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# Rational Design of Stimuli-responsive Magnetic Polymer Hybrid (Nano)materials

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## Abstract

Combining organic and inorganic materials is a fascinating strategy to produce hybrid materials that combine the advantages of both polymeric and inorganic materials. Among the various types of organic-inorganic hybrids, stimuli-Responsive Magnetic Polymer Hybrids (RMPH) are particularly promising materials for a wide variety of applications. While the magnetic properties are generally provided by the presence of magnetic nanoparticles (MNPs), such as iron oxide nanoparticles (IONPs), the polymeric compound brings the stimuli-responsiveness, e.g. responsiveness to pH, temperature, redox reaction or irradiation. Furthermore, as the chemical structure and architecture of the polymeric materials are diverse and easily tunable, stimuli-RMPH have found applications in various domains, including catalysis, biotechnology, (bio)imaging and cancer therapy. Given the importance of the hybrids' shape and morphology for the targeted application, this review presents the possible synthetic strategies to rationally design stimuli-RMPH of various morphologies, ranging from nanometric core-shell structure to nano- and microgels and membranes.

**Keywords:** magnetic nanoparticles, stimuli-responsive polymers, hybrids, synthetic pathways

## Introduction

The development of new classes of hybrid materials presenting both organic and inorganic properties has been extensively investigated over the past two decades. In particular, hybrid materials derived from magnetic nanoparticles (MNPs) and polymers have been combined into one single material exhibiting synergistic properties through the use of innovative chemical ligation strategies.<sup>1-4</sup> Indeed, while superparamagnetic nanoparticles (NPs) - such as iron oxide nanoparticles (IONPs) - exhibit magnetization upon the application of a magnetic field, their combination/incorporation within a polymer matrix will prevent their aggregation and stabilize them. In addition, the chemical, structural and architectural diversity of polymers opens the possibility for incorporating functional groups that are useful for numerous applications, in particular for sensing applications<sup>5,6</sup>, wastewater treatment<sup>7</sup> and biomedical applications<sup>8-11</sup>.

Magnetic hybrids comprising stimuli-responsive polymers that can respond to an external trigger, such as light (UV, near-infrared or NIR), temperature or pH, constitute a growing research field and have found applications in numerous domains.

The utilization and possible applications of such stimuli-Responsive Magnetic Polymer Hybrids (RMPH) are well documented in thorough reviews available in the literature.<sup>12-16</sup> Yet, to the best of our knowledge, none of them presents in detail the synthetic strategies employed to reach a targeted hybrids structure. Therefore, this review focuses on the structural and morphological features of stimuli-RMPH and provides

clues on how to fabricate the different morphologies, ranging from nanometric assemblies with isotropic shapes (spherical NPs, nanogels, micelles) or anisotropic morphology (e.g. elongated fibers) toward macroscopic materials. As illustrated in **Figure 1**, throughout the review, we describe different examples of stimuli-RMPH of various shapes. We will illustrate the different synthetic pathways used to functionalize and incorporate MNPs, into the stimuli-RMPH. The review ends with a discussion of the perspectives and ongoing developments in this fast-developing research field.

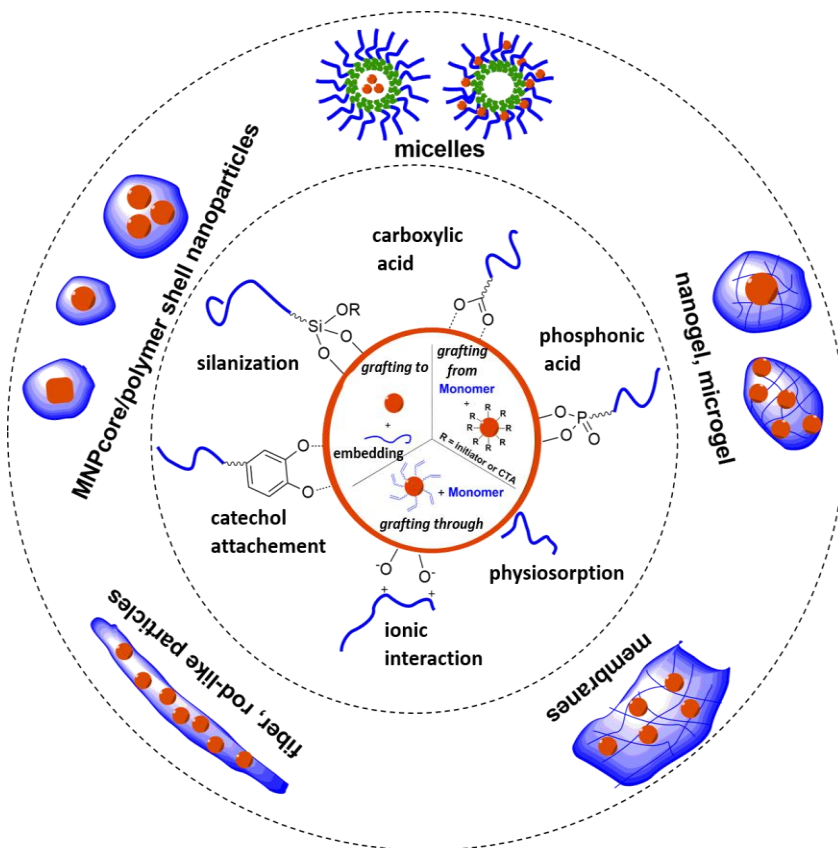


Figure 1. Inner circle: strategies to incorporate IONPs into stimulus-responsive polymers: embedding, “grafting from”, “grafting to” and “grafting through”; middle ring: common interactions between functional groups and IONP surface for hybrid formation; outer ring: common morphologies of stimuli-RMPH.

