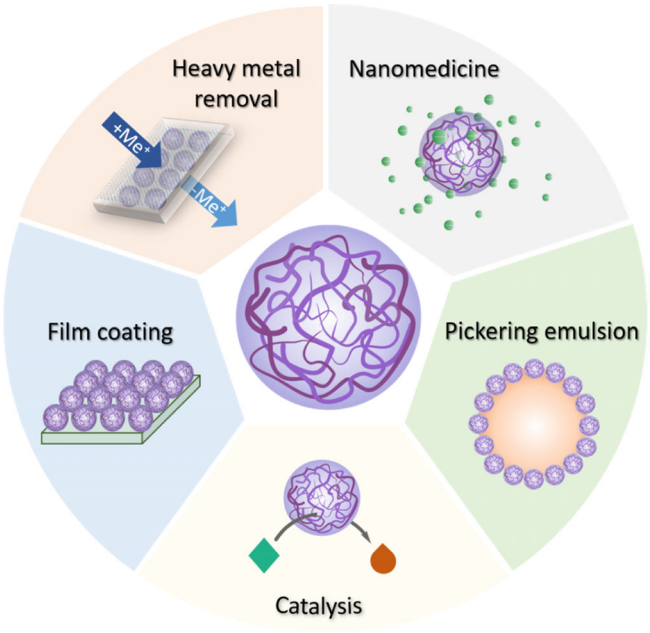

FIGURE 1 Emerging fields of applications for amphiphilic micro−/nanogels

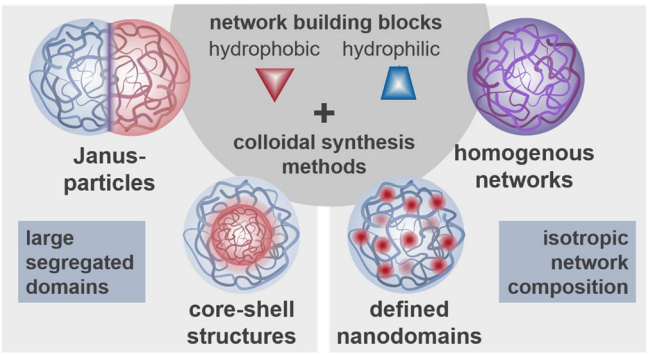

FIGURE 2 Different colloidal morphologies that can be obtained for amphiphilic nanogels. The structure of the micro−/nanogels depends crucially on the used colloidal synthesis method and the respective polymeric or monomeric building blocks

nanogels (e.g., the encapsulation of hydrophobic compounds[57,58]), the stability of these systems crucially depends on the polymer concentration.[59] As result, micellar aggregates can disassemble upon dilution, thus limiting their structural stability in comparison to micro−/nanogels. While core or corona crosslinked micelles are established to overcome such disassembly issues, controlling the colloidal features of the assemblies requires adjusting the molecular structure of the BCP building blocks. Thus, control over BCP molecular weight, dispersity, functionalization, and hydrophilic/hydrophobic (block) ratio is required, which limits the synthetic versatility.

Closely connected to such crosslinked micelles are amphiphilic micro−/nanogels—in fact, the classifications of such systems are often fluid. This class of colloidal materials is based on amphiphilic internal network structures, that is, copolymers with controlled or random distribution of hydrophobic and hydrophilic groups. Currently, these micro−/nanogels are emerging due to their unique combination of favorable features: hydrophilic networks, internal hydrophobic domains, colloidal stability, tunable size, and response to external stimuli. Thus, they exploit the outstanding hydrophobic characteristics of micelles or solid particles (high loading of hydrophobic drugs) and the hydrophilic features of nanogels (synthetic versatility, colloidal stability, and mechanical properties).[60]

Based on their unique properties, amphiphilic micro−/nanogels are promising to overcome current limitations of conventional micro−/nanogels in different areas of applications (Figure 1). In the area of biomedicine, these materials are of interest to combine the loading of (amorphous) hydrophobic cargoes with controlled release profiles and high-colloidal stability due to their amphiphilic networks. In addition, the introduction of functional, responsive, or reactive moieties can be used to tailor the network properties to applications in heterogenous catalysis, removal of heavy metals and contaminants as well as for film coatings. Furthermore, amphiphilic micro−/nanogels have been recently investigated as new stabilizers for Pickering emulsion.[24,61,62]

The potential for advanced applications of such colloidal systems crucially depends on their synthetic accessibility and versatility. For this, different synthetic routes have been established. Depending on such particle preparation methods and the respective building blocks, micro−/nanogels with different morphologies can be achieved. These structures vary in the relative distribution of the hydrophobic and hydrophilic components, for example, their separation into defined domains or compartments. For distinct hydrophobic and hydrophilic parts that are in the size range of the overall colloidal particles, Janus particles ore core-shell structures can be observed. In contrast, a more isotropic distribution of both functionalities results in spherical nanogels with homogenous distribution though the whole network or networks that contain isotropically distributed hydrophobic nanodomains (see Figure 2).

In this review, different pathways that are currently available to obtain such amphiphilic nanogels will be analyzed (Figure 3). A well-known pathway is the previously discussed self-assembly of amphiphilic random copolymers and subsequent covalent crosslinking to obtain the amphiphilic micro−/nanogels. In contrast, the utilization of facile and scalable (mini-) emulsion or precipitation polymerization techniques is of high interest to circumvent the synthesis of well-defined copolymer building blocks and their controlled assembly.[60,63,64] These heterogenous or homogeneous emulsion/dispersion techniques are well established for the

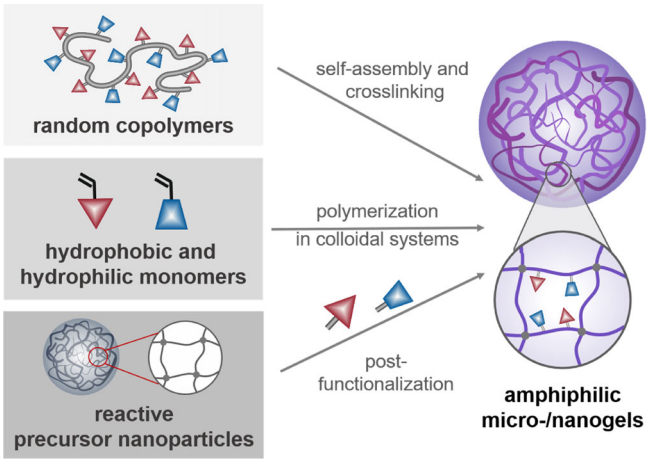

FIGURE 3 Schematic representation of current strategies available for the synthesis of amphiphilic micro−/nanogels

generation of micro−/nanogels through radical polymerizations of hydrophilic or inherently amphiphilic monomers such as *N*-isopropylacrylamide (NIPAM) or oligoethylenglycol methacrylates (OEGMA's).[65–67]

Still, the isotropic and simultaneous incorporation of hydrophobic and hydrophilic monomers with drastically different solubilities presents a significant challenge during such reactions. Consequently, varying the network amphiphilicity by tuning the hydrophilic/hydrophobic ratio can result in significant changes in the overall colloidal features, for example, size, size distribution, morphology. To overcome such limitations, a recent strategy, which is based on the synthesis of precursor nanoparticles and their post-functionalization, can control the amphiphilicity of the networks without altering the colloidal features. Here, the post functionalization can be either physically or covalently.

In this review, we give a brief overview over current synthetic developments to prepare amphiphilic micro−/nanogels and evaluate their main advantages and disadvantages. In addition, the broad spectra of applications for such attractive materials are discussed. Despite a clear focus on the biomedical field, also promising results are discussed that highlight the potential of such amphiphilic networks in emerging applications such as functional coatings, switchable catalysis, and Pickering emulsions.

2 | SYNTHETIC APPROACHES TO COVALENTLY CROSSLINKED NANOGELS AND MICROGELS

The main synthetic routes to amphiphilic micro−/nanogels can be categorized into three groups (Figure 2). First, the covalent crosslinking of self-assembled random copolymers. Second, the incorporation of both hydrophobic and hydrophilic moieties during the micro−/nanogel synthesis. Finally, the modification of precursor nanogels to generate amphiphilic internal networks after the particle preparation.

2.1 | Formation of amphiphilic micro−/nanogels via self-assembly of amphiphilic copolymers and subsequent covalent crosslinking

Amphiphilic BCP can self-assemble in aqueous solution through segregation of the hydrophobic blocks into micellar cores.[68–71] This micellization process is strongly dependent on the BCP concentration and occurs above a critical micellization concentration (CMC). For biomedical applications, this can portray a major drawback. For example, administration (intravenous, oral, etc.) of such self-assembled structures can lead to a dilution of the micelles. The lowered BCP concentration can then cause disassembly of the micelles, that is, compromising their colloidal stability. To overcome these drawbacks, the colloidal features of amphiphilic polymers can be fixated through covalent crosslinking of either core or shell.[72] Even though the crosslinked micelles are overall amphiphilic materials, the BCP architecture results in well-defined colloidal structures with a clear distinction between hydrophilic shell and hydrophobic core. This clearly distinguishes these architectures from amphiphilic micro−/nanogels where the whole crosslinked network is amphiphilic, thus enabling tunable diffusion and mechanical properties. Due to this difference, crosslinked BCP micelles are out of the scope of this review. In addition, the synthesis and application of such interesting materials has already been extensively reviewed elsewhere.[73–77]

In contrast to the well-defined segments of BCP, random amphiphilic copolymers contain both hydrophobic and hydrophilic moieties randomly distributed throughout the polymer. In water, the hydrophilic/hydrophobic balance determines self-assembly into micellar structures with low CMC's. However, the resulting colloidal systems do not show such clear distinctions between hydrophobic core and hydrophilic shell as their BCP analogs. If covalently crosslinked, these structures can rather show internal architectures similar to the networks of micro−/nanogels, that is, diffusion properties through the network and mechanical properties are tunable. Consequently, amphiphilic random copolymer micelles are promising for applications that bridge the gap between classical micelles and micro−/nanogels. However, the assembly process is often hard to control, for example, it is difficult to adjust the number of associated polymer chains per aggregate while changing the hydrophobic groups. In contrast, much more defined systems are evolving from dilute solutions where single chains can only interact with themselves, the so-called SCNP. To demonstrate the synthetic versatility and the resemblance to amphiphilic micro−/nanogels, the following section highlights recent advances in crosslinked random copolymers and SCNP.

2.1.1 | Self-assembly and crosslinking of amphiphilic random copolymers

Self-assembly of amphiphilic random copolymers is driven by the association of hydrophobic groups in aqueous solution (Figure 4).

In this approach, the colloidal features are determined by the primary structure of the polymer, such as composition, molecular weight, and branching.[78]

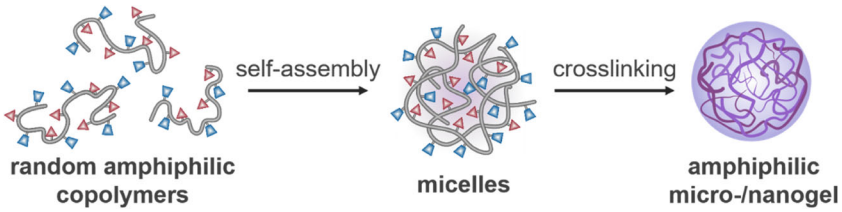

FIGURE 4 Schematic representation of synthesizing amphiphilic micro−/nanogels by self-assembly of random amphiphilic copolymers and subsequent covalent crosslinking

Especially distribution and type of hydrophobic groups need to be considered since they act as physical crosslinks, thus defining the internal gel-like networks. While this self-assembly strategy is very versatile, the sole utilization of physical crosslinks can limit mechanical properties and colloidal stability. Thus, reactive moieties can be incorporated into the amphiphilic copolymers to enable covalent crosslinking after the self-assembly process, thereby locking the colloidal features (Figure 4). This strategy leads to a variety of functional amphiphilic micro−/nanogels where the network properties can be controlled by the physical hydrophobic interactions and the covalent crosslinks.

As polymeric building blocks, amphiphilic natural biopolymers are often employed for micellar assemblies. In these materials, the structural simplicity of random copolymers is highly beneficial since challenging BCP syntheses can be avoided. Especially hydrophobically modified polysaccharides are well established as amphiphilic micellar building blocks.[79,80] However, these biodegradable polymers lack the definition and chemical versatility of synthetic random copolymers and have been extensively reviewed elsewhere.[81–85]

Thus, this section focuses on crosslinked synthetic random copolymers where an enhanced solubility of hydrophobic cargoes is combined with a soft colloidal structure that can enhance colloidal stability and biocompatibility (depending on the polymer building blocks, etc.). In addition, the covalently crosslinked network can be used to tune the mechanical features of the colloid itself.[86–88] By integrating stimuli-responsive monomers or crosslinkers in the network, its swelling or degradation can be controlled by external triggers such as pH, UV-irradiation, or reducing agents.[89,90] Therefore, crosslinked amphiphilic nanogels find their application in, for example, catalysis, as drug delivery systems (DDS) and protein conjugation.[80,91,92]

Covalent crosslinking of such self-assembled systems can be achieved through two main synthetic strategies: On one hand, all required reactive groups are incorporated in the amphiphilic copolymer. On the other hand, the reactive copolymers react with (bi-) functional crosslinkers. For both approaches, efficient and fast reactions are beneficial to ensure control over the final crosslinking density. In addition, reversible reactions or dynamic covalent bonds, can be used to introduce dynamic (stimuli-responsive) network properties.

Using light-induced reversible crosslinking, Wang et al. developed pH- and light-responsive nanogels, which can be used as emulsifiers for Pickering emulsion.[93] For this, random poly(methacrylic acid-*co*-methyl methacrylate-*co*-7-[4-vinylbenzyloxyl]-4-methylcoumarin) (P[MAA-*co*-MMA-*co*-VM]) was prepared by free radical copolymerization. The amphiphilic copolymer self-assembled into micelles with methacrylic acid (MAA) as hydrophilic shell and methyl methacrlyate (MMA) and VM as hydrophobic core in dimethylformamide (DMF)/water (H_2O). In its physically crosslinked state, the swelling behavior was controlled by varying the MAA content in the amphiphilic polymer and by changing the pH of the aqueous medium. Upon UV-irradiation of the micellar assemblies at low pH, the pendent coumarin moieties can undergo intraparticle crosslinking through light-induced cycloaddition. This leads to shrunken micellar assemblies. In contrast, inter-particle crosslinking is observed upon UV-irradiation at increased pH values. Under these conditions, the swelling of the copolymer segments at the micellar surface is enhanced and thus, the crosslinking among the micelles is favored. The emulsification properties of the crosslinked and un-crosslinked amphiphilic micelles were tested at different pH for a paraffin/water system. For uncrossslinked micelles O/W emulsification was possible in the whole range of pH. In contrast, crosslinked micelles only stabilized emulsions at a pH range from 2 to 6.5. When the pH exceeded 7.3, phase-separation occurred. This was attributed to the rigidity of the crosslinked micelles at basic conditions, which depends on the increasing inter-particle crosslinking and electrostatic repulsion of the deprotonated carboxylic groups. Hence, these crosslinked micelles could not be absorbed at the oil/water interface, leading to a lower emulsifying efficiency. This study demonstrated that particle swelling and conformational changes of dangling copolymer segments at the micellar surface play a key role in the emulsification properties. This highlights the importance of several nanogel parameters that must be considered to tune the final properties of the desired Pickering emulsion. For instance, the nanogels' crosslinking density crucially affects the mechanical properties of the stabilizing particles. Generally, a higher crosslinking will lead to harder particles, which will reduce the deformation of the particles at the liquid–liquid interphase. This influences the stabilization mechanism. Another

factor is the amphiphilicity. Balancing the hydrophobic interactions with the oil phase and the hydrophilic interactions with the aqueous phase determines the contact angel of the nanogels at the interphase and the swelling in the respective phases. Overall, the influence of all these parameters on properties of the Pickering emulsions is complex and requires further studies.

Photo-induced cycloadditions are especially interesting for crosslinking due to their fast and efficient reaction under mild conditions. In general, reactions that fulfill these criteria are the so-called click-reactions.[94] Due to their modular nature, high-thermodynamic driving force, stereospecificity, and robustness, they can occur efficiently in the presence of water and oxygen at room temperature. Thus, they are perfect candidates for crosslinking of micellar aggregates without affecting the self-assembled structures. Reactions that fall within this category are, among others, copper-catalyzed azide–alkyne cycloadditions (CuAAC),[95] strain-promoted azide–alkyne cycloadditions (SPAAC),[96,97] and thiol-Michael-Addition click reactions.[98]

Using CuAAC for crosslinking, Chiranchai and coworkers demonstrated the synthesis of amphiphilic nanogels based on "clickable" biodegradable crosslinkers.[99] For this, hydrophilic polyacrylic acid (PAA) was first subjected to partial post-polymerization modification with hydrophobic propargylamine to give alkyno-poly(acrylic acid) (alkyno-PAA). The resulting amphiphilic random copolymer self-assembled into nanoparticles in DMF. The pendant alkyne groups were then used for CuCAAC crosslinking with a mixture of two different diazido crosslinkers: the hydrophilic N_3-PEG-N_3 and the hydrophobic diazido terminated poly(butylene succinate) (N_3-PBS-N_3) (Figure 5). With this strategy, the amphiphilicity of the overall nanogel network can be tuned by varying the ratio and amount of polyethylene glycol (PEG) and poly(butylene succinate) (PBS) crosslinkers. The amphiphilicity was demonstrated by the swelling of the obtained nanogels in several solvents of different polarity. In addition, this amphiphilic nature was exploited to increase the colloidal stability of multiwalled carbon nanotubes (MWCNT's) in different materials. These carbon materials tend to aggregate in any solvents due to their strong van der Waals interactions. In this work, the MWCNT's were coated with a thin layer of the nanogels leading to a high-colloidal stability in water for weeks without observing any precipitation. This fact suggested that these nanogels, due to their amphiphilic nature, present great potential as dispersants for MWCNT's in aqueous solution.