## 1. Stimuli-responsive polymers

Numerous polymers have been reported to possess stimuli-responsive behavior as summarized in many reviews.<sup>17–21</sup> pH-, light-, redox- and thermo-responsive polymers are examples of stimuli-responsive polymers that have been combined with MNPs. In general, the stimuli-responsiveness of a polymeric system originates from its chemical structure. For instance, pH-sensitive polymers will bear functional groups, such as carboxylic acids, phosphonic acids or amines<sup>22</sup>, that protonate or deprotonate upon a change in the pH of the surrounding environment. Light-responsive polymers generally bear functional groups that can cleave or isomerize upon exposure to light and/or a change in wavelength, such as *o*-nitrophenyl esters or azobenzenes.<sup>23</sup> Redox-responsive polymers typically incorporate disulfides and diselenides bonds that can be cleaved in a redox reaction<sup>19</sup>. As far as thermoresponsive polymers are concerned, an increase (or decrease) of the solution temperature above a critical value induces a change in the polymer conformation due to the (de)hydration of the monomer units in the chain, which results in a switch in the polymer solubility (chain aggregation and precipitation or solubilization).<sup>18</sup> Within this polymer family, two classes of opposite behavior can be cited: polymers exhibiting (1) a Lower Critical Solution Temperature (LCST) or (2) an Upper Critical Solution Temperature (UCST). While LCST polymers are soluble below a critical temperature ( $T_c$ ), UCST polymers are soluble above such  $T_c$ . This  $T_c$  generally varies with the polymer concentration.

## 2. Generalities and properties of magnetic nanoparticles

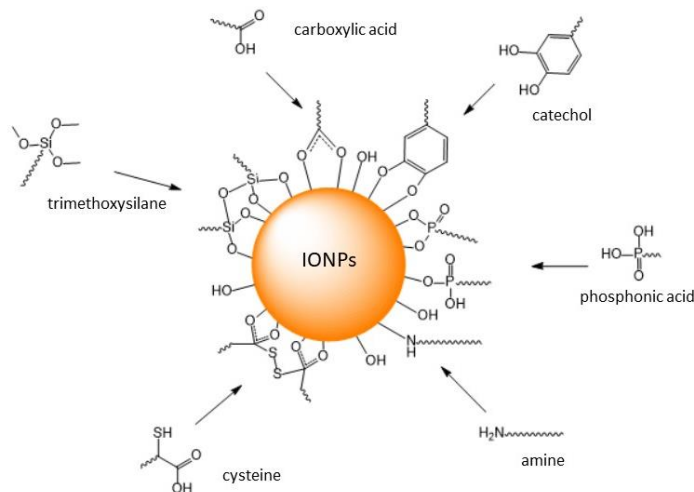
Since the pioneering work of Louis Néel in the 1950s, there is an ongoing and steady interest in the use of MNPs. The versatility of MNPs is well acknowledged and summarized in various reviews.<sup>24–26</sup>

MNPs can be prepared from various metals, mainly iron, cobalt, nickel and rare-earth metals. Among those, IONPs including magnetite ( $\text{Fe}_3\text{O}_4$ )<sup>27</sup> and maghemite ( $\gamma\text{-Fe}_2\text{O}_3$ )<sup>28</sup> are the most common ones. They are mostly used for biomedical applications,<sup>29</sup> because of their very small size (a few tens of nm) combined with their unique superparamagnetic properties. Most IONPs are synthesized by one of the four main synthetic strategies, *i.e.* co-precipitation, micro-emulsion, thermal decomposition and hydrothermal synthesis.<sup>30</sup>

Co-precipitation of iron salts in water is the most common technique due to its rapidity, simplicity and scalability. However, the disadvantage of this technique is that the obtained IONPs are often heterogeneous in size (between 10 - 100 nm). Alternately, the micro-emulsion pathway, which uses micrometric droplets formed in a microemulsion as nanoreactors, allows the preparation of well-defined IONPs below 10 nm in diameter. Nonetheless, this pathway requires a large volume of solvent, large quantities of surfactants and specific equipment to prepare the microemulsion, hence, limiting the scalability. In contrast, thermal decomposition is a scalable technique that provides NP with a very narrow size distribution (low polydispersity) and the possibility of shape control. Yet, synthesizing IONPs by thermal decomposition is quite difficult and requires long reaction times as well as high reaction temperatures. Finally, hydrothermal synthesis, while being less straightforward, is a versatile technique to prepare IONPs with low polydispersity and controlled shapes (e.g. spheres, cubes or rods). Additional information regarding the synthetic methods and their comparison can be found in excellent reviews.<sup>31–37</sup>

It should be pointed out here that “bare” IONPs, of which the surface is not modified or stabilized by surfactants, can be colloiddally stable in an acidic or basic aqueous medium (thanks to intrinsic charges present at the surface), but tend to aggregate close to their isoelectric point around pH 7. Therefore, their colloidal dispersion in water at pH 7 or in organic solvents generally requires a surface functionalization step<sup>38</sup> to introduce stabilizing groups. Apart from a gain in stability, their combination with organic compounds such as stimuli-responsive polymers<sup>38</sup> can also provide new interesting properties to the

magnetic hybrid. **Figure 2** depicts the main functional “anchoring” groups used to interact with the hydroxyl groups intrinsically present on the IONPs’ surface.<sup>10</sup>