In a similar approach, Sanyal and collaborators reported the formation of amphiphilic nanogels but using thiol-

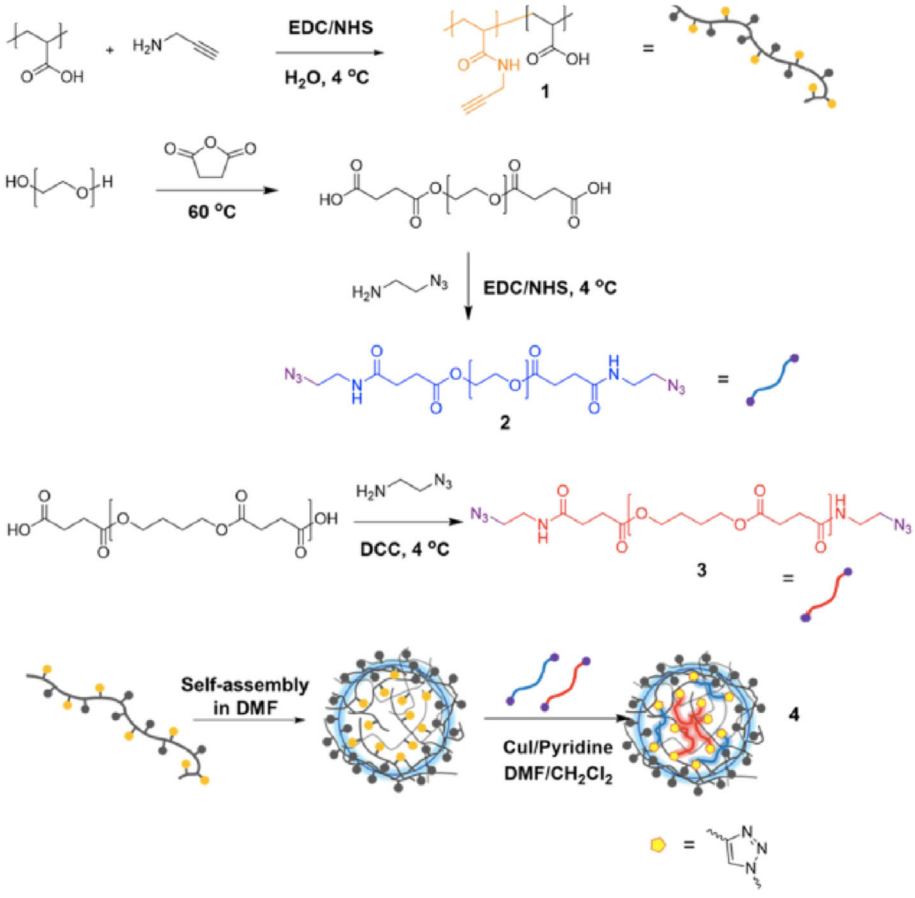

FIGURE 5 Illustration of the synthetic pathway by Chiranchai's group for the preparation of amphiphilic random copolymers (1) and their macromolecular crosslinkers (2) and (3). Amphiphilic nanogels (4) were obtained by the self-assembly of (1) and subsequent crosslinking with mixture of hydrophilic (2) and hydrophobic (3) to obtain amphiphilic nanogels with biodegradable and/or water-soluble crosslinkers. Reproduced from ref. 99 with permission from copyright © 2020, Elsevier Ltd

maleimide coupling.[100] In this strategy, an amphiphilic precursor copolymer was prepared containing reactive maleimide-methacrylate (MaMA). The resulting reactive copolymer poly(PEGMEMA-*co*-MaMA-*co*-HEMA) combines hydrophilic PEG and hydroxyethyl methacrylate (HEMA) side groups with hydrophobic maleimide moieties. From this amphiphilic structure, nanogels were obtained by self-assembly and subsequent covalent crosslinking through bifunctional thiols (2,2′-[ethylenedioxy]diethanethiol). Unreacted maleimide moieties were used for post-modification of the nanogel. The functionalization of the nanogels through the maleimides allowed the incorporation of a thiol-containing cyclic peptide as targeting group. The residual thiol groups could be employed for the conjugation of a maleimide-containing fluorescent indocyanine Cy5 dye. In addition to the maleimide functionalities, the pendant HEMA hydroxyl groups were reacted with N-hydroxysuccinimide (NHS) to obtain activated carbonate groups, which can easily react with amine-containing molecules. These were used to conjugate doxorubicin to the nanogel network through carbamate linkage with the NHS moieties. Cell internalization studies demonstrated that nanogels with the targeting cyclic peptide were faster internalized than the control. The in vitro cytotoxicity assay showed that nanogels with the peptide presented slightly higher toxicity in comparison with the nanogels only with doxorubicin. It was suggested that this is mainly due to the enhanced internalization of peptide. This highly tunable amphiphilic nanogel can act as a versatile platform for different theranostic application such as imaging, triggered release, and so forth.

As an alternative to click reactions, activated esters have been extensively studied for post-polymerization modifications with nucleophiles.[88,101] Most commonly, an activating alcohol group in the ester is substituted with an amine, thus resulting in a new amide bond. Using such strong nucleophiles can impart a certain selectivity into the system. For example, the reaction with amines occurs preferably in the presence of weaker nucleophiles like alcohols or water. Due to the abundance of reactive amine groups in nature and the stability of the resulting amides, this strategy enables efficient formation of stable crosslinks.[88,102,103]

Using polymeric active esters that are functionalized with amines, Noree et al. synthesized poly(pentafluorophenyl methacrylate)-*co*-poly(oligo[ethylene glycol methacrylamide]) PPFPMA-*co*-POEGMAM. This was obtained through a post-polymerization modification of the active ester polymer poly(pentafluorophenyl methacrylate) (PPFPMA) with oligo(ethylene glycol) methyl ether amine ($OEG\text{-}NH_2$).[104] The resulting amphiphilic random copolymer self-assembles into micellar structures in water. Subsequent addition of cysteamine as bifunctional amine, leads to crosslinking of the micelles. The resulting disulfide bonds in the crosslinks render the micelles reduction-sensitive. This was demonstrated by triggering the release of a hydrophobic guest-molecule (Nile red, [NR]) with glutathione (GSH).

The active ester-amine reaction can also be used the other way around, that is, by using polymeric amines that can be reacted with small functional molecules that contain an active ester group. This strategy has been utilized by the group of Thayumanavan, who prepared amphiphilic polymer precursors with pendant primary amines for further functionalization.[105] Amphiphilic random copolymers were prepared by copolymerization of 2-aminoethyl methacrylamide and 3-(9-methylcoumarinoxy)propyl methacrylamide. In water, the polymers then self-assembled into amphiphilic micellar aggregates with a hydrophobic core containing photo-crosslinkable coumarin groups. In contrast, the hydrophilic amino moieties mostly formed the outer shell exposed to the aqueous phase. This allowed the introduction of additional functional groups on the surface of the amphiphilic assembly through complementary moieties, such as NHS-/pentafluorophenyl (PFP)-ester and isocyanates after the particle assembly and crosslinking. These amphiphilic systems were able to encapsulate hydrophobic guest molecules. Overall, they represent a versatile polymeric platform, which can encapsulate hydrophobic cargoes and can introduce stimuli-responsive or targeting moieties through coupling with reactive groups at the surface.

Using polymers that contain amines and sulfides as two functional groups for crosslinking, Jackson et al. also designed nanogels with both dynamic covalent imine and sulfide crosslinks.[106] With this purpose, they synthesized two random copolymers: Polymer 1 was based on N,N′-dimethylacrylamide (DMA) as hydrophilic monomer, N-ethylacrylamide-2-(4-formylbenzamide) (EFB) to introduce reactive aldehyde side groups and 2-pyridyl disulfide ethylacrylamide (PDEA) to impart sulfide side groups. Polymer 2 was based on DMA, PDEA, and N-(tert-btoxycarbonyl)-propylaminoacrylamide (BPAA) as protected amine. These polymers were self-assembled and crosslinked both by imine bond between EFB and BPAA and disulfide exchange of PDEA in the presence of NR. In addition, unreacted aldehyde groups were modified with PEG-hydrazide. The nanogels presented pH- and redox- responsiveness due to the imine and disulfide bonds, respectively. These triggers could be used to induce the release of encapsulated NR as model cargo.

Similarly, the group of Thayumanavan exploited this strategy to synthesize amphiphilic nanogels crosslinked with sulfide bonds. The individual nanogels can form stimuli-responsive nanoclusters by employing a dialdehyde to introduced interparticle dynamic covalent imine bonds.[107] In a first step, amphiphilic random

copolymers containing 2-(pyridyldisulfide)ethyl methacrylate (PDSMA), polyethylene glycol methacrylate (PEGMA), and 2-aminoethylmethcrylate (AEMA) were prepared. In these building blocks, PEGMA and AEMA impart hydrophilic groups while the PDSMA monomer is hydrophobic. These amphiphilic copolymers self-assembled in water. The resulting amphiphilic micelles were subsequently crosslinked through the PDSMA units by using an in situ disulfide exchange reaction yielding nanogels of sizes around 10 nm. The surface of the nanogels is decorated with primary amine moieties, thus, these can be used to connect multiple nanogels to bigger clusters using bifunctional crosslinkers such as a dicarboxaldehyde, affording bigger nanogels of 24 nm with pH-responsive imine bonds.[107] The nanogels were uptake by HeLa cells showing promising results as nanocarriers.

In a following study, they used the disulfide exchange crosslinking for the development of nanogels from components that are generally recognized as safe (GRAS).[108] For this, glutamic acid and putrescine were chosen as monomers to prepare degradable polyamide backbones with functionalized hydrophilic oligoethylene glycol moieties and hydrophobic 2-(pyridyldisulfide) (PDS) moieties. These polymers self-assembled in water and the resulting micelles were crosslinked by the addition of GSH to form disulfide crosslinking points. Upon self-assembly, the hydrophobic dye 1,1-dioctadecyl-3,3,3′,3′-tetramethyl-indocarbocyanine perchlorate (DiI) was encapsulated. Using the triggered cleavage of the disulfide crosslinking points, a stimuli-responsive release of the dye was demonstrated. Thus, these systems are a perfect example of combining the excellent biocompatibility of the designed hydrogel networks with the ability to load and release hydrophobic compounds.[108]

In summary, these examples demonstrate that crosslinked random copolymer micelles enable the random distribution of hydrophobic and hydrophilic moieties in the polymer networks. In combination with the high-colloidal stability, enhanced loading capacity for hydrophobic compounds, and good biocompatibility, they represent interesting new micro−/nanogels for various applications. Despite these clear benefits, the preparation of such nanogels requires an additional step of synthesizing the amphiphilic copolymer building blocks. Thus, tuning the network characteristics requires each time the synthesis of a new polymer batch. However, this can also drastically influence the assembly characteristics and thus the colloidal properties, for example, number of chains per micelle, morphology, and so forth. Thus, comparability between systems can be limited.

2.1.2 | Crosslinked SCNP

Amphiphilic random copolymer micelles are promising materials to bridge the gap between classical BCP micelles and micro−/nanogels. In such aggregates, colloidal properties such as size, size distribution, stiffness, and viscosity, depend on the number of associated chains per micelle. However, controlling this number during the self-assembly of multifunctional polymers can be difficult. In contrast, much more defined systems are evolving from dilute solutions where single chains can only interact with themselves.

In such folded individual chains, the colloidal properties vary tremendously from those of their micellar analogs and respective unfolded counterparts.[109] In general, precisely adjusting the copolymer composition and the placement of functional groups along the multifunctional chains can be used to tune the folding properties of these systems, thus partially mimicking the natural folding process of peptide chains in proteins and enzymes.[51,110,111] This control over the assembly of synthetic materials is of high interest toward the realization of synthetic enzymes. Even though the field of crosslinked amphiphilic SCNP is still in its infancy, these materials show great potential in bioinspired applications, for example, as new catalytic systems.[112–114] If covalently crosslinked, the distribution of hydrophilic and hydrophobic moieties throughout the folded assembly bears properties of amphiphilic gel networks. Strategies for their fabrication involve the initial collapse or folding of a single linear polymer chain and subsequent intramolecular crosslinking to yield well-defined amphiphilic nanogels (Figure 6).[52]

Amphiphilic single-chain nanogels were reported by the group of Sawamoto.[115] In their work, folded star polymers were intramolecularly crosslinked to prepare amphiphilic nanogels. The amphiphilic random copolymer building blocks contained hydrophilic PEGMA and hydrophobic dodecyl methacrylate (DMA) to induce the

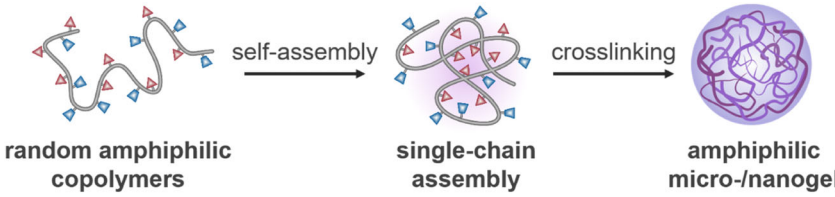

FIGURE 6 Schematic representation of self-assembly and posterior crosslinking of single random amphiphilic copolymer chains to obtain single-chain amphiphilic nanogels

folding. In addition, hydroxyl-moieties were introduced by using hydroxydodecyl methacrylate (HDMA) and HEMA during the Ruthenium-catalyzed CRP. In a second step, these pendant hydroxyl groups were then reacted with methacryloyl chloride to introduce methacrylate groups for radical crosslinking after the assembly. The authors successfully demonstrated the potential to tune the structure of the assembled SCNP through the architecture and composition of the amphiphilic random copolymer precursor. Ultimately, due to the presence of PEGMA, these systems presented a thermoresponsive swelling behavior, which further highlights their nanogel-like character.

In a follow-up study, the authors adjusted the copolymer structure to control the formation of well-defined compartments in single-chain polymer particles (Figure 7).[116] Key to the formation of distinctly different domains was the utilization of two different hydrophobic groups, that is, dodecylmethacrylate (DMA) and benzylmethacrylate (BzMA). In a BCP structure, dodecyl and benzyl units are located in the different block, whereas PEG groups are statistically attached along the whole chain: p(DMA-*co*-PEGMA)-*b*-p(BzMA-*co*-PEGMA). This structure enabled the orthogonal self-assembly of the two random amphiphilic blocks in water to give SCNP with two different hydrophobic compartments. Crosslinking was then achieved by free radical reaction of pendant methacrylate groups. In contrast, a tetra-random copolymer with the same monomer composition but completely statistic distribution of all monomers along the chain gave a mixed structure without clear compartmentalization. Finally, a tadpole structure was generated by using a crosslinked SCNP with a terminal chlorine group as macroinitiator for the CRP of a hydrophobic polymer tail (Figure 7). These structures were then able to assemble into multicompartment aggregates in water. Due to their defined compartmentalized morphology these nanoparticles show great potential to create biomimetic tandem catalysis systems, among others.

The unique internal structure of such crosslinked SCNP was examined by Hoffmann et al.[117] In their work, a random amphiphilic copolymer was synthesized by reversible addition−fragmentation chain-transfer polymerization (RAFT) copolymerization of hydrophilic PEGMA, and hydrophobic azidopropyl methacrylate (APMA) and 3-(trimethylsilyl)propargyl methacrylate (TMSPMA). For the intramolecular crosslinking of the folded single chains, copper-based click reactions were used to react the pendant azide and alkyne moieties (see Figure 8). Due to unreacted azide groups in the chain, the particles' networks could be labeled with alkyne modified 2,2,6,6-tetramethylpiperidine oxide (TEMPO), Rhodamine B, and aza-BODIPY (aBOD). Especially the paramagnetic nitroxide radical of spin TEMPO allowed studying the interior of these particles via electron paramagnetic resonance (EPR) experiments. These examinations

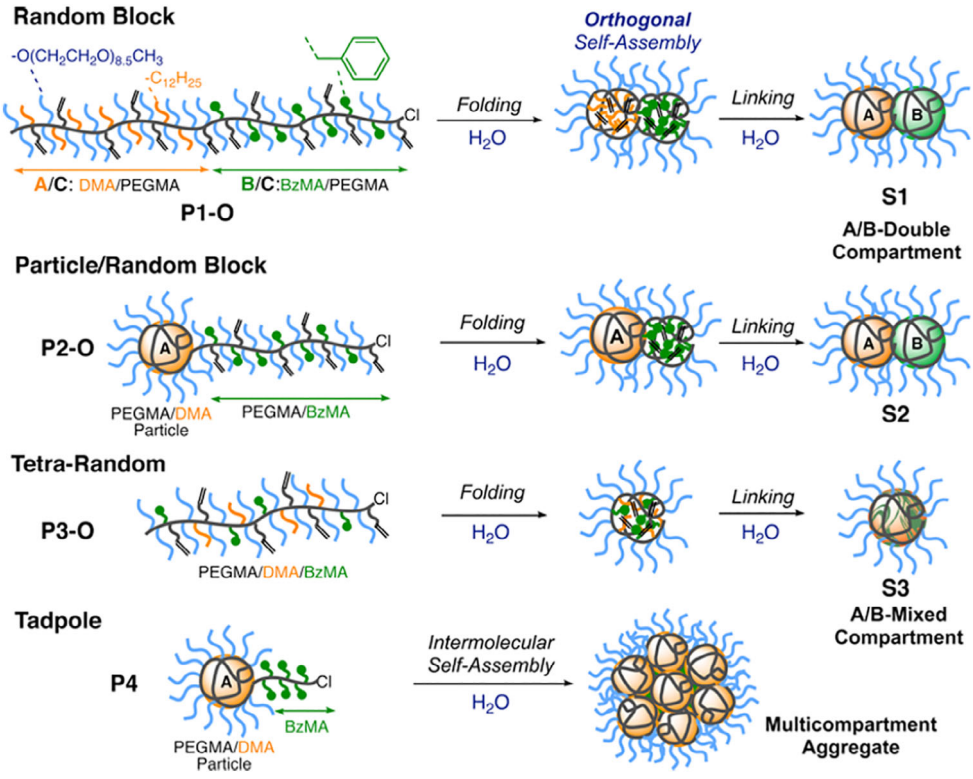

FIGURE 7 Different morphologies obtained via self-folding and crosslinking of amphiphilic random/block-copolymers in water. Influence of polymer structure on the final morphology of the nanomaterial. Reproduced from ref. 116 with permission from copyright © 2017, American Chemical Society

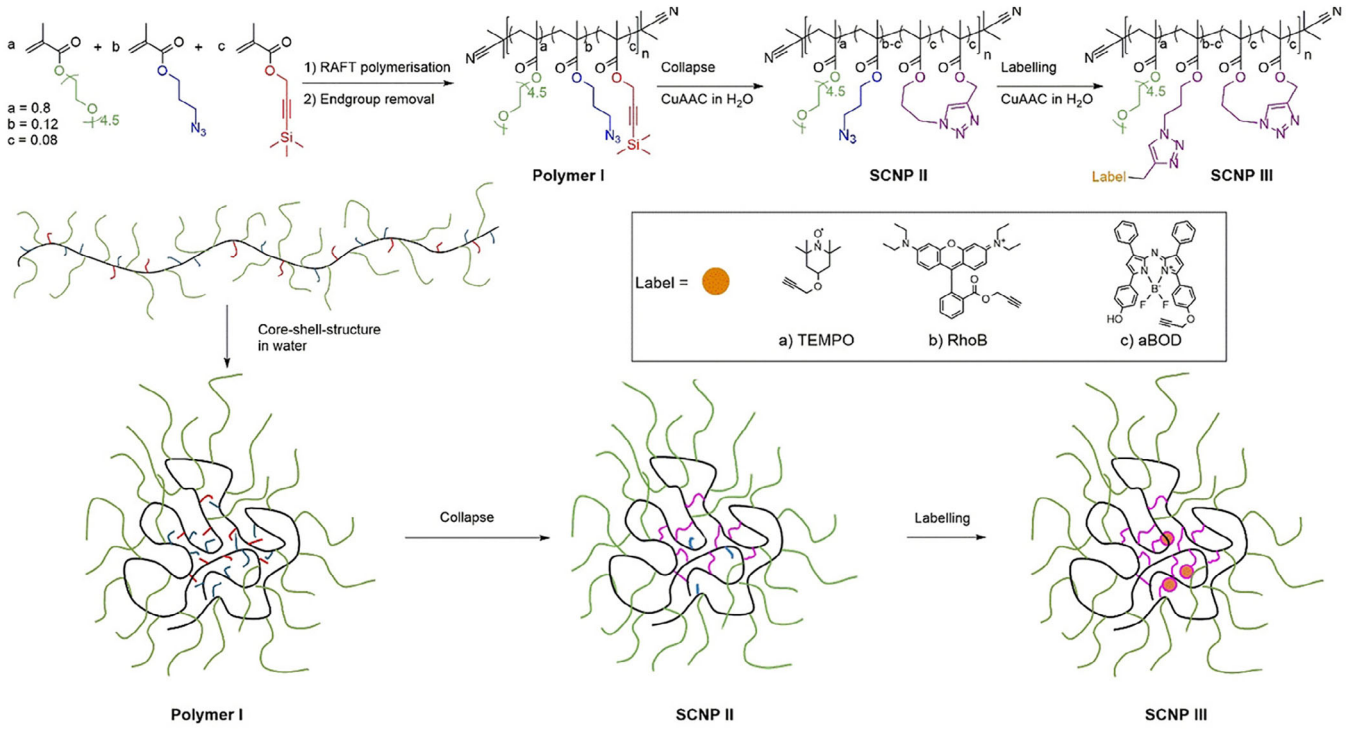

FIGURE 8 Schematic representation of the preparation of amphiphilic single-chain nanogels. Synthesis of the random amphiphilic copolymer followed by self-assembly and crosslinking to generate amphiphilic single-chain crosslinked nanoparticles that can be labeled with different molecules. Reproduced from ref. 117 with permission from copyright © 2021, Wiley-VCH GmbH

revealed a core-shell structure and demonstrated the presence of at least two covalently attached labels. Due to their fluorescence character, these systems are appealing as contrasting agents in photoacoustic imaging.