**Figure 2. Overview of the most common functional groups used to interact with the surface of IONPs.**

Among the existing synthetic pathways used to generate such surface-modified IONPs, one can mention the *grafting (on)to*, the *grafting through* and the *grafting from* techniques, which will be discussed in sections 3.1.3, 3.1.4 and 3.2.5, respectively. Concerning the chemical ligation, a variety of reactions has been used, such as silanization, nucleophilic substitution and notably click chemistries (e.g. azide-alkyne cycloaddition and thiol-ene reaction). Such reactions have been used for functionalizing IONPs by (i) monomers, in view of the *grafting through* approach, (ii) initiators (for *grafting from*), but also (iii) to covalently link polymeric chains on surface-functionalized IONPs (by the *grafting onto* approach or for the preparation of macroscopic covalent hybrids (networks)).

### 3. Stimuli-responsive magnetic polymer hybrids

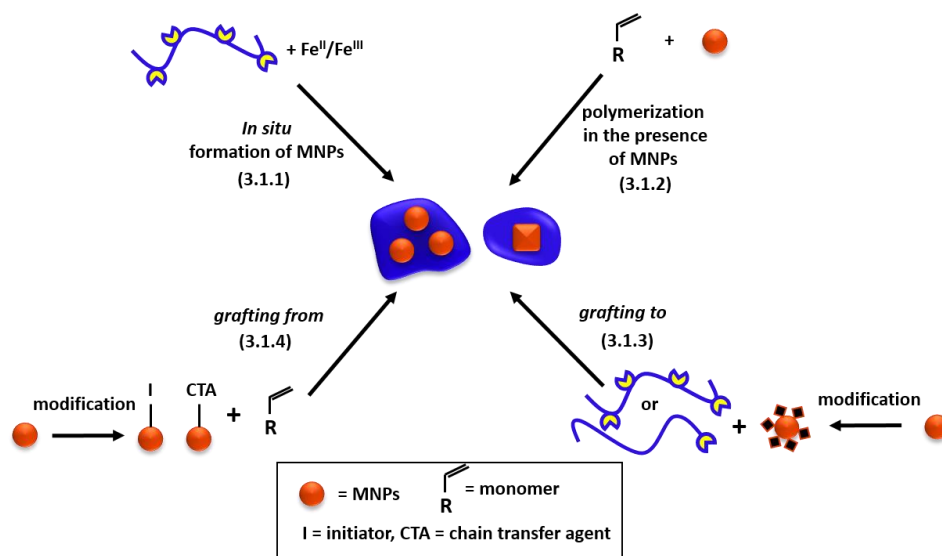
Using the strategies mentioned above, IONPs have successfully been combined with various polymeric systems to produce hybrid (nano)materials. A key feature of such hybrid systems relies on the possibility to use magnetic separation to retrieve and recycle them. In addition, their nanometric size and thus their large surface-to-volume ratio make IONPs ideal candidates as catalytic supports, for sensing applications or to concentrate relevant biological molecules.<sup>5,7,39</sup> Furthermore, IONPs can be guided under an external magnetic field (EMF) in a spatiotemporally controlled manner, which can be useful for biomedical applications.<sup>10,16,17</sup> Finally, upon exposure to an external alternating magnetic field (AMF) they can locally increase the temperature (therefore named “nanoheaters”), which is used for cancer treatment via hyperthermia.<sup>43–45</sup>

Interestingly, when combined with stimuli-responsive polymers, additional features - such as thermoresponsiveness, valuable for sensing and drug delivery applications for instance - are conferred to the hybrid systems. Thanks to their unique properties, stimuli-responsive polymer hybrids (RMPH), are employed in a wide range of research domains, including energy storage<sup>33</sup>, solid-phase extraction<sup>7</sup>, catalysis<sup>39,46</sup>, sensing/imaging<sup>5,47</sup>, biomedical devices<sup>48</sup>, and cancer theranostics<sup>12,40,49</sup>.

The following sections of this review illustrate the various strategies reported in the literature to develop stimuli-RMPH of different structures and shapes.

### 3.1. Magnetic core-shell polymer particles

In this review, we classify stimuli-RMPH as core-shell particles when one or several IONPs serve as the “core” that is surrounded by polymeric chains that constitute the “shell”. Such structures appear to be the most common ones reported in the literature. Core-shell stimuli-RMPH can be obtained by different synthetic approaches summarized in **Figure 3**: (i) the *in situ* formation of MNPs in the presence of preformed polymer chains (see section 3.1.1), (ii) the polymerization of relevant monomers in the presence of MNPs (see section 3.1.2), (iii) through the *grafting to* approach, where preformed polymer chains are grafted on MNPs thanks to functional groups (see section 3.1.3), and (iv) the *grafting from* approach, where the polymerization is performed in the presence of MNPs that are functionalized by an initiator or a chain transfer agent (CTA) (see section 3.1.4).



**Figure 3.** Summary of the different approaches used to prepare core-shell stimuli-RMPH.

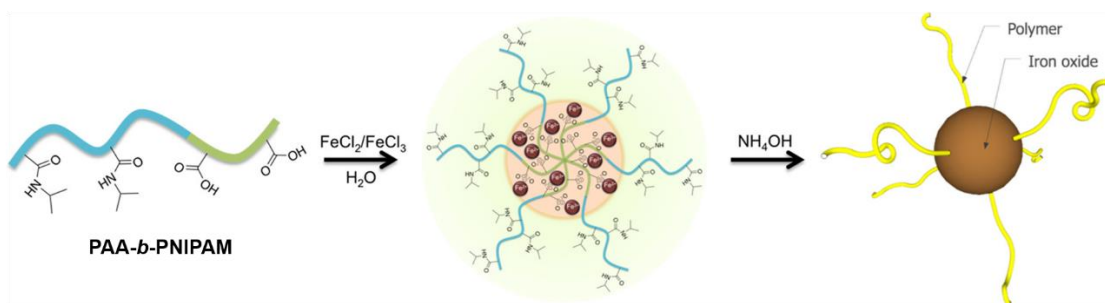
#### 3.1.1. *In situ* formation of magnetic nanoparticles through the co-precipitation of iron salts in the presence of preformed polymers

In general, this technique is based on the complexation of iron salts by specific functional groups that are present either at the end of a polymeric chain or distributed along it. The co-precipitation of iron salts is initiated by the addition of a base, triggering the *in situ* formation of IONPs embedded in the polymeric structure.

For instance, Hossain *et al.*<sup>50</sup> prepared thermal- and pH-RMPH through the co-precipitation of ferrous ( $\text{Fe}^{2+}$ ) and ferric ( $\text{Fe}^{3+}$ ) ions triggered by the addition of ammonium hydroxide ( $\text{NH}_4\text{OH}$ ) in the presence of poly(*N*-isopropylacrylamide-co-2-aminoethylmethacrylate hydrochloride) (P(NIPAM-co-AEMA<sub>H</sub>)) statistical copolymer chains. Due to the basic conditions, the AEMA<sub>H</sub> units are deprotonated and the resulting ammonium groups become available to interact with the surface of the IONPs formed *in situ*. Interestingly, the amide groups of the NIPAM units behave as additional weaker ligands. On the one hand, Fourier Transform Infrared (FTIR) spectroscopy and X-ray diffractometry (XRD) were used to confirm the formation of  $\text{Fe}_3\text{O}_4$  nanoparticles and to determine their crystalline structure. On the other hand, thermogravimetry analysis (TGA) allowed determining the hybrids' composition, *i.e.* the weight fraction of polymer and inorganic particles respectively. In addition, the morphology of the nanocomposites was

characterized by scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The latter techniques did not allow imaging unambiguously the polymeric domains, but dynamic light scattering (DLS) measurements confirmed the formation of nanometric particles, suggesting the formation of clusters of individual IONPs connected by the polymer chains. A vibrating sample magnetometer (VSM) was also used to confirm that magnetization of the hybrids was present. Using DLS and DNA adsorption essays, the authors evidenced that the core-shell hybrids were not only thermoresponsive (with an LCST-type temperature transition originating from the NIPAM units), but that they also exhibited a pH-sensitivity as a response to the protonation/deprotonation of the primary amine groups of the AEMA units.

Polymers possessing functional groups along the polymer backbone that are able to complex the cationic iron salts have also been used. The most common functional groups exhibiting a strong ability to complex with iron salts are carboxylic acid groups. Jauregui *et al.*<sup>51</sup> explored this approach using a pH- and temperature-responsive diblock copolymer, possessing carboxylic acid moieties, namely a poly(acrylic acid)-*block*-poly(*N*-isopropylacrylamide) (PAA<sub>22</sub>-*b*-PNIPAM<sub>150</sub>). As presented in **Figure 4**, the MNPs were synthesized *in situ* through the complexation of the iron salts with the carboxylic acid functional groups (present in acrylic acid, AA).<sup>51</sup> Their study highlighted that the size of the final hybrids, determined by DLS and size-exclusion chromatography (SEC) measurements, was tunable by changing the Fe/COOH ratio: the higher the ratio, the larger the size of the resulting hybrid particles. TGA evidenced that the hybrids were composed of nearly 44 wt% by the MNPs. TEM analysis was then performed to assess the shape and structure of the hybrids. While it could confirm the presence of well-defined spherical MNPs, unfortunately, it did not allow visualizing the organic polymeric shell of the hybrids. Thanks to the PNIPAM-block, the hybrids exhibited an LCST behavior with the possibility to capture and release biomolecules through the change in solubility of PNIPAM above (insoluble) and below (soluble) a critical temperature (34°C).



**Figure 4.** Formation of core-shell stimuli-RMPH by the *in situ* synthesis of MNPs in the presence of PAA-*b*-PNIPAM, adapted with permission from ACS Appl. Mat. Int., 2018, 10(40), 33847-33856, ©2018, American Chemical Society<sup>51</sup>.

### 3.1.2. Polymerization in presence of magnetic nanoparticles

In this approach, stimuli-RMPH are obtained by the polymerization of suitable monomers in the presence of preformed MNPs. In contrast to the former strategy, the MNPs are thus formed in a first independent synthesis step and incorporated in the polymer matrix while it is formed. The MNPs surface can be either bare or coated by small organic molecules, namely oleic acid (OAc) and oleyl amine (OAm) for polymerizations in organic media, or folic acid (FA) and citric acid (CA) for polymerization in aqueous media. Such coating will confer them stabilization during the polymerization process. Again, the MNPs will be durably incorporated into the hybrids thanks to their interaction with the functional groups present on the monomer units, typically carboxylic acid, phosphonic acid, catechol groups, and primary amines or amides, as depicted previously in **Figure 2**. Typical (co)monomers are therefore AA (carboxylic acid

anchoring group) and acrylamides such as NIPAM (weak ligand) because of their ability to interact with the IONPs before polymerization.<sup>52-54</sup>