In summary, these recent examples of crosslinked amphiphilic SCNP demonstrate an excellent combination of properties from micelles and nanogels. These systems present high-colloidal stability, possibility of encapsulation of both hydrophobic and hydrophilic drugs and triggered release due to their crosslinked structure, thus resembling micro−/nanogels. Therefore, these emerging materials show great potential for various applications such as nanomedicine, catalysis, sensing, among others. In particular, the ability to tune the copolymer structure with respect to conformation, amphiphilic balance, and reactive functional groups demonstrates the potential of these materials. In addition, the large number of available crosslinking reactions enables the introduction of further functionalities, for example, cleavable crosslinks. While modern controlled polymerization methods allow fine tuning of the polymer structure and amphiphilicity, the single-chain folding is still challenging. To address this, the synthesis must be carried out in very low concentrations of the polymers, thus restricting the synthetic versatility and scalability of this approach. In addition, the incorporation of cargoes as well as the utilization of different solvents during the self-assembly may alter the folding of the polymer chains.

2.1.3 | Concluding remarks

In this section, the synthesis of amphiphilic nanogels by self-assembly and crosslinking of random copolymers was discussed. Depending on the preparation conditions, this strategy can be used to prepare nanogels as multi chain assemblies or SCNP. In Table 1, the different possibilities regarding hydrophobic/hydrophilic moieties, crosslinking strategies, nanogel properties, and potential applications of each approach are summarized (For a detailed table of specific amphiphilic nanogels obtained by this strategy see Table S1 in ESI).

Table 1 demonstrates the versatility of this general strategy, considering the broad spectra of moieties that can be introduced in the copolymers in order to obtain the amphiphilic properties. Additionally, a wide range of crosslinking strategies is available for nanogel formation and introduction of stimuli-responsive degradability. This versatility in tuning amphiphilicity and crosslinking enables to tailor the particles' properties to the requirements of specific applications. Especially the assembly

TABLE 1 Summary of analyzed amphiphilic nanogels obtained by self-assembly

Approach	Hydrophobic moieties	Hydrophilic moieties	Crosslinker	Sizes	Stimuli response	Applications
Multi chain assemblies	MMA, VM, PBS, MaMA, PFPMA, coumarin, DMA, PDEA, PDSMA, PDS	MAA, PEGMA, HEMA, PEGMEMA, PEG, AA, EFB, BPAA, AEMA, OEG	Disulfide, imine, radical crosslinking, click chemistry, amidation	70–550 nm PDI: 0.1–0.4	Thermo-, redox-, pH-, light-, responsive	Mainly DDS, Pickering emulsion
Single-chain nanogels	DMA, BzMA, APMA, TMSPMA	PEGMA, HEMA	Intramolecular radical	4–9 nm SD: 0.4–0.6	Thermo-responsive	DDS and catalysis

Abbreviations: AA, acrylic acid; APMA, azidopropyl methacrylate; BzMA, benzylmethacrylate; DDS, drug delivery systems; DMA, dodecyl methacrylate; HEMA, hydroxyethyl methacrylate; MAA, methacrylic acid; MaMA, maleimide-methacrylate; MMA, methyl methacrlyate; PDEA, 2-pyridyl disulfide ethylacrylamide; PDS, 2-(pyridyldisulfide); PDSMA, 2-(pyridyldisulfide)ethyl methacrylate; PEGMA, polyethylene glycol methacrylate; PFPMA, poly(pentafluorophenyl methacrylate); TMSPMA, 3-(trimethylsilyl)propargyl methacrylate.

and crosslinking in purely aqueous systems is highly beneficial to improve overall economic and ecologic features of the materials' synthesis. Comparing the size of particles from self-assembly of random copolymers and single-chain nanogels a clear difference is observed. The self-assembly of multiple random copolymers leads to bigger nanogels, mostly between 70 and 150 nm, in some cases up to 550 nm, whereas single-chain nanogels are obtained with sizes around 10 nm. This is expected due to inherently different mechanisms. When forming single-chain nanogels, crosslinking is restricted to intramolecular interactions. While this is beneficial, a high dilution of polymers is often needed to ensure this structure. Since this limits the overall solid content of the final nanogel dispersions, additional concentration steps are often needed. In contrast, the multi chain assemblies of random copolymers can be crosslinked by both intra- and intermolecular interactions, thus yielding particles with larger sizes and dispersions with higher solid contents. These differences should be considered depending on the field of application.

Both structures, multi- and single-chain nanogels have been utilized mainly in the field of medicine with nanogels as promising DDS and as materials for theranostic applications. This can be attributed to the (tunable) optimal size of such nanogels and their great potential for versatile post-functionalization. Here, unreacted groups can be exploited for including different probes or targeting molecules. In other research areas, single-chain nanogels are of high interest to create biomimetic catalytic systems. Currently, research focuses on the precise design of amphiphilic copolymer structures to program and control the folding of the chain, thus, mimicking proteins.[118] It is envisioned that this programming will allow the control of the final structure of the polymer, being able to create subdomains with protein-mimetic functions for catalysis, ligand binding, etc.

2.2 | Introducing network amphiphilicity during particle synthesis: Radical copolymerization of hydrophilic and hydrophobic monomers

The preparation of amphiphilic nanogels through crosslinking of self-assembled copolymers benefits from simple colloidal chemistry. But it requires defined polymeric building blocks to guide the self-assembly. In contrast, generating the amphiphilic network copolymers during the nanogel formation circumvents the preceding synthesis of defined amphiphilic and reactive copolymers. However, this approach requires good control during the colloidal synthesis to adjust the final features of the micro−/nanogels. For this, free radical copolymerization of different monomers in the presence of a crosslinker is often used in colloidal systems. Thus, such strategies could combine the simultaneous introduction of hydrophobic and hydrophilic moieties with crosslinking in one synthetic step.[119]

In general, well-established processes include emulsion copolymerization, miniemulsion copolymerization, and precipitation copolymerization. The main advantage of such strategies is their synthetic simplicity that still enables certain versatility. Depending on the method, the colloidal features such as size, size distribution, morphology, and stability of the micro−/nanogels can be controlled through the process conditions. Parameters to vary include, among others, the choice of monomers, crosslinkers, surfactants, and concentrations of dispersed and continuous phase.[120–123] Up to now, these variations have been optimized mainly for monomers that are themselves amphiphilic, for example, NIPAM or OEGMA's.[124] Since these systems restrict the tunability of the network amphiphilicity, they are not included in this article and the reader is referred to several excellent reviews for more information.[124–130]

In contrast to using such inherently amphiphilic monomers, the incorporation of amphiphilicity through random (one-pot) copolymerization of hydrophilic and hydrophobic monomers is less explored. This can be attributed to severe synthetic challenges that stem from the drastically different solubility of the monomers. Since each monomer is soluble in a different phase of the colloidal system, the isotropic random incorporation in the polymer network is challenging. This can lead to core-shell structures or complex morphologies.[131]

Additionally, this effect also restricts the possibility to tune the network amphiphilicity through the ratio between hydrophobic and hydrophilic monomers. Varying the composition in such synthetic strategies can lead to variations in the colloidal properties of the micro−/nanogels such as different sizes, size distributions, morphologies, and so forth. The actual influence of monomer composition on such properties crucially depends on the colloidal preparation method. There is a great difference between heterogenous systems such as emulsions and miniemulsions, where monomers are soluble in either the dispersed or the continuous phase, or precipitation polymerizations, which require the start from a homogeneous solution of all monomers. In addition, for miniemulsions, the copolymerization of all monomers and crosslinkers should only occur in the nanodroplets, whereas precipitation and emulsion-based approaches crucially depend on the diffusion of the monomers in the aqueous media for copolymerization. Since the diffusion properties determine particle nucleation and growth, they also strongly influence the resulting morphology, that is, the distribution of both monomer types in the particle network.[66,67,132] Consequently, all these factors will affect the overall amphiphilic properties of the system.

To demonstrate how new approaches address these challenges, the following section discusses selected recent examples that focus on controlling the network amphiphilicity during the synthesis of amphiphilic micro−/nanogels by precipitation polymerization, miniemulsion, and emulsion polymerization.

2.2.1 | Precipitation polymerization

A precipitation polymerization, as mentioned before, starts from a homogeneous solution, that is, all compounds such as monomers, crosslinkers, and initiators soluble in the chosen solvent. Upon polymerization, a critical chain length is reached that causes the insolubility of the propagating oligomer/polymer. This leads to precipitation and the formation of particle nuclei, which then continue to grow upon monomer addition until the final particles are obtained (see Figure 9).[133,134] In some cases, a surfactant is used (at concentrations considerably below the critical micellar concentration, CMC) to enhance the colloidal stability of nuclei and particles.

In this process, precipitation of propagating oligomers is the key step, which can be controlled by tunable interactions between the chains and the solvent. Common examples use thermoprecipitation upon polymerization.[67] Here, monomers, crosslinkers, and initiators are all initially soluble in the reaction medium. Upon reaching a critical chain length, however, the oligomer/polymer shows a lower critical solution temperature (LCST). If the polymerization now proceeds at temperatures above the LCST, the chains begin to precipitate and nucleate growing particles. These particles grow by adsorption of monomers and initiators to give thermoresponsive micro−/nanogels.[135] In such structures, the LCST behavior of the polymeric building blocks translates to a volume phase transition temperature (VPTT) of the colloidal gel networks, that is, a swollen network below VPTT and a collapsed structure above the VPTT.[136–138] Monomers that offer access to such thermoresponsive colloids in aqueous media are mostly NIPAM, vinylcaprolactam (VCL), or OEGMA.[128,135,139]

To adjust the LCST of the final material, the balance between hydrophobic and hydrophilic monomers can be varied: While additional hydrophilic comonomers can increase the LCST of thermoresponsive polymers, including hydrophobic comonomers has the opposite effect, that is, the LCST is shifted to lower temperatures.[129,140] In the particular case of POEGMA-based nanogels, this

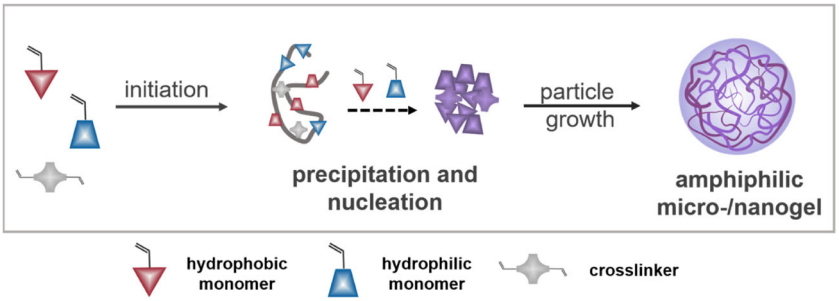

FIGURE 9 Synthesis of amphiphilic micro−/nanogels by precipitation polymerization of mixtures of hydrophobic and hydrophilic monomers

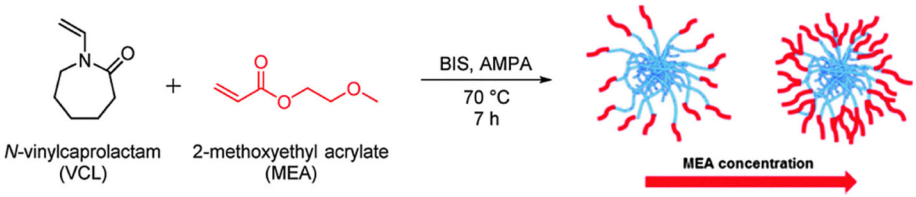

FIGURE 10 Schematic representation of the preparation of core-shell microgels by precipitation polymerization of VCL and MEA, using BIS as crosslinker. Reproduced from ref. 131 with permission from copyright © 2016, Royal Society of Chemistry. MEA, 2-methoxyethyl acrylate; VCL, N-vinylcaprolactam

balance can be controlled by changing the length of the pendant oligo(ethylene glycol) chain.[141,142] Overall, the thermoprecipitation polymerization represents a straightforward approach for the synthesis of micro−/nanogels with controlled size and internal network amphiphilicity. However, the relatively small library of suitable monomers to yield thermoresponsive polymers needs to be considered as a drawback that limits the versatility.[143] In addition, the simultaneous incorporation of both, hydrophobic and hydrophilic, monomers is challenging, potentially leading to complex morphologies.[131]

The influence of monomer solubility on the resulting microgel morphology was recently shown by the group of Pich.[131] The authors synthesized amphiphilic microgels by thermoprecipitation copolymerization of N-vinylcaprolactam (VCL) as hydrophilic monomer and 2-methoxyethyl acrylate (MEA) as hydrophobic oligoethylene glycol acrylate.[131] As previously discussed, the different solubility of the monomers restricts the random incorporation in the nanogel network, thus resulting in a final core-shell morphology (Figure 10). Microgels were able to integrate up to 32 mol% of MEA in their network with a gradient from a PVCL rich core to a PMEA-based shell. It was demonstrated that the amount of integrated MEA could control the cellular uptake of the microgels in HeLa cells, highlighting the importance of an amphiphilic nature in the design of nanocarriers. These results suggest that the amphiphilic microgel system is a promising carrier for drug delivery applications, for example, in cancer therapy.

The potential of using OEG-based monomers to tune the amphiphilicity and thermoresponsive behavior of micro−/nanogels was demonstrated by the groups of Strumia and Calderón.[144] In their work, thermoresponsive networks were synthesized by thermoprecipitation copolymerization of diethyleneglycol methacrylate (DEGMA) as hydrophobic monomer with OEGMA as hydrophilic comonomer (tetraethylenglycol dimethacrylate [TEGDMA] was used as crosslinker). As expected, the VPTT of the nanogels could be fine-tuned by changing the ratio of DEGMA and OEGMA. In addition, the incorporation of another hydrophilic monomer such as 2-HEMA could be used to increase the VPTT. Since the resulting nanogels showed good biocompatibility, the concept was expanded in a second study by using magnetic nanoparticles as crosslinkers (Figure 11).[145] In this case, the same tendency was observed for tuning the VPTT by the ratio between DEGMA and OEGMA. Due to the magnetic properties of the colloids, they show great potential for guided therapy applications, photothermal release, and magnetic resonance imaging. Their potential as theranostic agents was demonstrated by encapsulating hydrophobic doxorubicin and triggering the release by Near Infrared (NIR) light. This was caused by a photothermal effect, that is, a triggered local heating due to the translation of light to heat by the magnetic nanoparticles. Since this caused the heat-induced collapse of the thermoresponsive microgels, a corresponding drug release was induced. In vivo and in vitro results demonstrated their potential in combinational therapy.

The VPTT of POEGMA-based nanogels can also be tuned through the utilization of hydrophilic methacrylate-functionalized dendritic polyglycerol (dPG) as crosslinker. In a study by Calderón and coworkers, it was demonstrated that an increasing amount of the hydrophilic crosslinker, led to an increase in VPTT.[146] The resulting amphiphilic nanogels were studied as dermal delivery vehicles since it was suggested that the amphiphilic structure enables favorable interactions with the amphiphilic skin barrier. It was observed that nanogels showed a better penetration into the stratum corneum when the temperature was higher than the VPTT. In this state, the amphiphilicity of the networks is most pronounced. Ultimately, the VPTT can also be varied by incorporation of different acidic monomers such as acrylic acid (AA) and itaconic acid. At pH values higher than the pKa of the respective acids, the increased hydrophilicity of the networks also increased the VPTT, as shown by the group of Strumia.[147] Overall, these systems display a multi-responsive swelling behavior that depends on temperature and pH.

The great versatility of OEG's was also used by Gan and collaborators to combine the amphiphilic nature of OEG-based nanogels with redox-sensitive properties.[148] At first, it was demonstrated how the VPTT can be

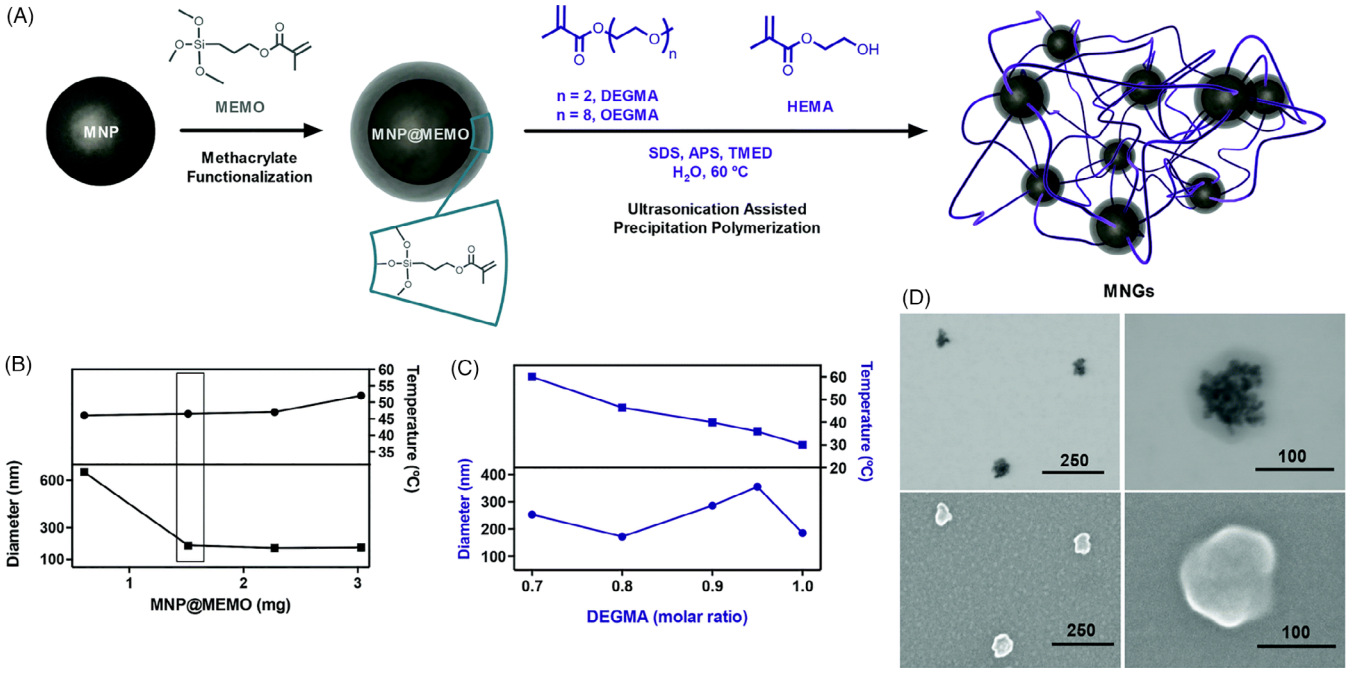

FIGURE 11 (A) Schematic representation of the synthetic route to magnetic OEG-based nanogels. Size and LCST depend on: (B) amount of magnetic nanoparticles and (C) ratio of DEGMA:OEGMA monomers, which can be used to tune the amphiphilicity of the system. (D) TEM/SEM images show the successful preparation of composite materials. Reproduced from ref. 145 with permission from copyright © 2020, Royal Society of Chemistry. DEGMA, diethyleneglycol methacrylate; LCST, lower critical solution temperature; OEGMA, oligoethylenglycol methacrylate

accurately tuned by adjusting the comonomer composition in a precipitation polymerization of OEGMA, DEGMA, and AA. Tuning the amphiphilicity could be used to obtain a VPTT close to 37°C and introduce pH responsiveness. In addition, N,N-bis(acryloyl)cystamine (BAC) was employed as disulfide-bearing crosslinker, thus introducing redox-responsiveness. These amphiphilic nanogels were able to incorporate doxorubicin and the triggered release was demonstrated. The hydrophobic/hydrophilic properties of these systems were evaluated in function of the pH. On one hand, they evaluated the interaction of the nanogels at different pH with fetal bovine serum. It was found that at lower pH (6.5) the nanogels showed higher protein absorption than at higher pH (7.4). This suggests a more hydrophobic state at acidic pH. In addition, it was shown that at pH 6.5, a higher amount of nanogels were phagocytosed by RAW264.7 macrophage cells, thus further confirming the hydrophobic nature of the nanogel at lower pH. Finally, triggered release of doxorubicin in response to the intracellular GSH was shown, demonstrating the potential of this material as nanocarrier for effective intracellular delivery.

In addition to the OEGMA monomers, another monomer widely employed for thermoprecipitation polymerization is NIPAM. While colloidal systems that solely use NIPAM have been extensively described, the copolymerization with hydrophobic or hydrophilic comonomers to tune the network amphiphilicity is less described. Such amphiphilic nanogels were also developed by the group of Gan as new drug delivery vehicles.[149] In their work, the thermoresponsive amphiphilic Poly(N-isopropylacrylamide) (PNIPAM) network was combined with hydrophilic methylallyl amine moieties. In addition, sulfobetaine methacrylate was employed for introducing hydrophilic zwitterionic features in the nanogel network. The resulting amphiphilic networks were crosslinked by incorporating N,N-bis(acryloyl) cystamine as disulfide-bearing crosslinker, providing redox responsiveness as demonstrated in their previous work.[148] The temperature and redox-sensitive amphiphilic nanogels were used to deliver doxorubicin upon NIR light irradiation and GSH influence. Here, NIR light induced a photothermal effect of encapsulated indocyanine green. This localized heating caused a collapse of the gel particles promoting the release of the drug. Additional degradation of the disulfide crosslinker by GSH further induced drug release, thus rendering these nanogels an interesting dual-response system for cancer therapy (Figure 12).

Another hydrophilic comonomer that was used to tune the amphiphilicity of PNIPAM networks is 2-acrylamido-2-methyl propane sulfonic acid (AMPS). Atta and coworkers reported the synthesis of amphiphilic nanogels based on NIPAM and AMPS using divinylbenzene (DVB) and N,N′-methylenbis(acrylamide) (BIS) as crosslinkers.[150]

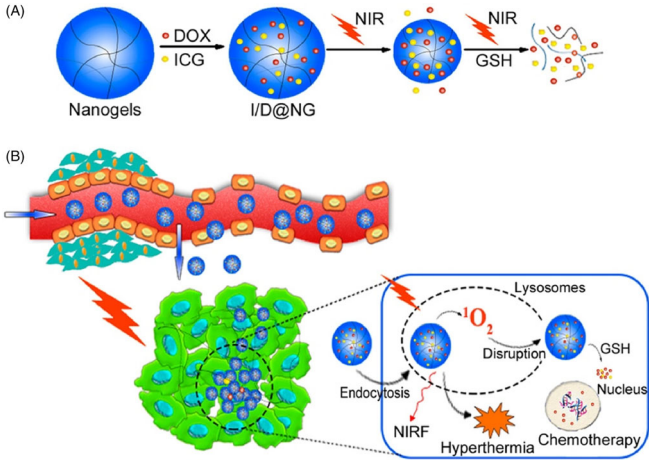

FIGURE 12 Amphiphilic nanogels as dual-response systems for cancer therapy. (A) Schematic representation of encapsulation of doxorubicin and indocyanine green dye, NIR triggered released and nanogel degradation in presence of glutathione. (B) Representative scheme of action of smart nanogels inside the body. Reproduced from ref. 149 with permission from copyright © 2017, American Chemical Society

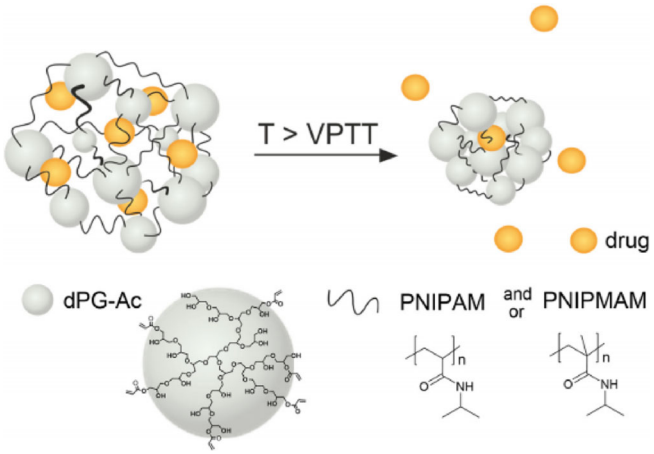

FIGURE 13 Swelling of thermoresponsive nanogels based on NIPAM and NIPMAM monomers below and above the VPTT leading to triggered release of drugs. Reproduced from ref. 154 with permission from copyright © 2019, Elsevier Ltd. NIPAM, *N*-isopropylacrylamide; NIPMAM, N-isopropoyl methacrylamide; VPTT, volume phase transition temperature

The amphiphilicity of the nanogel networks enabled their utilization as colloidal surfactants, thus preparing Pickering emulsions. This was demonstrated by their potential to stabilize aqueous emulsion polymerizations. In follow-up studies, they evaluate the potential of these nanogels as thin film coatings to protect surfaces from corrosion.[151] In addition, a core-shell nanogel with a polyvinyl alcohol core and NIPAM, AMPS shell was evaluated.[152] Due to the amphiphilic nature, the nanogels were able to adapt to the surrounding environments and change the wettability and adhesion of different species, thus acting as a protecting film. The researchers demonstrated that both nanogels presented corrosion inhibition on steel surfaces in acidic conditions.

Apart from the introduction of such hydrophilic comonomers, another strategy to increase network hydrophilicity, as shown before, is the incorporation of hydrophilic crosslinkers such as dPG.[146] Employing this strategy, the group of Calderón synthesized PNIPAM based nanogels using acrylated dPG as crosslinker.[153] They demonstrated that an increasing amount of crosslinker increased the nanogels' VPTT, thus suggesting an increase of hydrophilicity of the system. These nanogels presented high biocompatibility, thus exhibiting high potential as tunable nanocarriers in drug delivery applications.

In a second study, the structural influence of comonomers was investigated by the same group. They examined nanogels based on NIPAM and N-isopropoyl methacrylamide (NIPMAM) for temperature triggered protein delivery.[154] It is known that the extra methyl group in PNIPMAM induces a shift of the LCST to higher temperatures. Thus, the influence of the ratio between NIPAM and NIPMAM on the amphiphilicity of the system and the VPTT was examined. In these systems, acrylate-functionalized hPG was used as hydrophilic crosslinker (Figure 13). As expected, it was shown that the VPTT increased with the amount of NIPMAM. Using bovine serum albumin as model protein cargo, the potential of these amphiphilic structures for dermal delivery applications was examined. It was found that the nanogels with VPTT values lower than 37°C successfully promoted the penetration of the encapsulated macromolecule.

In conclusion, the synthesis of amphiphilic nanogels through a one-pot thermo-precipitation polymerization is an attractive choice due to its simplicity. Yet, multiple reaction parameters such as monomer (and crosslinker) solubility, reactivity, and diffusion must be considered. In addition, the scope of suitable monomers is limited since a thermoresponsive behavior of the polymer must be ensured. This also limits the incorporated amount of functional co-monomers. For example, hydrophilic comonomers can only be integrated to a certain extend since the increase in VPTT requires higher reaction temperatures to guarantee thermoprecipitation. This, however, might hinder the utilization of labile crosslinkers or the encapsulation of sensitive biomolecules during the synthesis. Finally, varying the network amphiphilicity by adjusting the feed composition of different monomers can lead to changes in the micro−/nanogel morphology, thus demonstrating the need for optimization of process conditions, for example, by sequential addition of monomers.

2.2.2 | Miniemulsion polymerization

Miniemulsions are kinetically stable emulsions prepared by applying high-shear forces (e.g., through ultrasound) to a mixture of immiscible liquid phases, for example, oil and water. In the presence of a surfactant and a cosurfactant, stable and narrowly dispersed droplets in the size range between 50 and 500 nm are generated.[155] While the surfactants limit the coalescence of the droplets, the cosurfactants are unique to the miniemulsion systems. These compounds act as osmotic pressure agents to counteract the Laplace pressure in the droplets, thereby hindering Ostwald ripening. In conventional miniemulsions (oil in water), the osmotic agent is an ultrahydrophobic molecule (e.g., hexadecane), whereas in inverse miniemulsions (water in oil) it is an ultrahydrophilic compound such as sodium chloride.[156–158] As a result, the net diffusion of the monomers in and out of the droplets is limited and the droplets act as "nanoreactors" that contain the same composition as the dispersed phase before the emulsification. Due to these characteristics, miniemulsion systems are of high interest for the preparation of polymer nanoparticles, especially through radical polymerizations in the dispersed droplets.[156]

Micro−/nanogels can be synthesized with this technique by using mixtures of monomers and bifunctional crosslinkers in the dispersed phase. A schematic representation of the synthesis of amphiphilic nanogels through miniemulsion polymerization is depicted in Figure 14. One of the benefits of the "nanoreactor" principle is the isotropic distribution of monomer(s) and crosslinker in the nanodroplet. Since this translates to the network gradual core-shell structures that are often observed in precipitation polymerizations, can be generally avoided. In contrast to oil-in-water systems, inverse miniemulsion polymerizations often use an aqueous solution of hydrophilic and ionic monomers dispersed in a continuous phase of organic solvents or oils.[156,159,160] Both, miniemulsion and inverse miniemulsion, are well-known methodologies for the synthesis of micro−/nanogels due to their synthetic versatility, the narrow size distribution of the resulting micro−/nanogels, and the facile introduction of active molecules (crosslinkers, cargoes, functionalities, etc.) during the synthesis.[66,132,161] Yet, drawbacks to consider include use of surfactants, purifications steps, and transfer from organic solvents to an aqueous phase for inverse systems.

Using miniemulsion polymerizations for the preparation of amphiphilic micro−/nanogels is challenging due to the different solubility of hydrophilic and hydrophobic monomers in the dispersed and continuous phase. Employing miniemulsions, Pich and collaborators reported multicompartment microgels with degradable hydrophobic domains.[162] For this, they used a synthetic trick to enhance the distribution of hydrophilic and hydrophobic groups in the network: the miniemulsion contained the molten monomer VCL as dispersed phase in water. The crosslinkers BIS and hydrophobic star-shape acrylate functionalized poly(ε-caprolactone) (PCL) were then dissolved in the molten VCL. Subsequent polymerization of this mixture yielded PVCL microgels with hydrophobic PCL pockets. These materials could be used to incorporate hydrophobic cargoes such as NR and ibuprofen. More importantly, the encapsulation efficiency increased when increasing the amount of star PCL crosslinkers, thus demonstrating that the loading can be fine-tuned by changing the amount of hydrophobic domains in the network of amphiphilic micro−/nanogels. It was demonstrated that the release of the payloads is based on diffusion and can be combined with degradation of the nanogels due to the enzymatic degradability of the PCL crosslinker.

Using a similar synthetic strategy of a molten VCL dispersed phase, the same group recently developed amphiphilic microgels based on VCL as hydrophilic monomer and 4-tert-butylcyclohexylacrylate (TBCHA) as hydrophobic monomer with BIS as crosslinker (Figure 15).[163] It was shown that the co-monomer ratios

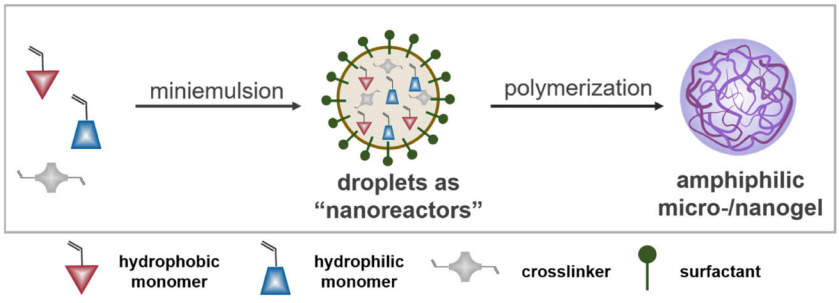

FIGURE 14 Schematic representation of using miniemulsion polymerization as a synthetic pathway for the synthesis of amphiphilic micro−/nanogels. The copolymerization of two monomers occurs in the droplets, since net diffusion is limited, thus generating "nanoreactors." The incorporation of both monomers into the network depends on the different solubility in continuous and dispersed phase

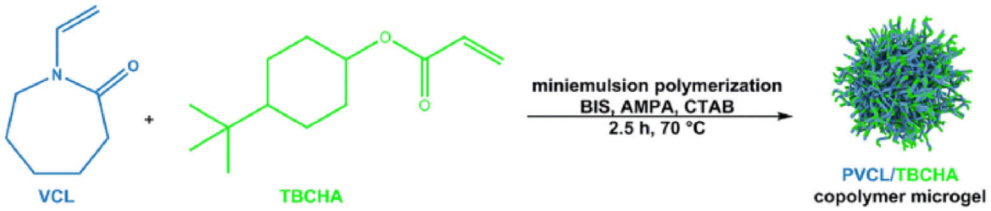

FIGURE 15 Synthetic pathway to p(PVCL-*co*-TBCHA) microgels: Precipitation polymerization of VCL in presence of TBCHA with BIS as crosslinker. Reproduced from ref. 163 with permission from copyright © 2020, Elsevier Ltd. TBCHA, 4-tert-butylcyclohexylacrylate; VCL, vinylcaprolactam

can be tuned easily and that the hydrodynamic diameter of the particles decreases when increasing the hydrophobic monomer content. Also, the thermoresponsive behavior was suppressed when the fraction of hydrophobic monomer exceeded the hydrophilic monomer content. This study showed that the amphiphilicity of the microgels could be tuned easily by varying the hydrophilic/hydrophobic ratio, thus enabling control over colloidal properties such as swelling and thermoresponsiveness.

All in all, the miniemulsion approach represents an appealing strategy for the synthesis of amphiphilic micro−/nanogels due to the narrow size distributions as well as uniform distribution of both hydrophobic and hydrophilic segments throughout the polymer network. Nevertheless, tuning the hydrophobic/hydrophilic balance is limited by the solubility of the selected monomers in the continuous and dispersed phase.

2.2.3 | Emulsion polymerization

Emulsion polymerizations are well-known and industrially established methodologies for the scalable synthesis of polymeric nanoparticles from water-immiscible vinyl monomers.[164,165] A major advantage of these systems is the good control over particle size and size distribution without the need for high-shear forces. In contrast to miniemulsion polymerizations, where a net diffusion of monomers is suppressed, monomer diffusion represents a key step in emulsion polymerizations. This statistical process causes a very narrow particle size distribution.[65,164,165]

In general, the emulsion polymerization consists of a poorly water-soluble vinyl monomer, water, a surfactant, and a water-soluble initiator. In this process, mainly three regions can be defined: (a) In the first step, the monomer forms large, microscopic droplets stabilized by the surfactant. In addition, surfactant micelles are present in the aqueous phase and contain small amounts of monomers. Radicals formed in the aqueous phase start polymerizing the very low concentrations of dissolved monomer. The resulting oligomeric radicals grow until they become hydrophobic and enter the hydrophobic core of the surfactant micelles. (b) The second step involves the particle growth. Here, the polymerization continues within the micellar cores. In this stage, the large monomer droplets continuously supply monomer to the growing particles by diffusion through the aqueous phase. (c) In the third stage, the monomer droplets vanish and the polymerization continues in lower rate consuming all the monomers available. Under surfactant free conditions, water-soluble initiators such as potassium peroxodisulfate (KPS) introduce charged end groups to initiated hydrophobic oligomers in the water phase, thereby generating surfactant-like oligomers in situ.[166,167] A general description of the process is represented in Figure 16.

Advantages of this approach are the absence of organic solvents and the avoidance of tedious purification steps, particularly for surfactant free systems. However, due to the diffusion-based mechanism, the isotropic

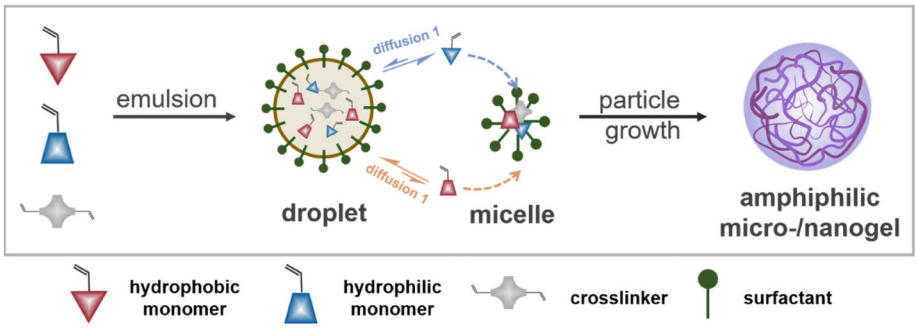

FIGURE 16 Schematic representation of the synthesis of amphiphilic micro−/nanogels by emulsion polymerizations of hydrophilic and hydrophobic monomers. The incorporation of both monomers into the network crucially depends on their solubility, reactivity, and diffusion properties

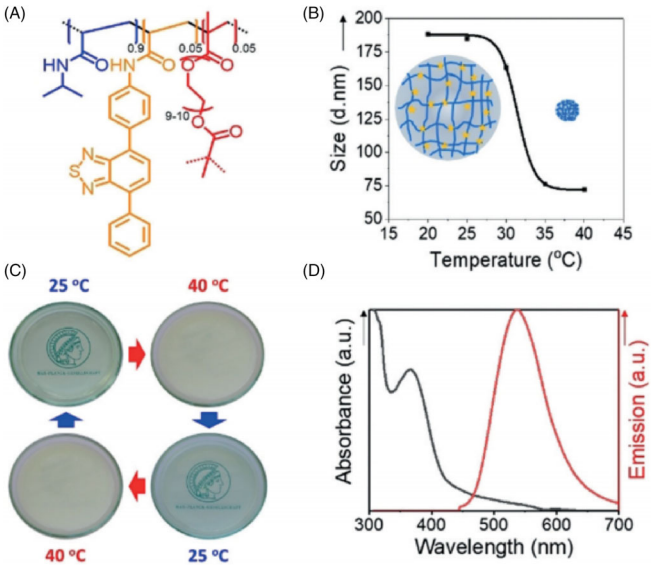

FIGURE 17 (A) Chemical structure of amphiphilic nanogels with photocatalytic moieties based on thermoresponsive NIPAM monomer. (B) Temperature-dependent turbidimetry showing the thermoresponsive behavior of the nanogels. (C) Optical examination of temperature-dependent light transmission in nanogel suspensions. (D) Absorbance and emission spectra of NG's. Reproduced from ref. 16 with permission from copyright © 2019, Wiley-VCH GmbH. NIPAM, *N*-isopropylacrylamide

incorporation of different monomers and crosslinkers in the resulting network is hindered. In general, the monomers should rather be poorly soluble in water. Moreover, since diffusion coefficients in the aqueous phase are linked to monomer hydrophilicity, a combination of such hydrophobic monomers with hydrophilic comonomers can result in core-shell morphologies. Consequently, incorporating large amounts of hydrophilic (co-) monomers to obtain amphiphilic nanogels is challenging.

Regarding this challenge, the group of Zhang and Landfester developed dual-responsive photocatalytic polymer nanogels.[16] In this case, an amphiphilic and thermoresponsive network based on NIPAM and polyethyleneglycol dimethacrylate (PEGDMA) contained a photocatalytic active monomer, N-(4-(7-phenylbenzo[c][1,2,5]thiadiazol- 4yl)phenyl)-acrylamide (PhBTPhAM) (see Figure 17). The acrylamide group in the photocatalytic monomer was chosen to ensure similar reactivity as NIPAM, thus promoting the incorporation of the hydrophobic catalytic species throughout the whole network. The particle preparation was suggested to occur via a surfactant free emulsion polymerization. The LCST of the resulting nanogels was 31.6°C, which is slightly lower than the transition temperature of pure PNIPAM nanogels, which can be attributed to the incorporation of the hydrophobic photocatalytic moieties in the network. Temperature-dependent swelling controlled the access of reagents to the photocatalytic unit, thus producing switchable deactivation/activation of the photo catalytic sites. Also, due to the stark transition of the size when increasing the temperature, nanogel precipitation occurs, thus allowing the efficient recovery of the catalyst from the reaction solution which facilitates recycling of the nanomaterial. Therefore, this study demonstrated the utility of these nanogels as switchable nanocatalysts for various reactions.

The challenge of randomly incorporating different monomers in the network was observed by Serrano-Medina et al.[168] They investigated a one-pot surfactant free emulsion polymerization of hydrophilic PEGMA with hydrophobic 2-methacry-loyloxybenzoic acid (2MBA) and amphiphilic NIPAM in the presence of different crosslinkers (e.g., ehtylenglycol dimethacrylate [EGDMA]). This synthetic approach resulted in a clear core-shell morphology due to the different hydrophilicity of the monomers. In the resulting dual-responsive nanogels, PEGMA formed the shell and stabilized the particles, while crosslinked P(2MBA-*co*-NIPAM) formed the pH and temperature-responsive core. The presented synthesis was fast and feasible to scale up, with a maximum crosslinking percentage of 5 mol%.