As an example, Jaiswal *et al.*<sup>54</sup> used this approach to prepare thermo-RMPH by the polymerization of NIPAM in water in the presence of MNPs (which were stabilized by OAc, poly(ethylene glycol) (PEG) and polyhedral oligomeric silsesquioxane (POSS)) and initiated by ammonium persulfate (APS). The amount of embedded Fe<sub>3</sub>O<sub>4</sub> MNPs and their crystalline structure were determined using ion-coupled plasma atomic emission spectroscopy (ICP-AES), XRD and FTIR respectively. Then, SEM, STEM and atomic force microscopy (AFM) were used to determine the shape and size of the resulting hybrids, which appeared spherical and of roughly 200 nm in diameter. The hybrids exhibited an LCST-type transition temperature of around 40°C and proved to be excellent candidates for theranostics.

However, compared to the *grafting to* technique described in the next section, fewer examples of such an approach can be found in literature, presumably because distinct core-shell structures are more difficult to achieve.

### 3.1.3. *Grafting of preformed polymers onto magnetic nanoparticles (grafting to or grafting onto approach)*

The *grafting to* technique relies on the interaction of specific anchoring groups present at the chain-end of the polymer or along the polymer backbone with functional groups present on the surface of bare (hydroxyl groups) or modified IONPs (see **Figure 2 & 3**).

In the literature, the most frequently employed anchoring group for *grafting to* are carboxylic acid groups.<sup>55-58</sup> It is worth mentioning that the presence of carboxylic acid groups, for instance in the monomer units (such as in AA), does not only allow interactions with the MNP, but also confers pH-responsiveness to the hybrids. As an example, Liu *et al.*<sup>56</sup> synthesized pH-, ionic strength (IS) and temperature-RMPH via electrostatic interactions between ( $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>) and poly(acrylic acid)-*block*-poly(vinyl alcohol) (PAA-*b*-PVOH) in PBS buffer solution. The composition of the final nanometric hybrids was determined by TGA, IR and X-ray photoelectron spectroscopy (XPS), which confirmed the presence of the polymeric shell. A diameter of 120 nm was determined by DLS. The hybrids were stable in water and exhibited the expected LCST-type behavior in water inducing methylene blue (MB) release upon heating or upon the application of an AMF.

Apart from the use of functional monomers (e.g. AA), such functional groups can also be generated by the chemical modification of preformed non-functional polymers. For example, Ghamkhari *et al.*<sup>58</sup> prepared dual stimuli-RMPH starting from poly(2-hydroxyethylmethacrylate)-*block*-poly(*N*-isopropylacrylamide)-*block*-poly(*N,N*-dimethylaminoethylmethacrylate) triblock copolymers (PHEMA-*b*-PNIPAM-*b*-PDMAEMA), which do not form strong complexes with MNPs. The hydroxyl groups of the PHEMA block were subsequently reacted with succinic anhydride to generate carboxylic acid pendant groups that can interact with the surface of magnetite (Fe<sub>3</sub>O<sub>4</sub>) MNPs. Using similar characterization techniques (TGA, XRD, SEM), spherical hybrid particles were obtained with a diameter around 35 nm, that exhibited pH- and thermoresponsiveness in water.

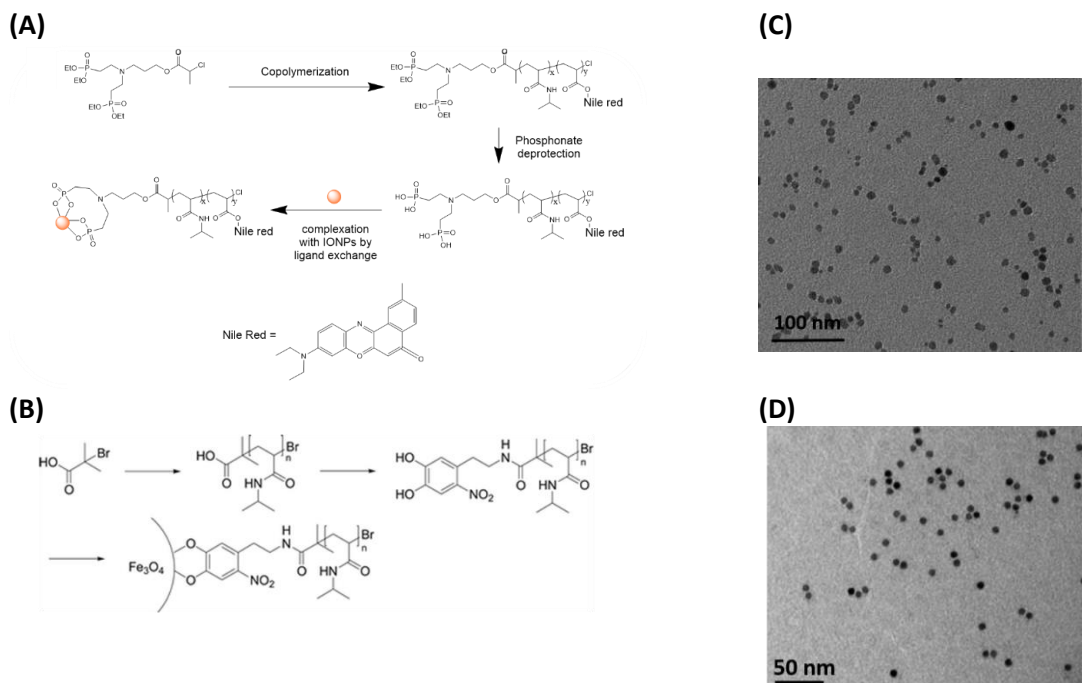
In addition to carboxylic acids, phosphonic acids can also interact with the metallic cations on the surface of IONPs (cf. **Figure 2**). For instance, Boyer *et al.*<sup>59</sup> reported the synthesis of a specific CTA bearing a phosphonic acid moiety on its R-group and a carboxylic acid group on its Z-end. Using this CTA, the reversible addition-fragmentation chain transfer (RAFT) polymerization of several monomers including NIPAM and oligo(ethylene glycol) acrylate (OEGA) were performed. The obtained stimuli-responsive polymers were then grafted preferentially onto the surface of IONPs *via* the phosphonic acid chain-end. Although the influence of the polymer's molar mass and the MNPs' size on the hybrid formation was discussed using DLS, SEM and TEM, surprisingly, the thermoresponsiveness of the hybrids was not examined.<sup>59</sup> Similarly, a bis(phosphonate)-containing initiator was used by Balasubramaniam *et al.*<sup>60</sup> to