It becomes obvious that circumventing such core-shell morphologies with mixtures of hydrophilic and hydrophobic monomers is far from trivial. To address this challenge and realize amphiphilic nanogels with a more random distribution of both monomers in the network, Bahramian and coworkers developed a seeded semi-batch emulsion polymerization strategy.[169] In this approach, hydrophilic and ionizable AA was combined with hydrophobic butyl acrylate (BA) and EGDMA as crosslinker (Figure 18). Key to an isotropic morphology is that after an initial formation of growing particles, additional monomer mixture is added to swell the seed particles with both monomers. Since this was realized in a one-pot approach without requiring protecting groups for the AA or expensive/toxic solvents, the strategy is scalable and highly promising. Interestingly, the nanogels exhibit a dual responsive behavior: On one hand, the presence of AA caused a pH-sensitive swelling profile due to protonation/deprotonation. On the other hand, a thermoresponsive behavior was observed due to the presence of BA hydrophobic moieties. It was suggested that these groups act as additional physical crosslinks, which can be broken at higher temperatures. Ultimately, it was reported that the morphology of the nanogels changes as function of the pH: at acidic pH, they show a uniform spherical shape. At intermediate pH, a core-shell structure is observed and when increasing the pH, the morphology reverts to a spherical structure. At very basic conditions, nanogels transformed into a thin-walled

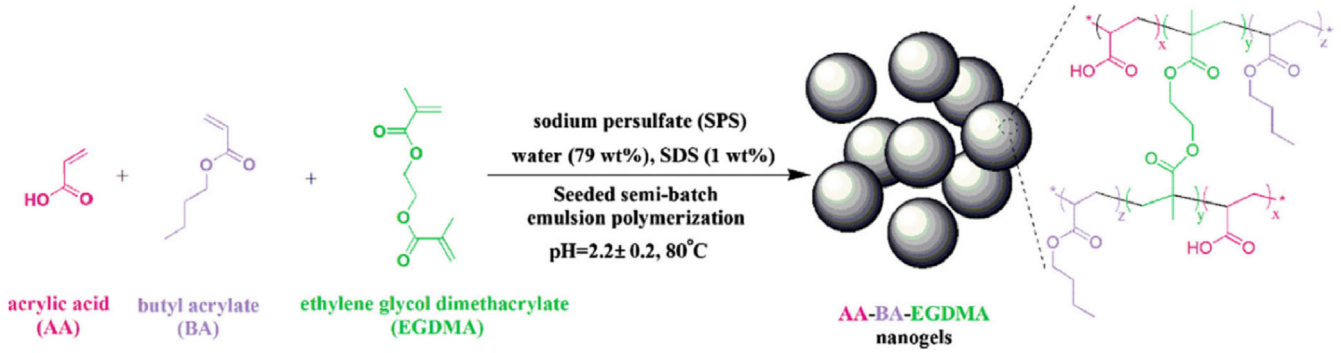

FIGURE 18 Schematic representation of synthesis of amphiphilic nanogels based on AA and BA by seeded semi-batch emulsion polymerization. Reproduced from ref. 169 with permission from copyright © 2019, Elsevier Ltd. AA, acrylic acid; BA, butyl acrylate

sphere. It was proposed that this behavior could be attributed to a radical change in copolymer composition and chemical crosslinking density. While the seeded semi-batch strategy can avoid a distinct core-shell morphology, the spatial network composition is still affected by the partitioning of monomers in the different co-existing phases. Thus, there remains a tendency toward a radial distribution with higher contents of BA and crosslinker in the nanogel center and more AA toward the surface.

The semi-batch emulsion approach was also used by Atta and coworkers to incorporate hydrophobic silver nanoparticles capped with oleic acid into amphiphilic microgels. For this, they combined hydrophobic styrene (St) with AMPS as hydrophilic monomer and NIPAM as thermoresponsive monomer.[170] In this study, the nanogels were formed in the presence of the oleic acid capped silver nanoparticles. Hydrophobic St was used to enhance interaction with the hydrophobic capping agent, thus promoting the incorporation of the inorganic materials in the polymeric matrix. For this, St and NIPAM were first copolymerized in the presence of the hydrophobic silver nanoparticles. In a second step, an aqueous solution containing AMPS, NIPAM, and BIS was added, and the polymerization continued. In this report, only around 5 wt% of the hydrophilic monomer (related to the weight of NIPAM and St), AMPS, was incorporated. This demonstrates the challenging introduction of large amounts of hydrophilic monomers. In the final application, the silver nanoparticles are employed as corrosion inhibitor since they can block the active sites of the metal surface, providing hardness, durability, and thermal stability.[171] To demonstrate this potential, the hybrid nanogels were tested as a corrosion protective film for steel. Resulting nanogels inhibited both anodic metal dissolution and cathodic reaction. In addition, they were effective corrosion inhibitors for steel in acidic media, which demonstrates their potential for applications in protective film coatings.

In a similar seeded emulsion approach, Lally et al.[172] studied the influence of microgel composition on pH-triggered swelling and gelation. Employing a seeded emulsion copolymerization, they synthesized a library of pH-responsive microgels by varying the hydrophobicity of the monomers and the crosslinker. Microgels were prepared from either ethyl acrylate (EA), methyl methacrlyate (MMA), or butylacrylate (BMA) as hydrophobic monomers. These were combined with MAA as acidic hydrophilic comonomer and two different crosslinkers, butanediol diacrylate (BDDA) or EGDMA. In this approach, a hydrophobic monomer, comonomer MAA, and the crosslinker were first copolymerized in an emulsion polymerization. In a second step, more monomer solution and initiator were added. All microgels presented a pH-responsive behavior that is influenced by the amphiphilicity. Microgels with the most hydrophobic compositions (e.g., MMA/MAA/EGDMA and BMA/MAA/BDDA) presented higher pKa values. Moreover, swelling capacity of the microgels was assessed. Comparing the hydrophobic BDDA to the more hydrophilic EGDMA, all BDDA microgels showed lower swelling than the EGDMA ones. Also, the influence of pH on the swelling of the microgels was studied. Microgels with the most hydrophobic composition, BMA/MAA/BDDA, showed the lowest swelling degree. As expected, when increasing the amount of the hydrophilic/pH-responsive monomer, MAA, the pH-triggered swelling degree increased. Finally, the most hydrophilic microgels showed gelation due to jamming of the swollen particles. In comparison, gelation for the more hydrophobic microgels was suggested to depend on repulsive interparticle interactions. It was proposed that materials with low swelling capacity but hydrophobic microdomains, are highly charged with strong electrostatic repulsion between particles. Overall, these experiments demonstrate the crucial influence of network amphiphilicity on the overall material properties.

TABLE 2 Summary of analyzed amphiphilic nanogels obtained by incorporation of hydrophobic and hydrophilic moieties during the synthesis via emulsion, miniemulsion or thermoprecipitation polymerization

Approach	Hydrophobic monomers	Hydrophilic monomers	Crosslinker	Sizes	Stimuli response	Applications
Thermoprecipitation	DEGMA, NIPAM, VCL	VCL, OEGMA, NIPAM, AA, IA, HEMA, MEA, dPG, SBMA, MAA, AMPS, PVA	TEGDMA, BIS, MNP@MEMO, dPG, BAC	65–765 nm PDI: 0.1–0.2	Thermo, redox, pH, magnetic responsive	Mainly DDS, film coating
Miniemulsion	Star-PCL, TBCHA	VLC	Star-PCL, BIS	150–800 nm PDI: 0.05–0.9	Thermoresponsive, enzymatic degradable	DDS
Emulsion	NIPAM, 2MBA, PhBTPhAM, BA, St, EA, MMA, BMA	NIPAM, 2MBA, PEGMA, AA, MAA, AMPS	EGDMA, DVA, BIS, BDDA	60–750 nm PDI: 0.1–0.2	Thermo, pH, responsive	DDS, film coating, catalysis

Abbreviations: AA, acrylic acid; AMPS, 2-acrylamido-2-methyl propane sulfonic acid; BAC, N,N-bis(acryloyl)cystamine; BDDA, butanediol diacrylate; DEGMA, diethyleneglycol methacrylate; DDS, drug delivery systems; dPG, dendritic polyglycerol; EGDMA, ehtylenglycol dimethacrylate; HEMA, hydroxyethyl methacrylate; MAA, methacrylic acid; MEA, 2-methoxyethyl acrylate; MMA, methyl methacrlyate; NIPAM, *N*-isopropylacrylamide; OEGMA, oligoethylenglycol methacrylate; PEGMA, polyethylene glycol methacrylate; VCL, vinylcaprolactam; 2MBA, 2-methacry-loyloxybenzoic acid.

In summary, these examples demonstrate the synthetic challenges in randomly incorporating hydrophilic and hydrophobic groups in micro−/nanogel networks by emulsion-based approaches. As mentioned before, drastic differences in monomer solubility and reactivity often lead to core-shell morphologies, thus limiting the synthetic versatility. In addition, parameters such as surfactants and solvents must be considered. Furthermore, they also offer only limited control to overcome the partitioning effects. Thus, with advances in seeded semi-batch polymerizations, it is envisioned that gradients, which would lead to core-shell structures could be counteracted by feeding the monomers respectively. While such approaches require thorough optimization, they are already being investigated in the area of precipitation polymerization to control the radial distribution of crosslinking density.[173] Translating such concepts to control the radial distribution of amphiphilicity bears great potential for future materials.

2.2.4 | Concluding remarks

In this section, different approaches were evaluated to incorporate hydrophobic and hydrophilic moieties during the colloidal synthesis. For this, the copolymerization of different monomers in emulsion, miniemulsion or thermoprecipitation polymerization was discussed. In Table 2, the different monomers, crosslinkers, physicochemical properties and applications of each strategy are summarized (for a table of with detailed properties of amphiphilic micro/nanogels obtained by such polymerizations see Table S2 in ESI). As seen in Table 2, micro−/nanogels afforded by these strategies are in the size range from 60 to 800 nm, with miniemulsion polymerizations only showing 150 nm as lowest reported diameter. Mainly, this demonstrates that these synthetic tools allow tuning the size of such colloidal materials over a broad range. For this, usually the synthetic conditions are varied, for example, the type and concentration of surfactants is changed. Regarding the width of the size distributions, it can be seen that in all cases respectable PDI values are reported, thus indicating fairly uniform particle sizes. Interestingly, no dramatic improvements in the PDI's for the emulsion-based systems are observed when compared to the miniemulsion/thermoprecipitation polymerizations. Generally, emulsion polymerization is the technique that leads to very narrow size distribution of nanoparticles due to the underlying statistical distribution of monomers to the different polymerization loci. Nevertheless, since this distribution is based on diffusion of the monomers from large droplets to the growing micelles, drastically different diffusion coefficients of the required hydrophilic and hydrophobic monomers can disturb this process. Since this difference in monomer solubility influences all particle preparation methods, it is assumed that all size distributions are strongly governed by this factor, thus reducing differences that are normally observed for particles from only one monomer type.

Regarding the thermoprecipitation polymerization, an additional benefit is that exhaustive purifications steps are avoided. Nevertheless, it needs to be considered that the utilization of hydrophilic monomers leads to an increase of the VPTT. Since thermoprecipitation polymerization requires a reaction temperature higher than the VPPT for the successful particle synthesis, the incorporation of such hydrophilic monomers is limited.

Independent of the synthetic differences, the majority of the reported systems present a thermo-responsive behavior, which leads to potential applications in nanomedicine, in particular for triggered drug delivery. Due to colloidal sizes around 150–200 nm, these materials are often suggested for cancer therapy via intravenous administration, thus taking advantage of the enhanced permeability and retention effect (EPR) for passive targeting. Also, it was demonstrated that such nanogels can be used as nanocarriers for dermal delivery. These applications benefits from the amphiphilic nature and soft mechanical properties that enhances the interaction with the amphipathic skin barrier. In other applications, the potential of such micro−/nanogels is being investigated in areas such as catalysis and film coating.

2.3 | Introducing network amphiphilicity after particle synthesis: Internal functionalization of reactive precursor particles

The biggest challenge in preparing amphiphilic micro−/nanogels is to ensure the random distribution of hydrophilic and hydrophobic units throughout the network. As shown in the previous sections, conventional colloidal synthetic strategies only give limited access to such unique networks. On one hand, crosslinking of self-assembled amphiphilic random copolymers lacks design flexibility due to the strict requirements in polymer architecture and composition for self-assembly.[64,88] On the other hand, copolymerization of hydrophobic and hydrophilic monomers in colloidal systems (e.g, precipitation polymerizations or [mini-]emulsions) only works for a small set of monomers with similar solubility and reactivity. Moreover, these approaches require the preparation of a new batch each time the network amphiphilicity is varied. This often results in batch-to-batch variations of colloidal properties like particle size, morphology, size distribution, and crosslinking density. Consequently, decoupling the hydrophobicity from the colloidal features is challenging, thus limiting the determination of accurate structure–property relations.

To address these challenges, a new concept is emerging to introduce the network amphiphilicity after the particle synthesis. This concept is inspired by well-established post-polymerization modification strategies in polymer chemistry where similar problems are addressed.[88] For non-crosslinked polymers, varying the functionalization of one reactive precursor polymer enables the preparation of polymer libraries with comparable features such as similar degrees of polymerization or comparable molecular weight distributions (dispersities).[101,174,175] The translation of this concept to colloidal synthesis uses reactive precursor particles for a post-particle-formation functionalization, thus ensuring similar particle sizes and size distributions. In general, the concept employs monomers with reactive moieties that are orthogonally reactive to the polymerization. Once polymerized, the resulting pendant reactive groups can be transformed without changing the degree of polymerization of the original polymer.[176] This allows the random incorporation of multiple different groups along the polymer chains. In colloidal particles, the first polymerization step includes a particle formation method to give a master batch of crosslinked polymer particles with reactive groups in the network. This master batch of particles can then be functionalized to install the desired network functionalities afterwards through a variety of either physical interactions or covalent reactions. As a result, even very different functional groups can be distributed throughout the polymeric network without altering the colloidal properties of the particles.[88]

The synthetic versatility of reactive precursor particles is of high interest for the formation of amphiphilic micro−/nanogels since it allows to circumvent the above-mentioned problems that occur upon incorporating hydrophilic and hydrophobic groups during the colloidal synthesis. Using hydrophilic and/or hydrophobic groups to functionalize preformed reactive networks enables to randomly distribute these moieties in the particles, thus preventing core-shell morphologies that are often observed for other strategies. Moreover, the ratios between hydrophobic and hydrophilic groups can be varied in order to tune the internal network compositions of nanogels, thus creating a library of nanogels with well-tuned amphiphilicity and constant colloidal features.[177–179]

To prepare such internal amphiphilic networks, mainly four synthetic options are available depending on the structure and reactivity of the preformed nanoparticles (Figure 19). (a) If the master batch of nanoparticles is already hydrophilic, partial functionalization with additional hydrophobic moieties results in an amphiphilic network. (b) In direct contrast, hydrophobic nanoparticles can be modified partially with hydrophilic functional groups. (c) Partial hydrophilicity can also be introduced into hydrophobic networks by the removal of hydrophobic protecting groups, for example, through hydrolysis. (d) Ultimately, reactive nanoparticles can be post-functionalized with both hydrophobic and hydrophilic moieties.

The advantages and disadvantages of these strategies depend on the different (colloidal) synthetic conditions.

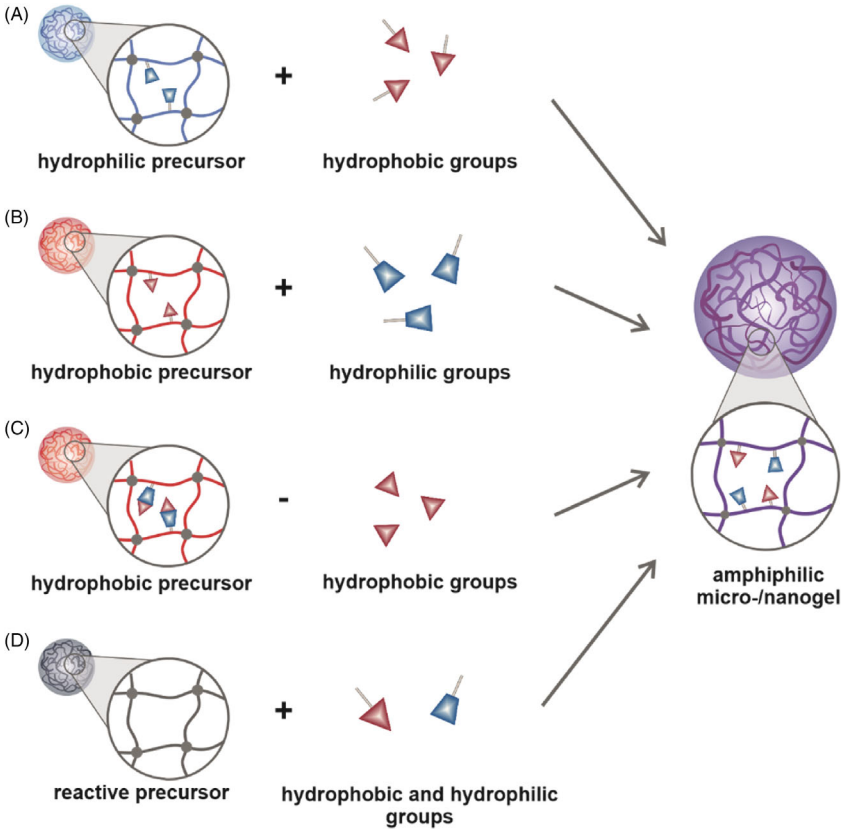

FIGURE 19 Representation of the four possible pathways to achieve amphiphilic nanogels through post-functionalization of precursor nanogels. (A) Post-functionalization of hydrophilic precursor nanoparticles with hydrophobic moieties, (B) post-functionalization of hydrophobic precursor nanoparticles with hydrophilic moieties, (C) deprotection of hydrophilic moieties of a hydrophobic precursor nanoparticle, for example, hydrolysis, (D) post-functionalization of reactive precursor nanoparticles with both hydrophobic and hydrophilic functional moieties

For instance, approaches (a), (b), and (c) only require one reactant. However, this also limits their versatility. For example, different hydrophilic groups can be introduced easily into a specific reactive hydrophobic particle. However, changing the type of hydrophobic groups in such systems requires the synthesis of a new particle batch with potential different reactivity and colloidal features. In contrast, strategy (d) allows better control over the amphiphilicity since both, hydrophilic and hydrophobic, groups are introduced in the reactive network. However, this strategy may require a thorough optimization of controlling the amphiphilic balance, that is, optimizing the feed ratio of hydrophobic and hydrophobic groups to access a certain incorporation.

In addition to these specific challenges, all approaches require a careful selection of the solvent for the functionalization reaction. As a crucial parameter the solvent needs to fulfill certain requirements. It should: (1) solubilize the functional groups (hydrophobic, hydrophilic, or both) and (2) ensure swelling of the polymer network. This is needed to guarantee penetration of the functional groups into the micro−/nanogel, thus guaranteeing homogeneous modification of the whole particle.

Overall, only few synthetic strategies focus on the post-functionalization of the interior networks of precursor nanoparticles (NP's). However, this strategy is currently evolving. Thus, in this section, we highlight different approaches to realize amphiphilic micro−/nanogels through precursor nanoparticle modification.

2.3.1 | Network functionalization through physical interactions

Amphiphilic micro−/nanogel can be prepared by introducing hydrophilic and hydrophobic groups into the network via physical interactions. For this strategy, reactive precursor micro−/nanogels need to contain specific groups that can allow physical bonds with different functional groups. Generally, a wide variety of such bonds is available in the materials science area and includes ionic interactions, hydrogen bonds, and host-guest complexations.[180–184] While these strategies are highly advantageous due to the mild reaction conditions, they can lack specificity and stability due to the non-covalent interactions. This labile character can also be used to impart stimuli-responsive properties, for example, triggering a release of cargoes.

Synthetically, this approach is mostly realized by hydrophilic networks, which contain functional groups that can physically interact with hydrophobic, or amphiphilic moieties. Especially acid–base interactions and hydrogen bonds have been investigated to functionalize internal networks. Using such strategies for the

preparation of amphiphilic micro−/nanogels will be discussed in the following section.