synthesize - by atom transfer radical polymerization (ATRP) - fluorescent thermo-responsive copolymers comprising NIPAM and fluorescent Nile Red acrylic monomer units. After deprotection of the phosphonate chain-end, thermo-RMPH were prepared through ligand exchange between OAc-stabilized MNPs and the bis(phosphonic acid)  $\alpha$ -end functionalized copolymer, as shown in **Figure 5A**. ICPAES was used to determine the final composition of such hybrids ( $\approx 65$  wt% of polymer) and -similarly as before- TEM only allowed visualizing the magnetite cores (**Figure 5C**). Using DLS, fluorescence spectroscopy and NMR relaxometry, the temperature-dependent aggregation behavior of such well-defined Nile Red-tagged core-shell hybrids was assessed. These characterizations indicated that these hybrids could be used as “smart  $T_2$  contrast agents” for magnetic resonance imaging (MRI) applications.

Mussel-inspired attachment of catechol-based compounds on metallic substrate is another common strategy to prepare inorganic-organic hybrid. For instance, Yang *et al.*<sup>62</sup> prepared a core-shell redox RMPH with IONPs as the core. The polymer shell consisted of a poly(isobutylene-*alt*-maleic anhydride) statistical copolymer. Through reaction with the anhydride moieties, three different compounds were grafted on the polymer backbone: First, dopamine (DPA) - a catechol - for complexation with IONPs, second  $\alpha$ -methoxy-PEG- $\omega$ -NH<sub>2</sub> for stealth properties, and finally cystamine incorporating a disulfide bond to confer redox responsiveness and allow chemical ligation of a fluorophore, namely Chlorin e6 (Ce6). After characterization using XRD and high-resolution TEM (HR-TEM), the authors evidenced that these redox-RMPH exhibited  $T_2$ -weighted contrast-enhanced capacity and could be used as a theranostic agent for tumor-therapy.

An alternative to the functionalization of polymer backbones with catechol moieties is the use of catechol end-functionalized polymers that can be covalently grafted onto MNPs through a ligand exchange reaction.<sup>61,63</sup> For instance, Kurzhals *et al.*<sup>61</sup> reported the use of a nitrodopamine (NDPA) ATRP initiator to synthesize a PNIPAM presenting a NDPA chain-end. Such NDPA units were used as anchors for magnetite (Fe<sub>3</sub>O<sub>4</sub>) IONPs to achieve core-shell thermo-RMPH core-shell (**Figure 5B**). The presence of the polymer shell was confirmed through attenuated total reflectance-FTIR (ATR-FTIR) and TGA experiments. Spherical, well-dispersed individual core-shell NPs were obtained as evidenced by TEM (**Figure 5D**). Interestingly, the authors proved that the LCST behavior of the thermo-RMPH was independent of the grafting density.



**Figure 5. Preparation of core-shell stimuli-RMPH via grafting to, using PNIPAM end-functionalized by (A) phosphonic acid or (B) catechol. (C) and (D): Representative TEM images of the resulting PNIPAM-coated MNPs (adapted from Chem. Mater, 2011, 23(14), 3348-3356, ©2011, American Chemical Society<sup>60</sup> and adapted from ACS Appl. Mat. Int., 2015, 7(34), 19342-19352, ©2015, American Chemical Society<sup>61</sup>)**

Silanization is another universal technique commonly used for the surface modification of various organic and inorganic substrates, which has also been applied to the preparation of stimuli-RMPH.<sup>64,65</sup> In this approach, bare MNPs or OAc-, OAm- or CA-stabilized MNPs are coated by alkoxysilanes by silica condensation. For example, Hervault *et al.*<sup>64</sup> synthesized a thermoresponsive diblock copolymer presenting alkoxysilane pendant groups via the RAFT copolymerization of diethylene glycol methyl ether methacrylate (DEGMEMA), oligo ethylene glycol methyl ether methacrylate (OEGMA) for the first block, followed by the copolymerization of vinyl benzaldehyde (VBA) and 3-(trimethoxysilyl)propyl methacrylate (MPS) for the second block. While the thermal responsiveness of the hybrid originated from the first block, the hybridization occurred thanks to a silanization step between the MPS co-monomer and the hydroxyl groups present on the surface of the bare IONPs. The benzaldehyde side groups were ultimately used for covalently grafting doxorubicine (DOX) *via* the formation of imine groups, which can be cleaved through pH modification. XRD was used to confirm the crystalline structure of the IONPs embedded in the hybrids, while TGA and FTIR confirmed the presence of the polymer shell (an average of 24 polymer chain per IONPs was calculated). Finally, the thermoresponsive behavior of the hybrids, with a diameter around 120 nm, was confirmed by UV-VIS spectroscopy recording the transmittance at  $\lambda = 540$  nm over a broad range of temperature (turbidimetry measurements).