Acid–base interactions

Acid–base interactions play a key role in defining and tuning specific materials' properties in biology, chemistry, and physics.[185,186] This finds application in a variety of different fields including chromatography, medicinal chemistry, adhesions, and coatings.[187–189] Of special interest to such applications is the tunable strength of the bonds which is inherently defined by the pKa and pKb of the employed groups.[190–193] Also, external factors such as pH and ionic strength will influence the interaction, which can limit the stability and trigger the release of the electrostatically bound molecules, for example, for drug delivery.

In colloidal systems, acid–base interactions are mostly used for the generation of polyion complexes (polyplexes)[194–196] or for surface modification of the colloids.[197] Up to now, only few examples are reported to use this strategy for the introduction of amphiphilic network properties into micro−/nanogels. In these approaches, the precursor micro−/nanogels are mostly hydrophilic due to the acidic or basic groups required for functionalization. Introduction of amphiphilic properties then occurs through introducing the orthogonal functionality thereby generating acid–base pairs with reduced hydrophilicity. In addition, the molecular structure of the introduced functional groups can be used to further adjust the hydrophobicity.

This was demonstrated by Möller, Pich, and coworkers.[63] They established a simple route to synthesize amphiphilic microgels consisting of hydrophilic networks with hydrophobic domains. These structured microgels could be used to encapsulate and transport hydrophobic cargoes. In this example, the crosslinked precursor microgel is hydrophilic and is modified with hydrophobic molecules (strategy (A) in Figure 19). The hydrophilic polymer network was obtained by thermoprecipitation copolymerization of VCL, acetoacetoxyethyl methacrylate (AAEM), and vinylimidazole (VIm). The presence of the basic imidazole moieties in the resulting copolymer microgels allowed the incorporation of acidic wedge-shaped sulfonate molecules by acid–base interaction. The modification with such molecules containing C12 aliphatic chains (sodium 4-N-[30,-40,50-tris[dodecyloxy]benzamido] benzene-4-sulfonic acid) was carried out in tetrahydrofuran (THF) to guarantee their random incorporation in the swollen microgel network. When modified, microgels were re-dispersed in aqueous medium and the wedge-shaped amphiphiles self-assembled into discrete hydrophobic nanodomains in the interior of the colloid. The authors demonstrated that the network amphiphilicity could be modulated by two factors: First, by varying the amount of imidazole groups in the network

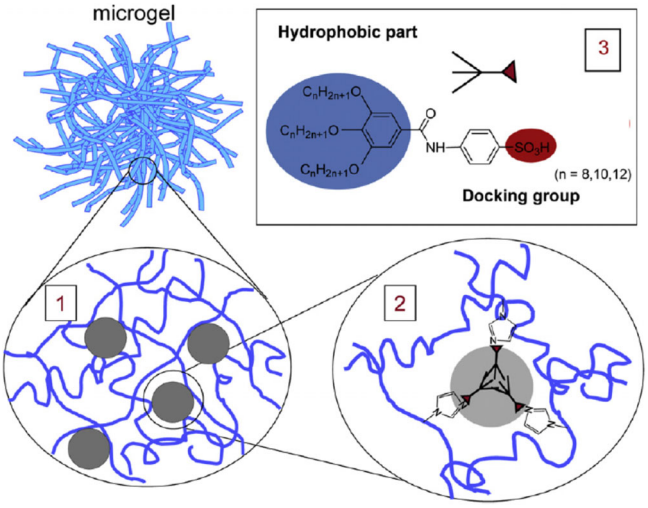

FIGURE 20 Schematic representation of amphiphilic nanogels by electrostatically incorporation of wedge-shaped molecules. Representation of (1) hydrophobic domains in the microgels and (2) electrostatic interaction between polymer network and wedge-shaped molecules. (3) Wedge-shaped molecule. Reproduced from ref. 198 with permission from copyright © 2012, Elsevier Ltd

during the synthesis of the precursor particles. Second, by changing the equivalents of added hydrophobic wedge-shaped molecules during network functionalization, that is, by changing the neutralization degree of the existing imidazole groups. The resulting microgels showed significant changes in properties such as surface charge, temperature, and pH responsiveness. For instance, a lower degree of neutralization led to a larger swelling of the nanogels whereas a higher degree of neutralization showed minimal swelling. In addition, the particle size was reduced when increasing the amount of VIm. This demonstrates that these parameters have a great influence on the aggregation of the hydrophobic wedges within the hydrophilic nanogel. Also, the thermoresponsive properties were affected by network functionalization. It was found that incorporation of a certain amount of hydrophobic wedge-shaped molecules causes the thermoresponsive behavior to disappear. The authors suggested that this effect could be attributed to the rigidity of the interior caused by additional hydrophobic interactions between the introduced wedge-shaped groups in the network. Finally, the encapsulation of hydrophobic cargoes was demonstrated by using NR as model compound.

The synthetic versatility of this approach was further demonstrated in follow-up studies by the same groups.[198] It was shown that the alkyl length of the amphiphilic wedge-shaped molecules influences the particle size and the environmental sensitivity of the microgels (Figure 20). An increase of the microgel size was observed when decreasing the chain length of the wedge-shape molecules. This was

attributed to decreased hydrophobic interactions between shorter wedge-shaped molecules, which reduce the additional hydrophobic crosslinking in the network, thus permitting higher swelling ratios. In addition, the microgels were loaded with NR and it was observed that upon heating, the dye absorbance showed a blue shift. This solvatochromic effect points toward an increasingly hydrophobic network interior at elevated temperatures. To assess the potential of such amphiphilic networks in drug delivery, a hydrophobic drug, dexamethasone was encapsulated, showing larger loading capacities and slower release kinetics in comparison to the unfunctionalized hydrophilic microgels.

While the synthetic implementation of such hydrophobic groups has been demonstrated successfully, understanding the resulting physicochemical properties these new materials required additional examination. Especially, the influence of hydrophobic functionalization on the resulting internal amphiphilic microenvironment remained unclear. To address this question, Pich and coworkers recently introduced wedge-shaped molecules that contain an additional azobenzene group as spectroscopic and kinetic probe.[199] This functionality was incorporated through the standard network modification strategy and can be used to determine the polarity of the microenvironment within the microgel. Upon heating, these systems presented a strong increase of the molar absorption of the azobenzene group, thus suggesting a temperature-induced increase of hydrophobicity in the interior of the polymer network. Furthermore, it could be demonstrated that an increase in the number of hydrophobic molecules in the network corresponds to an increase of hydrophobicity inside the microgel, that is, a reduction in polarity of the azobenzene microenvironment.

Thus, tuning the network amphiphilicity by incorporating hydrophobicity through electrostatic interactions is a straightforward synthetic approach. In this strategy, the amphiphilicity of the microgel can be controlled by changing both the amount and the structure of the incorporated hydrophobic molecules. Nevertheless, only a limited number of hydrophobic molecules can be incorporated without altering the colloidal stability of the system.

Hydrogen bond interactions

Hydrogen bond interactions can be employed as strong bonds in the design of various polymeric (bio-)materials.[200] Especially the utilization of multiple hydrogen bonds in one system shows a synergistic effect, that is, a stronger interaction that exceeds the sum of the single hydrogen bonds.[201–203] Thus, such designs are of great relevance in biological mechanisms and biomaterials where the formation of strong interactions under mild conditions is required, for example, folding of proteins and DNA to 3D structures.[204,205] Similarly, the specific interactions of multiple hydrogen bonds play a key role in various forms of molecular recognition, for example, in the active sites of enzymes.[206,207] Another relevant feature of these interactions is their dynamic nature. In synthetic polymeric systems this has been used, among others, to change the chemical and physical properties of gel networks or to adjust conductivity via tunable proton transport.[208,209]

Therefore, using these strong interactions to introduce either hydrophobic or hydrophilic moieties into micro−/nanogel networks is appealing due to the mild reaction conditions. Nevertheless, the strong influence of the reaction medium on the formation and stability of these labile bonds needs to be considered. Thus, utilization of this concept is still in its infancy and requires multiple hydrogen bonds per molecule to enhance the stability.

The benefits of multivalent interactions were demonstrated by the group of Atta who developed hybrid amphiphilic nanogels containing silica nanoparticles as hard crosslinking domains.[210] Stable incorporation of these inorganic materials into a polymeric gel network was achieved by using the large number of hydroxyl groups on the particle surface to form multiple hydrogen bonds with amide bonds in the polymer network. For this, acrylamide (AAm) and sodium AMPS were copolymerized in the presence of the crosslinker, BIS, and the silica nanoparticles, thus ensuring the successful incorporation. These hybrid systems were able to remove dyes and heavy metals from wastewater at neutral and slightly basic pH effectively at room temperature. This example demonstrates the possibility of introducing different inorganic nanoparticles in the polymer network and thus, tuning the amphiphilicity of the system. In addition, combining the properties of both organic and inorganic nanomaterials leads to promising features.

In summary, the possibility of tuning the amphiphilicity of micro−/nanogels by introducing hydrophobic or hydrophilic moieties in the network through hydrogen bond interactions represents an easy and straightforward approach. Nevertheless, the introduction of such moieties is limited both by the chemical composition of the particle network and the incorporated moiety. Thus, the introduction of large amounts of hydrophobic or hydrophilic moieties is hindered. In addition, such physical interactions are highly dependent on the environmental conditions, such as pH, ionic strength, and so on.

2.3.2 | Network functionalization through covalent bonds

In contrast to network functionalization via physical interactions, covalent modifications represent a more robust but still versatile pathway. In general, covalent

bonds ensure a more stable attachment of functional groups to the network but utilization of labile or dynamic covalent bonds can also be used to impart stimuli-responsive cleavage of the functional groups. This can be used to trigger a change in network properties, for example, swelling, degradability, and so on. While the stability of covalent bonds is of high interest, their formation also requires harsher reaction conditions than the physical bonds. These might not be suitable for every system. Thus, careful selection of the coupling strategy should be taken into consideration. For this, various synthetic methods are available as mentioned above in Figure 19. Network functionalization by covalent bonds can use: (a) hydrophilic polymer networks for modification with hydrophobic moieties, (b) hydrophobic networks for the introduction of hydrophilic functional groups, or (c) hydrophobic networks for the removal of hydrophobic protecting groups. Also, (d) reactive polymer networks can be functionalized with both hydrophobic and hydrophilic moieties. In this category a variety of different covalent reactions are available, for example, click chemistry, reactive ester reactions, and so on. This section highlights recent examples of amphiphilic micro−/nanogels obtained by covalent functionalization of precursor nanoparticles.

Deprotection of masked hydrophilic moieties

In this approach, completely hydrophobic nanoparticles are synthesized initially. These consist of a crosslinked copolymer network that contains at least two hydrophobic monomers. However, one of the monomers is only hydrophobic due to a hydrophobic protecting group, which masks a hydrophilic moiety. Thus, by removing these protecting groups after the particle synthesis, the hydrophilic monomers are unmasked and generate an amphiphilic network (in combination with the other non-labile hydrophobic monomers). Such labile hydrophobic protecting groups can include acetals for hydroxyls, tertiary esters, or anhydrides for carboxylic acids and carbamates such as *tert*-butyloxycarbonyl (BOC) or benzyloxycarbonyl (i.e., carboxybenzyl [Cbz]) for amines.[211,212]

The key advantage of this strategy is its ability to circumvent the problem of randomly incorporating hydrophilic and hydrophobic monomers in a colloidal system. By using two hydrophobic monomers, the utilization of standard emulsion/droplet-based copolymerization approaches is possible. Since drastically different monomer solubilities are avoided, the random incorporation of the two monomers is enhanced which translates to a more isotropic amphiphilic network.

This pathway can be combined with different emulsion-based copolymerization methods. In a standard emulsion copolymerization strategy, Walther and coworkers have used *tert*-butyl methacrylate (tBMA) as a hydrophobically-protected MAA monomer in combination with the non-labile MMA.[213] By exploiting similar diffusion properties and monomer reactivities, homogenous and well-defined copolymer nanoparticles could be obtained. Subsequent hydrolysis of the tBMA monomers gave then hydrophilic anionic MAA units in the copolymer network, as shown in Figure 21. This resulted in the formation of an amphiphilic structure that consists of a hydrophile network with internal hydrophobic pockets. The amphiphilicity could be tuned by changing the feed ratio of tBMA:MMA in the initial emulsion polymerization. The versatility of this approach was demonstrated by copolymerizing the tBMA monomers with N,N′-diethylaminoethyl methacrylate) (DEAEMA). In such system, the opposing pH-responsiveness of the hydrolyzed acidic MAA units and the basic DEAEMA units gave access to polyelectrolyte microgels with switchable hydrophobic pockets.

Despite diffusion-based emulsion polymerizations, also the concept of droplets as microreactors is compelling in such systems. For this, Georgiou et al. used microfluidics for the preparation of amphiphilic microgels.[214,215] First, hydrophobic microparticles were synthesized by copolymerizing the protected form of AA, tetrahydropyranyl acrylate (THPA), with EGDMA as hydrophobic crosslinker in microfluidic droplets. The molar ratios of hydrophobic THPA and EGDMA were varied. Thus, the resulting p(THPA-*co*-EGDMA) particles possessed different crosslinking densities, which translate into different hydrophobic contents after hydrolyzation of the THP protecting groups. The resulting amphiphilic anionic microgels showed promising properties for drug delivery due to the strong interactions with cationic membranes of biological cells.[214]

In a second study, butyl acrylate (BuA) was used as an additional non-labile hydrophobic monomer.[215] In combination with THPA, varying the ratio of BuA:THPA enabled to change the hydrophobic content. In this research, the crosslinker (EGDMA) content was kept constant and polymerizations were performed in a newly designed microfluidic chip that allowed rapid and automated in situ polymerization. The resulting microparticles were then hydrolyzed, resulting in the formation of acidic amphiphilic microgels with similar crosslinking density but different hydrophobicity. As microgels in both studies are amphiphilic, it was possible to encapsulate hydrophobic (Sudan I) as well as hydrophilic (Trypan Blue) cargoes. The release of the payloads was influenced by changing the hydrophobic content, which demonstrates the potential of using such amphiphilic microgels as drug delivery vehicles. Moreover, controlling the release of drugs can also be tailored by varying the pH-dependent swelling of the anionic amphiphilic networks.

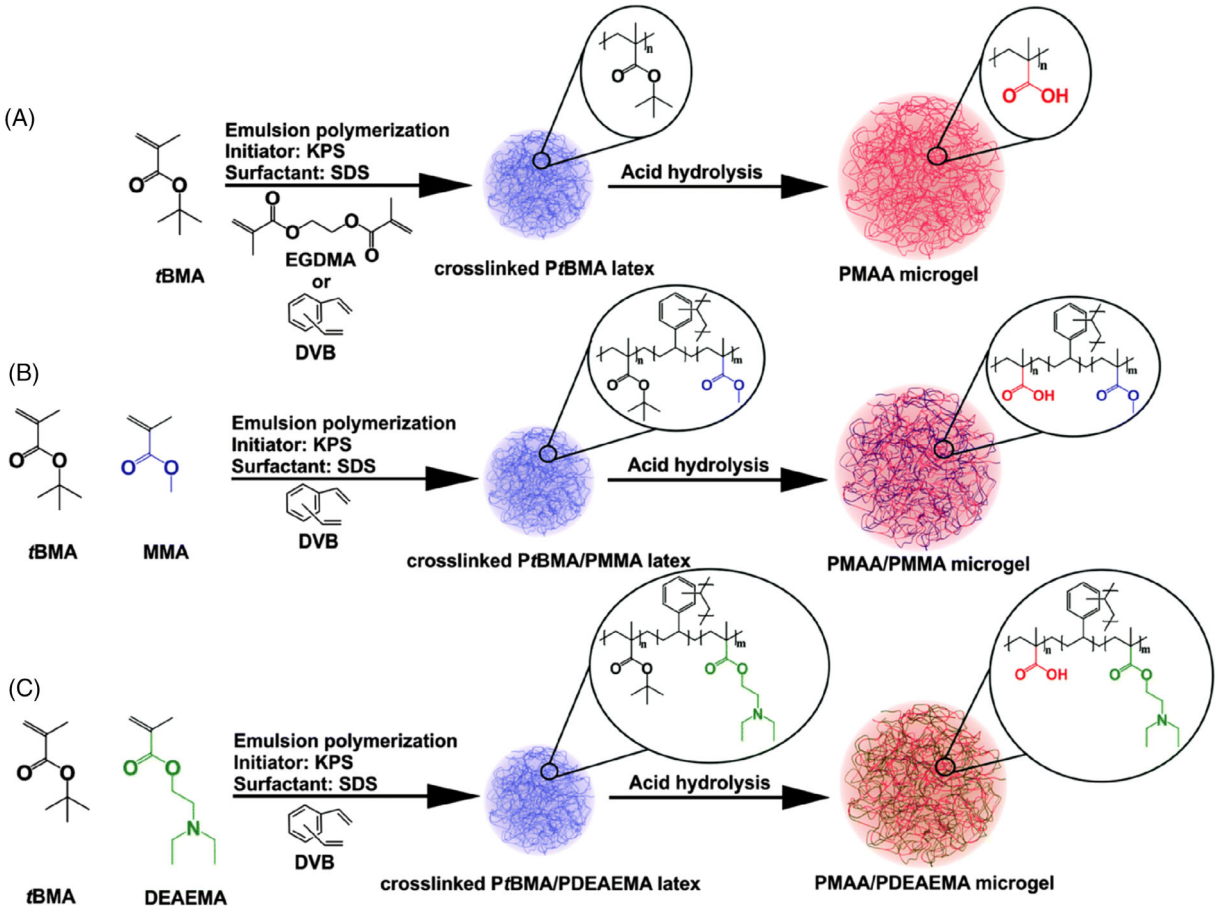

FIGURE 21 Synthesis of a microgel library by hydrolysis of hydrophobic precursor microgels obtained from emulsion (co-) polymerization. (A) Hydrophilic microgel obtained by hydrolysis of tBMA moieties in a hydrophobic precursor microgel. (B) Amphiphilic microgel achieved by hydrolysis of tBMA moieties in a tBMA/MMA precursor particle. (C) Amphiphilic microgel acquired by hydrolysis of tBMA moieties in a tBMA/DEAEMA precursor particle. Reproduced from ref. 213 with permission from copyright © 2015, Royal Society of Chemistry. DEAEMA, N,N′-diethylaminoethyl methacrylate); MMA, methyl methacrlyate; tBMA, *tert*-butyl methacrylate

The versatility of combining this synthetic approach with microfluidic droplet generation was demonstrated in another study by Haney et al. Here, the authors were able to generate more complex amphiphilic microgel morphologies, that is, dual stimuli-responsive Janus microgels.[216] In these particles, one side consists of a thermoresponsive PNIPAM network whereas the other side contains an initially hydrophobic polymer network based on pentenoic anhydride (PA) as comonomer. Hydrolysis of the anhydride groups after the particle preparation could be used to realize the amphiphilicity. These colloidal materials were synthesized by mixing two different monomer solutions in a microfluidic device. On one hand, a solution of NIPAM with polyethylene glycol diacrylate (PEGDA) as crosslinker was used for free radical photopolymerization. On the other hand, a thiol-ene step growth polymerization was employed to form the network between pentaerythritol tetra(mercaptopropionate) (PETMP), triethyleneglycol divinylether (TEGDVE), and PA. These solutions were pumped through the microchannels forming Janus droplets due to their incompatibility. Upon photopolymerization, Janus morphology microgels with an amphiphilic PNIPMA phase and a hydrophobic p(PETMP-*co*-TEGDVE-*co*-PA) part were generated. Upon hydrolyzing the PA groups in the hydrophobic phase, pH-responsive carboxylic acid groups were generated, thus transforming this side of the Janus microparticles into an amphiphilic pH-responsive network (see Figure 22). Upon hydrolysis, the crosslinking density was also decreased which even further improved the swelling properties of the system. The impact of morphology and network amphiphilicity on the colloidal properties was examined and it was found that these microgels showed amphiphilicity only at specific conditions, that is, at low temperatures (19°C) in acidic pH, and at high temperatures (40°C) in basic pH. Using these amphiphilic and anisotropic structures, the microgels were used as stabilizers for water and oil emulsions.