Alternatively to the use of bare MNP, bare IONPs functionalized by a variety of reactive groups have been used to enhance their interaction with the functional polymers by hybridization or enable covalent bonding by various chemical reactions. The latter approach seems to be the most fruitful one for the preparation of stimuli-RMPH since – compared to the use of bare MNP or the in situ preparation of MNP or polymers - a wider range of covalent and non-covalent bonds can be employed. Conveniently, the pre-modified MNPs and the responsive polymers can be prepared, examined and characterized separately.

Among the reported synthetic strategies, a common strategy relies on the reaction between MNPs functionalized with reactive amine groups and stimuli-responsive polymers presenting carboxylic acid groups.<sup>66–69</sup> For example, Sahoo *et al.*<sup>67</sup> reported the reaction of PNIPAM-*b*-PAA block copolymer with 3-(aminopropyl)triethoxysilane (APTES)-modified magnetite IONPs, providing MNP@PAA-*b*-PNIPAM hybrids through amide bond formation. The usual characterization techniques (XRD, FTIR, HR-TEM) confirmed the crystalline structure of magnetite and the formation of core-shell hybrids. The hybrids were then further functionalized by folic acid (FA) and loaded with DOX for cancer treatment applications.

Exploiting silanization using tetraethylorthosilicate (TEOS) and MPS, Wang *et al.*<sup>70</sup> demonstrated that thiol-end functionalized LCST-thermoresponsive polymers can react with the methacrylate functional groups present on the silane-functionalized MNPs via a Michael addition-type thiol-ene reaction. They therefore synthesized a thermoresponsive diblock copolymer incorporating L-proline units (P(NIPAM-*co*-L-ProA)-*b*-POEGA) by RAFT polymerization followed by an aminolysis step to generate the thiol end-group. The “click” reaction with the methacrylate-functionalized MNPs generated core-shell thermo-RMPH that were characterized using the same aforementioned standard characterization techniques, as well as by elemental analysis (EA). The hybrids could be used as recyclable nanocatalysts in aldol reactions. Similarly, Yang *et al.*<sup>71</sup> yielded core-shell thermo-RMPH as presented in **Figure 6A**. First, they created a catechol formaldehyde resin (CFR) around the magnetite MNPs. Then, through a Michael addition-type thiol-ene reaction between the catechol groups present on the magnetite (Fe<sub>3</sub>O<sub>4</sub>) MNPs and thiol-end functionalized PNIPAM they prepared core-shell NPs presenting spherical shapes and quite large diameters (> 200 nm), as depicted on **Figure 6B**. These core-shell structures were further functionalized by carbon quantum

dots/palladium (CD/Pd) NPs to yield recyclable nanocatalysts. The presence of the MNPs allowed the recovery of the nanospheres through magnetic separation.

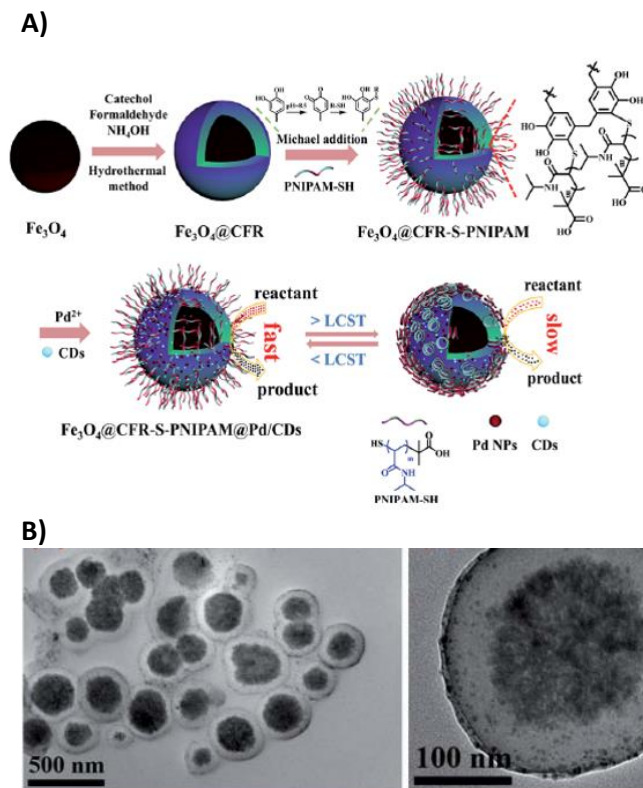


Figure 6. A) Preparation of thermo-RMPH by *grafting to* using thiol-ene click chemistry, B) TEM images of  $\text{Fe}_3\text{O}_4\text{@CFR-S-PNIPAM@Pd/CD}$  nanohybrids (from reference <sup>71</sup> with permission from the Royal Society of Chemistry)

Using an original approach, Yang *et al.*<sup>72</sup> engineered pH-RMPH suitable for water-oil separation. After the modification of the IONPs by TEOS, a second silanization reaction was performed to graft iodopropyl functional groups to their surface. Finally, poly(4-vinylpyridine)-*block*-poly(dimethylsiloxane)-*block*-poly(4-vinylpyridine) triblock copolymers (P4VP-*b*-PDMS-*b*-P4VP) were covalently linked to the MNPs *via* a quaternization reaction between the iodopropyl groups and the pyridyl groups on the P4VP block. The composition of the hybrids and of their surface were determined using FTIR and TGA. Spherical core-shell pH-RMPH were obtained, displaying tunable diameter depending on pH (44 to 75 nm determined by TEM and DLS).