In contrast to the copolymerization of different monomers during the colloidal synthesis, hydrophobic precursor particles can also be prepared from preformed polymers that

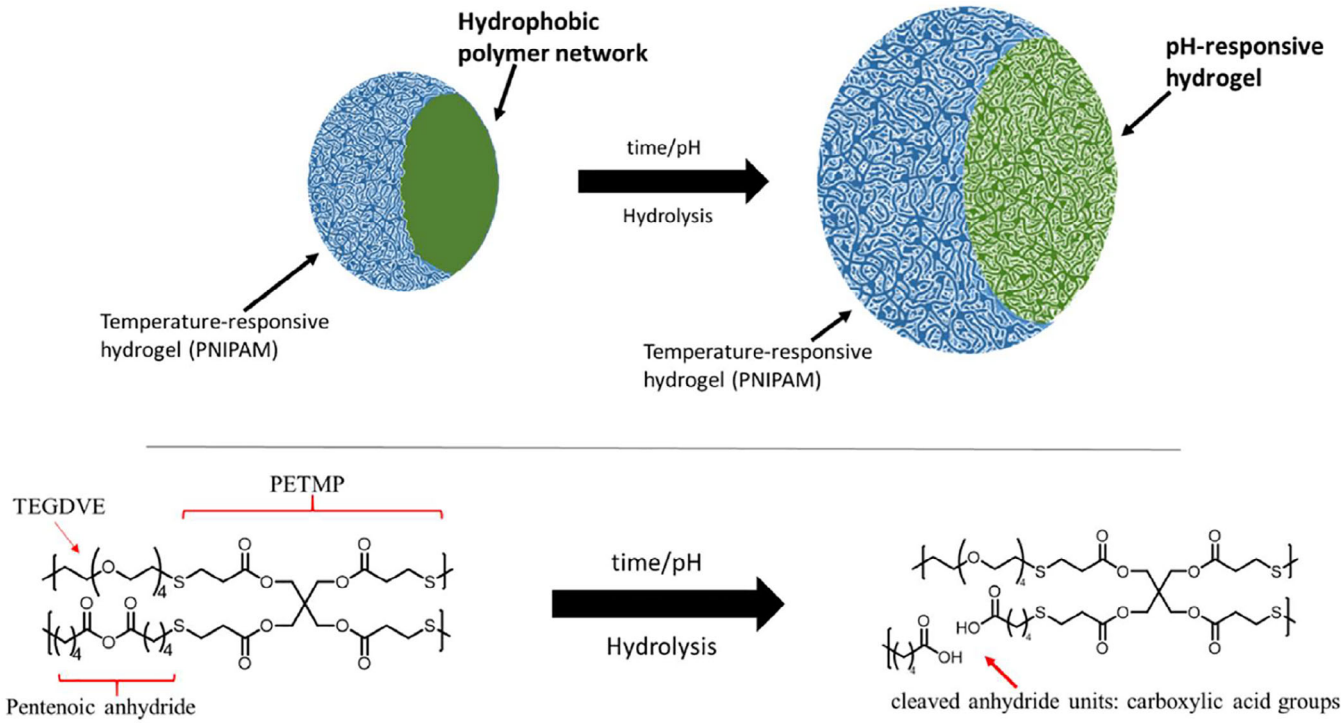

FIGURE 22 Schematic representation of amphiphilic Janus microgels based on PNIPAM and a pentenoic anhydride-based copolymer. Hydrolysis reaction of the pentenoic anhydride carried out in the polymer network yields pH-responsive Janus nanogels. Reproduced from ref. 216 with permission from copyright © 2020, Royal Society of Chemistry

contain the protected hydrophilic groups. Following this strategy, the group of Möller used preformed poly glycidyl ethers as building blocks to fine tune the amphiphilicity of microgels upon hydrolysis of protected groups.[217,218] For this, they first synthesized prepolymers by anionic ring opening polymerization using protected monomers such as ethoxy glycidyl ether (EEGE) and *tert*-butyl glycidyl ether (tBGE) in combination with hydrophobic allyl glycidyl ether (AGE).[217] Thus, the two resulting types of polymers presented protected hydroxyl functions (EEGE and tBGE) and allyl groups that allow the crosslinking of the polymers via thiol-ene chemistry, also enabling further post-functionalization (Figure 23). Different ratios of the monomers were evaluated for the synthesis of the prepolymers and the microgels were obtained by crosslinking the AGE units with 2,2′-(ethylenedioxy)diethanethiol in miniemulsion droplets. The amphiphilicity of the microgels from EEGE-based prepolymers was controlled by in-situ hydrolysis of the protected EGDE. In contrasts, for tBGE-based prepolymers, post-functionalization with mercaptopropionic acid was employed to introduce the amphiphilicity.

This strategy enabled circumventing the extreme conditions needed for the deprotection of tBGE. To compare the influence of the prepolymer structure on the morphology of the final amphiphilic microgels, random and BCP of similar compositions were used. In microgels from BCP, it was found that the swelling properties depend on the crosslinking density. But this dependence was not found in the systems achieved by crosslinking of random copolymers. This suggests a clear influence of nanostructure of the polymers, where crosslinking of the BCP systems favors a more compact core-shell type morphology. This assumption was supported by cryo-transmission electron microscopy (TEM) images: In the case of microgels from random copolymers, much smaller hydrophobic domains were observed than for microgels from BCP. Thus, this approach enables tuning both amphiphilicity and morphology of microgels by the structure and composition of the precursor polymers.

The versatility of this approach was further expanded by blending the hydrophobically protected p(EEGE-*co*-AGE) prepolymers with different amounts of other hydrophobic prepolymers to tune the amphiphilicity of the final systems.[218] The hydrophobic prepolymers employed were a polystyrene homopolymer (PS) and a random copolymer, poly(THF-*stat*-3-allyloxymethyl-3-ethyl-oxetane), (poly[THF-*stat*-AllylEHO]). While PS is a nonreactive polymer, poly(THF-*stat*-AllylEHO) can participate actively in the crosslinking reaction through the allyl side groups. Hence, the difference in these polymers enables different pathways to tune morphology and amphiphilicity of the final microgels. For this, it was shown that PS, which is not involved in the crosslinking process, led to a core-shell microgel with a hydrophobic

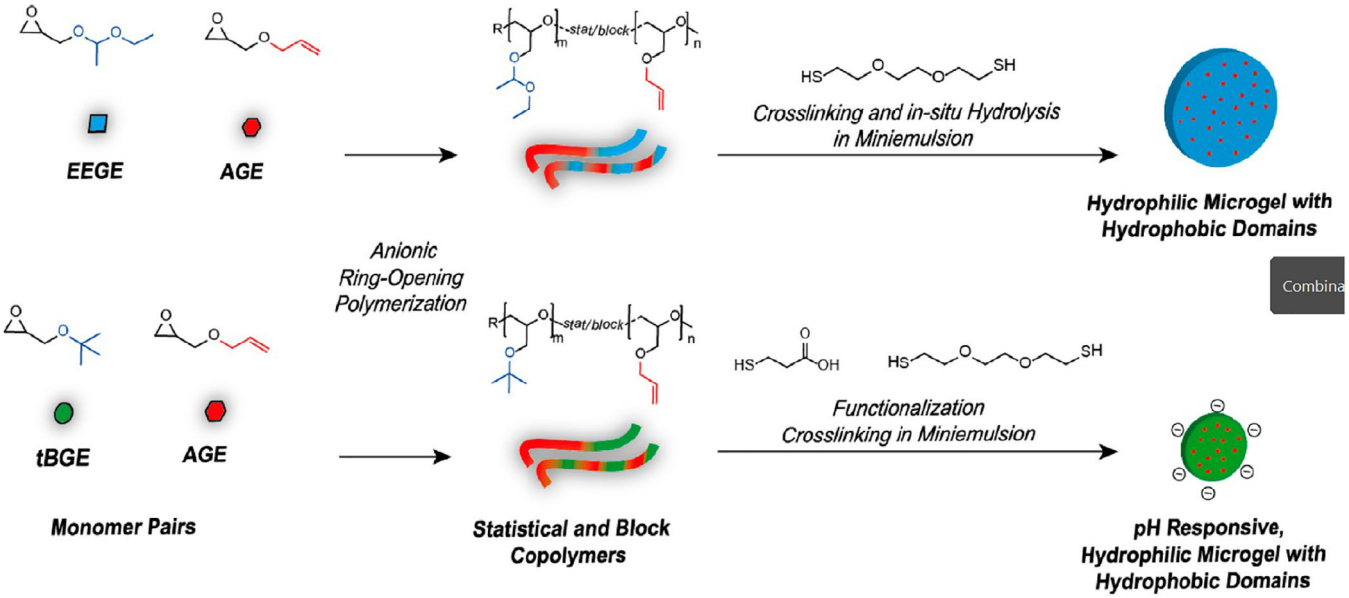

FIGURE 23 Prepolymer approach for the synthesis of amphiphilic nanogels. Synthetic route A is based on crosslinking of prepolymers containing EEGE and AGE in miniemulsion droplets and in situ hydrolysis. Synthetic pathway B is based on crosslinking and functionalization of prepolymers based on tBGE and AGE in miniemulsion droplets. Reproduced from ref. 217 with permission from copyright © 2014, American Chemical Society. AGE, allyl glycidyl ether; EEGE, ethoxy glycidyl ether; tBGE, *tert*-butyl glycidyl ether

PS core. This is assigned to a strong tendency for phase segregation of PS. For microgels employing poly(THF-*stat*-AllylEHO), the hydrophobic domains were also involved in the crosslinking and they were homogenously distributed. In addition, in situ hydrolysis of the EEGE group led to the formation of a hydrophilic corona. This was confirmed both by NMR and cryo-TEM. Furthermore, analyzing the hydrophobicity of the nanogels with pyrene fluorescence spectroscopy revealed that microgels with PS provide the most hydrophobic internal environment. Finally, the amphiphilic nature was also examined by the incorporation of NR. Based on these results, it is envisioned that these materials can be employed as nanocarriers or as colloidal catalytic supports.

An alternative strategy for the formation of amphiphilic networks through labile bonds is based on disulfide chemistry. These reactions are common in biological systems such as proteins, where disulfide bonds are formed, cleaved, and rearranged due to the presence of reducing agents, oxidizing species or excess thiols. This redox-responsive and dynamic character has found widespread use in the synthesis of functional polymeric materials.[219,220] Especially, the degradation of disulfide crosslinkers as response to intracellular GSH has been used to design new nanogel carriers for drugs and biomolecules.[221]

In contrast to such labile crosslinks, the reduction of disulfides can also be exploited to introduce hydrophilicity due to the generated thiol groups in a hydrophobic nanogel. Using this strategy, Lowry and colleagues reported amphiphilic nanogels containing hydrophilic thiols for mercury removal applications.[222] Taking advantage of the disulfide chemistry, they first synthesized hydrophobic nanogels based on DVB and bis(2-methacryloyl) oxyethyl disulfide in a minemulsion copolymerization. In a second step, the disulfide bonds were reduced with tributyl phosphine to obtain free thiol groups (Figure 24). The combination of the hydrophobic benzene moieties and the hydrophilic thiols groups made this system amphiphilic. Thus, the nanogels could be dispersed in aqueous and hydrocarbon phases. In both systems the nanogels demonstrated high affinity toward different mercury species, thus presenting high potential to remove environmentally relevant mercury.

As demonstrated by these examples, tuning the amphiphilic properties by deprotection of masked hydrophilic moieties represents a promising approach to favor random incorporation of hydrophilic and hydrophobic groups in the network. Although this strategy is scalable, it shows some limitations. For instance, the design is limited to hydrophilic monomers that can be hydrophobically protected. Also, variations in the hydrophobic groups require the synthesis of new particle batches. In case of diffusion-based emulsion polymerizations, this might change the morphology of the particles thus requiring optimization of the process conditions again.

Covalent attachment of hydrophobic and/or hydrophobic moieties

The internal modification of micro−/nanogel networks can also be carried out by covalently attaching new

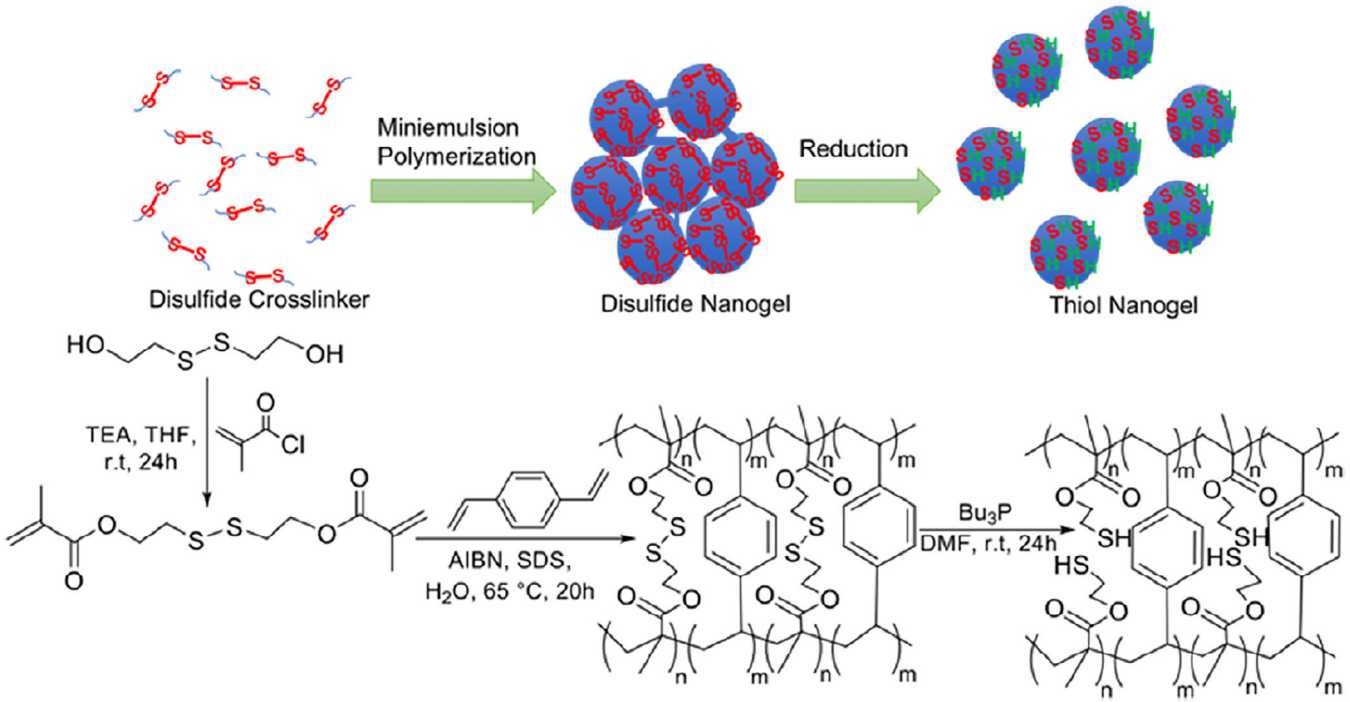

FIGURE 24 Synthetic route to amphiphilic nanogels by reduction of disulfide bonds: Synthesis of hydrophobic precursor nanoparticles by miniemulsion polymerization using DVB and bis(2-methacryloyl) oxyethyl disulfide as bifunctional monomers. This is followed up by reduction of disulfide bonds in the nanogels' network to give hydrophilic thiols. Reproduced from ref. with permission from copyright © 2021, American chemistry society. DVB, divinylbenzene

functional groups. In principle, this strategy allows the introduction of hydrophilic groups into reactive hydrophobic particles[179,223,224] or the functionalization of hydrophilic particles with hydrophobic groups.[225,226] However, outstanding synthetic versatility is achieved by controlling the introduction of both groups (hydrophilic and hydrophobic) in reactive precursor networks. In such approach, adjusting the ratio between hydrophilic and hydrophobic reagents can be used to tailor the network amphiphilicity accurately. Using one master batch of reactive particles, this strategy enables maximum synthetic flexibility while ensuring optimum colloidal comparability. It allows varying type and amount of both, hydrophilic and hydrophobic, groups while particle size, size distribution, and crosslinking density are mainly governed by the reactive precursor particles.

To ensure successful and homogenous network modifications, the selected reactions must meet certain requirements, that is, they must be quantitative, fast, generate easily removable side products, among others. Thus, well-established click reactions and active ester modifications are promising examples to realize such amphiphilic networks. The selection of a specific post-functionalization reaction depends on several factors such as availability of the respective reactive monomers, compatibility of the reactive moieties with the particle preparation method, the final application, and so forth.[88]

Among suitable reactions, thiol-ene click reactions provide access to fast and efficient modifications in aqueous environments.[98,227,228] Moreover, versatile libraries of functional thiols and alkenes are readily (commercially) accessible. Taking these benefits into consideration, thiol-ene click chemistry is well-established for post-functionalization of functional polymer materials.[88] Translating this strategy to the functionalization of micro−/nanogel networks was demonstrated by Hawker, Klinger, and coworkers.[229] In this approach, reactive nanogels were prepared by thiol-ene crosslinking of poly(allyl glycidyl ether) (PAGE) with penta-erythritol-tetrakis(3-mercaptopropionate) (PTMP) as degradable crosslinker in miniemulsion droplets. Since the crosslinkers were used in a sub-stochiometric amounts, the network still contained a majority of the reactive alkene groups. Thus, the resulting precursor nanoparticles could be post-functionalized with different thiols. For this, either thiol-containing acidic (mercaptoacetic acid) or basic (thiol-functionalized histamine) moieties were introduced to realize either anionic or cationic nanogels. Using a 50:50 mixture of these thiols, novel ampholytic nanogels were achieved. These systems presented amphiphilic behavior at low and high pH. At lower pH, the

basic histamine moiety is positively charged, thus generating a cationic nanogel. At the same time the acidic moiety remains protonated and, thus, is more hydrophobic. In contrast, at higher pH, the carboxylic acid is deprotonated yielding anionic nanogels. Here, the histamine remains neutral, thus representing a relatively hydrophobic moiety. Advantages associated with this system are the facile and scalable synthesis of precursor nanoparticles, which provided a control over morphology, size, and crosslinking density. Moreover, a versatile library of stimuli responsive functionalities can be created with the benefit of avoiding side reactions that may lead to a change in crosslinking density and the colloidal features.

The synthetic versatility of thiol-ene click chemistry can also be combined with other colloidal preparation methods to tune the amphiphilicity of micro−/nanogel networks to specific applications. In an example by Saraswathy et al., the authors use a free radical solution copolymerization of hydrophobic 3-(trimethoxy silyl) propyl methacrylate (3TSMA) with a hydrophilic crosslinker, polyethylene glycol diacrylate (PEGDA 575), to obtain amphiphilic nanogels (Figure 25).[230] After the synthesis, the unreacted acrylate groups in the nanogels can be functionalized with mercaptosuccinic acid to adjust the amphiphilicity of the networks. The resulting increase in hydrophilicity ensured facile dispersion of the nanogels in water. In general, the specific combination of silyl- and PEG-based monomers/crosslinkers is of high interest for the formation of biocompatible coatings on contact lenses. In such materials, the PEG components impart high biocompatibility. In addition, the hydrophobic TSMA groups ensure oxygen transportability, biological inertness, and transparency. However, combining these two materials to prepare suitable coatings is challenging. In common bulk coating methods, mixing the pure incompatible monomers causes a bulk phase separation upon polymerization. The resulting scattering of the microdomains causes turbid materials. This hinders the application of these polymer networks as coatings on lenses materials, since these require optically clear coatings.[231,232] To address this challenge, the homogeneous incorporation of both materials in nanogels was examined. In a suitable solvent, the problem of bulk phase separation could be overcome and both components were distributed throughout the network. These composite nanogels could be applied as uniform, crosslinked coatings on the surface of contact lenses from aqueous dispersions. The coated materials were optically clear with enhanced hydrophilicity due to the crosslinked hydrophilic units of the nanogel coating. Additionally, these were capable to enhance the sustained release of dexamethasone.

Despite classical click reactions, the nucleophilic addition-substitution reaction of activated esters is also well-established for post-polymerization modifications.[174] The major advantage behind active ester chemistry is the high selectivity and reactivity of various amines toward such active esters.[103] Out of many active esters, NHS, and PFP esters have been the most frequently employed. Comparing both esters, PFP ester group containing polymers convince with their good hydrolytic stability and very good solubility.[88,233] Currently, the most widely used PFP-based monomers are pentafluorophenyl acrylate (PFPA) and -methacrylate (PFPMA) which can be easily polymerized by (controlled) radical polymerization methods.[88]

Translating the advantages of such active esters from linear polymers to colloidal materials is currently emerging. For instance, the group of Théato used pentafluorophyl ester chemistry for the development of reactive BCP micelles with potential in medicine.[234–236] Also, Nuhn and De Geest have pushed the PFP chemistry to the synthesis of BCP micelles with reactive cores.[237–240] In contrast, the group of Walther developed emulsion-polymerized nanoparticles based on PPFPA.[213,241]

While these substitution reactions show good compatibility with various polymer and colloidal synthesis methods, using them for the introduction of amphiphilic network properties is less explored. In addressing this challenge, Klinger and coworkers recently developed crosslinked PPFPMA precursors particles as synthetic platform for the generation of amphiphilic nanogels.[64] For this, a master batch of PPFPMA precursor nanogels was post-functionalized through nucleophilic amidation reactions with various mixtures of hydrophobic and

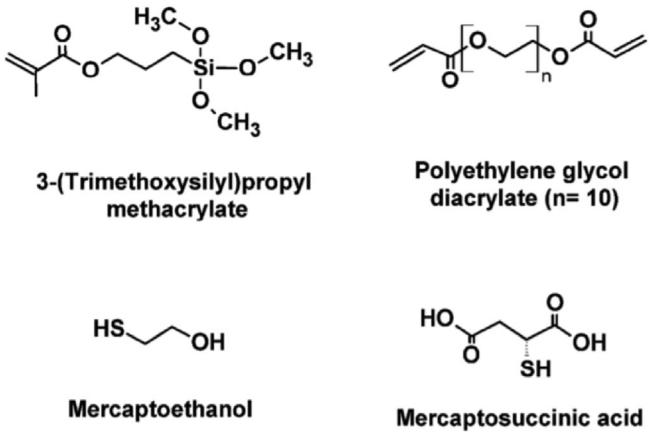

FIGURE 25 Monomers employed for the synthesis of amphiphilic nanogels based on PEG and silyl monomers for coating applications. Reproduced from ref. 230 with permission from copyright © 2016, Royal Society of Chemistry. PEG, polyethylene glycol

hydrophilic amines. As a result, the hydrophilic and hydrophobic side groups were randomly distributed on the polymer network, thus giving access to homogeneous amphiphilic nanogel structures. By varying the structure of hydrophobic groups and changing the feed ratio of hydrophilic and hydrophobic amines, the network amphiphilicity could be tuned precisely (Figure 26).[64] At the same time, the resulting library of amphiphilic nanogels showed similar colloidal features (particle size and size distribution) as defined by the precursor particles. Further investigations by small angle X-ray scattering (SAXS) revealed that the hydrophobic moieties are randomly distributed in the nanogel network forming hydrophobic domains.[242] This feature allowed the incorporation of hydrophobic cargoes such as NR and the loading and release could be fine-tuned by changing the amphiphilicity of the network.[64] In vitro studies demonstrated that these materials are biocompatible with various cell types despite their pronounced hydrophobic content. In addition, protein absorption studies showed that the amphiphilic network properties also translate to the particle surface properties. The protein corona composition and cellular uptake of each nanogel were highly influenced by their amphiphilicity.[60,64] Overall, this strategy demonstrated the potential for developing accurate structure–property relations from well-defined nanogel libraries with varying network amphiphilicity. For example, this high comparability between systems enabled accurate evaluation of the influence of different functional groups on the potential of the nanogels for dermal delivery applications.[243]

In summary, the post-modification approach of colloidal structures is an effective tool to program the properties of micro−/nanogels to match the needs of a desired application. In analogy to post-polymerization modifications on linear polymers, the formation of libraries with similar colloidal features enables the determination of a new level of structure–property relations. This is of crucial importance for the development of new advanced materials for a variety of applications.

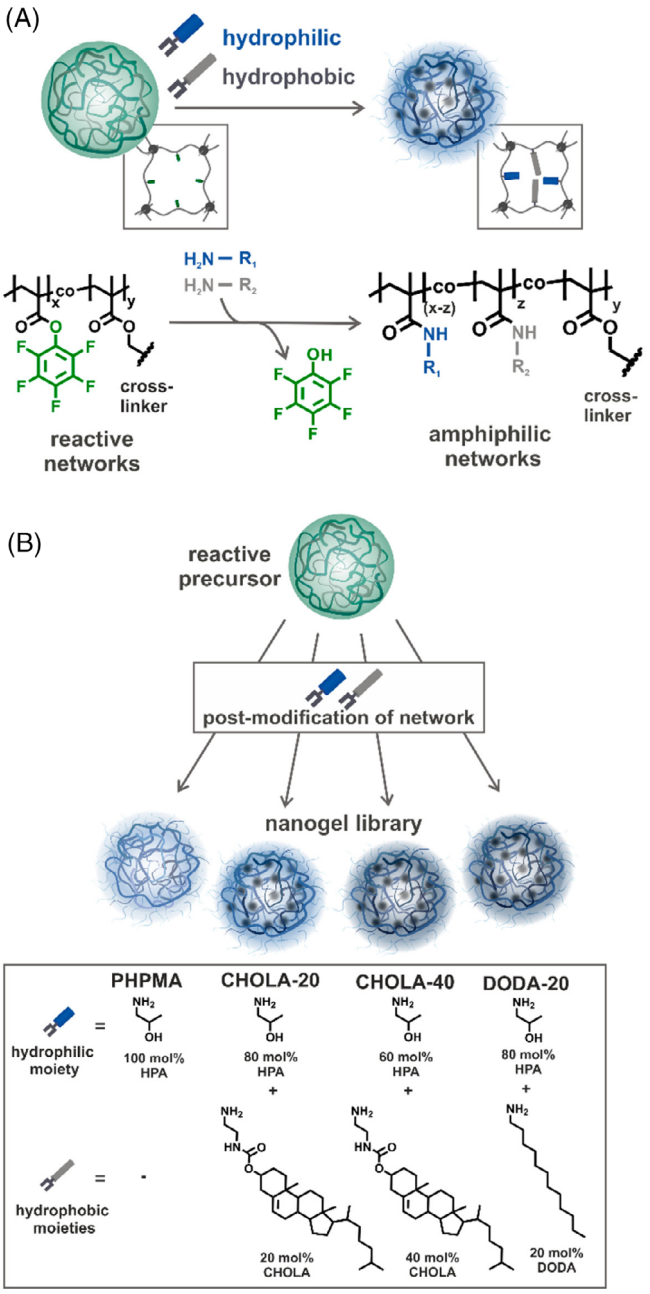

FIGURE 26 Generation of amphiphilic nanogels with tunable hydrophobicity from reactive precursor nanoparticles. (A) Precursor nanogels with reactive pentafluorophenyl ester PFP moieties can be modified by post-functionalization with different amines. (B) Using hydrophilic amines (HPA) in combination with hydrophobic amines (e.g., CHOLA, DODA) can give access to libraries of amphiphilic nanogels from one master batch of reactive precurors nanogels. Reproduced from ref. 242 with permission from copyright © 2020, American Chemical Society. PFP, pentafluorophenyl

2.3.3 | Concluding remarks

In this section, different approaches to prepare amphiphilic micro−/nanogels by post-functionalization of precursor nanoparticles have been discussed. The post-functionalization strategies can be separated into physical and covalent incorporation of hydrophilic and/or hydrophobic groups into a preformed nanogel network. A summary of all approaches, building blocks, micro−/nanogel properties and applications is given in Table 3 (for a detailed table of amphiphilic micro/nanogels obtained by post-functionalization see Table S3 in ESI).

Regarding the particle sizes, it can be seen that this strategy gives access to a wide range of particle sizes from 40 nm up to 80 μm. This range is much wider than for other preparation strategies of amphiphilic micro−/

TABLE 3 Summary of analyzed amphiphilic nanogels obtained by post-functionalization of precursor nanoparticles

	Approach	Hydrophobic/ hard domain	Hydrophilic domain	Crosslinking	Sizes	Stimuli response	Applications
PHYSICAL NCORPORATION	Acid–base interaction	Wedge shaped sulfonic acid molecules	VCL, AAEM, VIm	Radical	250–1200 nm PDI: 0.06–0.13	Thermo-responsive	DDS
	Hydrogen bond	Silica NP's	AAm, AMPS, BIS	Radical	55–158 nm PDI: 0.01–0.74	pH-responsive	Water decontamination
COVALENT INCORPORATION	Deprotection of masked hydrophilic moieties	NIPAM, MMA, tBMA, DEAEMA, EGDMA, THPA, BuA, PA, PETMP, TEGDVE, AGE, PS, DBV, tBGE	NIPAM, AA, EEGGE, hydrolyzed EEGE and tBGE, reduced thiol	Radical, Thiol-ene	86 nm-80 μm PDI: 1.06–1.30	pH-responsive	Pickering emulsion, DDS, water decontamination
	Covalent attachment	PAGE, 3TMSA, BDODA, DODA, HEXA, BENZA, CHOLA	His-SH, MAA, PEGDA,	Radical, Thiol-ene	43–370 nm SD 2–3 nm	pH-responsive	Biomedical, DDS, coating of contact lenses

Abbreviations: AA, acrylic acid; AAm, acrylamide; AAEM, acetoacetoxyethyl methacrylate; AGE, allyl glycidyl ether; AMPS, 2-acrylamido-2-methyl propane sulfonic acid; BuA, butyl acrylate; DDS, drug delivery systems; DEAEMA, N,N′-diethylaminoethyl methacrylate); EGDMA, ehtylenglycol dimethacrylate; MMA, methyl methacrlyate; NIPAM, *N*-isopropylacrylamide; NP's, nanoparticles; PA, pentenoic anhydride; PAGE, poly(allyl glycidyl ether); PETMP, pentaerythritol tetra(mercaptopropionate); PS, polystyrene; tBGE, *tert*-butyl glycidyl ether; tBMA, *tert*-butyl methacrylate; TEGDVE, triethyleneglycol divinylether; THPA, tetrahydropyranyl acrylate; VCL, vinylcaprolactam; VIm, vinylimidazole.

nanogels and can be attributed to the utilization of mostly hydrophobic precursor monomers. Only using one type of monomer (or multiple monomers with comparable hydrophobicity) circumvents the problems that arise from using monomers with different solubilities in other strategies. Thus, this strategy can be combined with different well-established particle preparation methods where optimization of reaction conditions does not involve the consideration of different diffusion coefficients or monomer solubilities. As a result, this strategy can easily be employed in synthetic methods ranging from (mini-)emulsion polymerizations to polymerizations in microfluidic droplets. Here, the size and size distribution of the final amphiphilic micro−/nanogels is determined by the colloidal preparation method employed for the precursor nanoparticles.

Another parameter to be considered is the desired functionality and the "functionality-to-spacer-ratio." When using this strategy to incorporate hydrophobic/hydrophilic moieties, a spacer or linking group between the particle network and the functionality itself is needed (e.g., a triazole for CuAAC and SPAAC). Since this spacer or linker does not contribute to the desired function, minimizing the ratio of atoms from spacer to functional group is often required. Thus, the corresponding selection of the coupling chemistry depends on the final application and the functional group that is introduced. For example, if the final goal is to incorporate a simple carboxylic acid, using CuAAC click chemistry will lead to incorporation of triazoles in addition to these carboxylic acids. These large aromatic rings might change the overall properties of the colloidal system. In comparison, employing a simple method such as hydrolysis might be the suitable solution in this example since it can avoid this extra spacer group. As an alternative, active ester and thiol-ene chemistry present a good "functionality-to-spacer- ratio." In general, reactions that introduce bulky spacers such as CuAAC or SPAAC might be better suited for the incorporation of high molecular weight moieties. In the case of the comparably large spacers that are introduced by SPAAC, the benefit is the biorthogonality of this coupling strategy. Thus, such reactions are mostly suited for the incorporation of large biomacromolecules or functionalities that require coupling in in complex biological environments.

Another key factor to be considered is the selection of the chemistry employed. For example, as mentioned before, thiol-ene chemistry presents a good "functionality-to-spacer- ratio." Nevertheless, it is known that alkene bearing monomers cannot be easily polymerized by free radical polymerization, thus limiting the techniques that can be employed for the generation of the precursor particles. All these factors must be considered when preparing amphiphilic micro−/nanogels and the best strategy will depend on the desired properties and applications, the precursor particle synthesis, moieties to be incorporated, and so forth.

Regarding the application of such amphiphilic micro−/nanogels from post-functionalization, modification of precursor particles has been used to prepare particles for a variety of applications ranging from drug delivery over coatings to materials for water

decontamination. This broad spectrum of applications highlights the potential of this versatile technique.

3 | CONCLUSION AND PERSPECTIVE

Amphiphilic micro−/nanogels are characterized by their combination of micro−/nanoscale dimensions with a hydrophilic network that contains internal hydrophobic domains. This unique colloidal structure bridges the gaps between hydrogel particles, solid particles, and micellar aggregates. As discussed in this review, the resulting amphiphilic properties open up a broad variety of advanced applications. These range from the area of pharmacy/medicine over film coatings, catalysis, and heavy metal removal, to emulsion stabilization.

In the area of nanomedicine, amphiphilic micro−/nanogels show high potential as new nanocarriers for poorly water-soluble drugs. Here, the hydrophilic network can provide good biocompatibility and ensures colloidal stability due to dangling hydrophilic chains that prevent the need for additional surfactants. The internal hydrophobic domains can be used to load hydrophobic compounds. In combination with tunable network properties by external triggers, this enables controlled release applications. In addition, they can present antifouling properties, which make them good candidates for film coatings or antibacterial applications. While, up to now, different carriers are designed each time for a different biological target and therapeutic cargo, it is assumed that future research will focus more on platform approaches that allow investigating the underlying amphiphilic structure–property relations in more detail. Such investigations could serve as guideline for tailoring amphiphilic nanogels to a specific application. In this context, it is of high interest to determine the competing influence of hydrophobic and hydrophilic network components. While hydrophobic nanodomains are required to enhance the loading and release of poorly water-soluble drugs they can also reduce the overall biocompatibility and colloidal stability of such carriers. Balancing both features will be of high importance to develop advanced nanocarriers. Also, the utilization of post-functionalization reactions to modify nanogel platforms is assumed to be of high interest for the development of tailormade carriers toward personalized (nano-)medicine. For this, the functionalization of reactive precursor particles is assumed to be of high importance.

The amphiphilic network structure is also highly beneficial for applications outside the field of health care. For example, the potential of such amphiphilic colloidal networks as support for catalytically active molecules or metal ions/nanoparticles was demonstrated. Even though using such soft carriers for catalytic applications is still in its infancy, the incorporation of catalytic centers into an amphiphilic network holds great potential. Especially when considering reactions that require reactants with different solubility, the internal network amphiphilicity might be able to promote mixing and co-localization, thus acting as a nanoreactor, enhancing the catalytic efficiency. Combining this effect, with the great potential of amphiphilic micro−/nanogels to stabilize emulsions (Pickering emulsions, high-internal phase emulsions) might lead to new catalytic systems at the water/oil interface. Moreover, being able to combine the amphiphilic networks with inorganic materials such as silica, gold, silver, and magnetic nanoparticles, results in hybrid systems that can show new composite properties. These can find application in catalysis, functional coatings, removal of heavy metals from water, antibacterial films, theranostic, and so forth. While the potential of such nanogels as colloidal stabilizers has been demonstrated, more profound insights in to the underlying mechanisms are still limited. For example, varying the amphiphilicity of such nanogels influences both, swelling with solvents and mechanical properties, for example, particle deformation or spreading. Both factors determine the behavior of such colloidal particles at liquid–liquid or liquid–air interphases. Accurate determination of such structure–property relations is still hindered by difficulties in determining the underlying physicochemical parameters of the individual nanogels, for example, the surface hydrophobicity of single particles. Thus, studying the behavior of such amphiphilic colloidal systems at liquid interphases represents an interesting research area that is assumed to generate important insights in the future.

Considering the great potential of amphiphilic micro−/nanogels for new applications, robust and versatile synthetic strategies are required to adjust the properties of such promising materials. For this, the ratio between hydrophilic and hydrophobic groups in the network can be used to adjust the amphiphilicity. However, such strategies are difficult to realize since two functional groups of drastically differing solubility need to be introduced homogenously into one colloidal system without changing the colloidal features. Since comparable particle sizes, size distributions, etc., are needed to develop accurate structure–property relations, the synthetic realization is challenging. In this review, several methods and recent examples were presented that can address this challenge successfully. Table 4 shows a summary of the analyzed strategies including their specific advantages and disadvantages.

First, self-assembly of random amphiphilic copolymers with subsequent covalent crosslinking is a popular

TABLE 4 Comparison of different approaches for the synthesis of amphiphilic micro−/nanogels

Approach	Classification	Advantages	Disadvantages
Self-assembly	Random copolymer, single-chain nanogel	Versatile, several functional moieties can be incorporated, several crosslinking strategies	Synthesis of amphiphilic copolymer building blocks, final properties depend on the conditions of the assembly, difficult homogenous incorporation of the moieties, batch to batch variation
Incorporation in synthesis of hydrophobic and hydrophilic moieties	Thermoprecipitation, miniemulsion, emulsion	Facile, scalable, narrow size distribution	Influence of monomers' solubility, difficult homogenous incorporation of the moieties, batch to batch variation
Precursor nanoparticles	Physical interaction, covalent reactions	Versatile, homogenous incorporation of moieties, change of amphiphilicity without changing colloidal features	More synthetic steps, complex, need of a solvent in which the particles can swell and moieties are soluble

method. This strategy is strongly governed by the copolymer composition and structure. Even though the amount and type of hydrophobic and hydrophilic groups can be adjusted precisely in the copolymer building blocks, it remains difficult to achieve self-assembled structures with varying amphiphilicity but similar colloidal properties. Especially controlling the number of chains per micellar aggregate is challenging and can have big impacts on the resulting properties. To overcome this limitation, SCNP are emerging. Since these materials consist of only one chain per aggregate, well-defined structures are obtained. However, this approach encounters its own drawbacks. The particle formation procedure is more difficult and not as scalable since highly dilute conditions are required.

Second, direct copolymerization of various hydrophobic and hydrophilic monomers in the presence of a crosslinker represents a scalable synthetic alternative. In general, heterogenous (emulsion/miniemulsion polymerization) or homogenous (precipitation polymerization) systems are well-established to prepare defined colloidal particles. However, in these strategies the simultaneous incorporation of monomers with different hydrophilicity is challenging since they are soluble in different phases of the emulsion/dispersion. Thus, changing the hydrophilic/hydrophobic balance is difficult since it can result in core-shell morphologies rather than a homogenous amphiphilic structure. To overcome such problems in heterogenous systems (emulsion polymerizations or droplet-based particle preparations), labile monomers are used that contain a hydrophilic functionality, which is masked by a hydrophobic protecting group. Copolymerization with other nonlabile hydrophobic monomers can be used to enhance the homogeneity of the network where the amphiphilicity can be unmasked by deprotecting the hydrophilic groups. In contrast, in homogenous particle preparation methods, such as thermoprecipitation polymerizations, seeded semi-batch processes are investigated to enhance the homogenous distribution of both monomers throughout the nanoparticle. It is assumed that recent advantages in such techniques will play a key role in future attempts to control the amphiphilic network structure not only by composition but also by morphology.

Third, the internal network functionalization of precursor micro−/nanogels is emerging as a versatile alternative. In this synthetic strategy, a master batch of reactive particles with well-defined colloidal features is synthesized. Afterwards, the amphiphilic balance of the reactive network can be tailored by post-modification with mixtures of hydrophilic and/or hydrophobic reagents. This enables the preparation of nanogel libraries with varying amphiphilicity but similar colloidal features. This strategy crucially depends on a suitable solvent to ensure swelling of the reactive network and solubility of the hydrophobic/hydrophilic moieties that should be incorporated. However, this strategy is assumed to enable new structure–property relations due to the enhanced comparability between different micro−/nanogels.

Overall, the question remains whether a perfect strategy to achieve a facile, scalable, and controlled synthesis of amphiphilic nanogels can be developed. Thus, all the advantages and disadvantages of the currently existing strategies need to be considered carefully when targeting a certain application of amphiphilic nanogels. With this review, we aim to give the readers a critical overview over selected approaches that might help to guide their

selection process and stimulate further research in this exciting area.

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