Overall, the *grafting to* approach allows the preparation of well-defined core-shell nano-objects with the advantage that both constituents (IONPs and polymers) can be characterized individually before the hybrid synthesis.

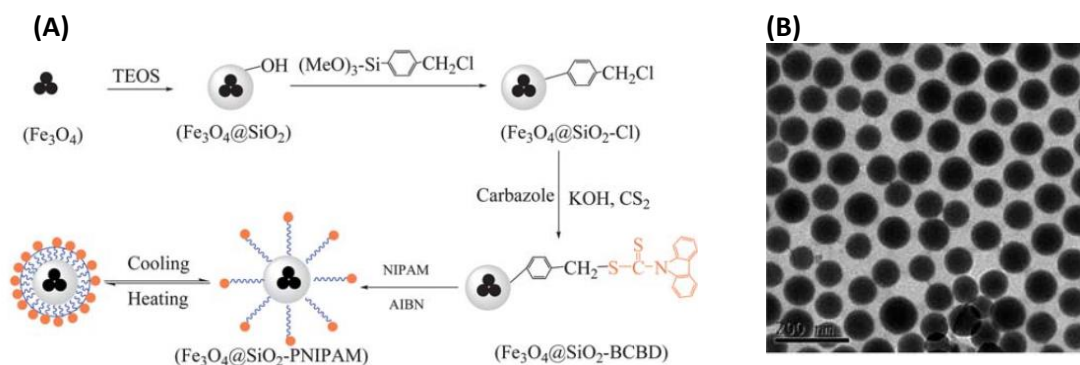
#### 3.1.4. Grafting from

The *grafting from* strategy requires MNPs that are functionalized at their surface by initiating sites or CTAs to graft polymer chains through initiation from the MNP surface or through transfer reactions. Generally, radical initiators (e.g. ATRP initiators) or CTAs (e.g. RAFT agents) allowing for a controlled radical polymerization mechanism have been used. Interestingly, by changing the IONPs' initiating sites/monomer

ratio, the grafting density of the IONPs' surface can be controlled and the polymer chain length can be tuned.

Similar to the surface functionalization presented in section 3.1.3, bare MNPs, or MNPs stabilized by OAc, OAm (in organic media) or CA (in aqueous media), are usually chemically functionalized by initiators or CTAs via two main approaches: either ligand exchange<sup>73–80</sup> or silanization<sup>81–89</sup>, as depicted in **Figure 2**. Regardless of the approach, the resulting functionalized-MNPs are used to promote and control the polymerization of various monomers, mainly using either RAFT or ATRP to prepare the stimuli-RMPH.<sup>90</sup>

For instance, Qiang Li *et al.*<sup>91</sup> reported the synthesis of thermoresponsive PNIPAM@MNPs composites by surface-initiated RAFT (SI-RAFT) polymerization of NIPAM. First, the magnetite ( $\text{Fe}_3\text{O}_4$ ) NPs were chemically modified through several reaction steps (**Figure 7A**) to prepare fluorescent CTA-modified MNPs (CTA@MNPs). While XRD analyses showed that the MNPs embedded within the silica matrix exhibited a typical spinel crystalline structure, TGA analyses confirmed the successful grafting of the RAFT agent onto the silica layer. The CTA@MNPs were then successfully used to grow the PNIPAM chains from the surface of the MNPs. The resulting hybrids were spherical, as evidenced by TEM images, with mean-diameters changing from 208 nm to 165 nm upon temperature increase from 24 °C to 40°C (**Figure 7B**).



**Figure 7. (A) Synthesis of core-shell RMPH hybrids by surface-initiated RAFT polymerization. In a first step, the  $\text{Fe}_3\text{O}_4@\text{SiO}_2$  were functionalized with a RAFT agent *via* a silanization approach, (B) TEM images of the resulting  $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-PNIPAM}$  NPs (reproduced from reference<sup>91</sup> with permission from the Royal Society of Chemistry)**

A similar synthetic approach, relying on surface-initiated ATRP (SI-ATRP) was employed by other research groups<sup>89,92,93</sup> using various monomers, such as NIPAM, OEGMA, DEGMEMA and/or 2-diaminoethylmethacrylate (DEAMA), to achieve thermo- and pH-RMPHs for drug delivery applications.

As discussed previously, carboxylic acid groups are prone to form complexes with iron cations. Therefore, ATRP initiators or RAFT agents bearing carboxylic acid groups can be directly linked to the surface of MNPs.<sup>76–80</sup> For example, using SI-RAFT polymerization, Wang *et al.*<sup>76</sup> prepared a thermoresponsive  $\text{Fe}_3\text{O}_4@\text{PNIPAM}$  thanks to the grafting of a trithiocarbonate CTA possessing a carboxylic acid functional Z-group on the MNPs. Depending on the targeted degree of polymerization (DP), various core-shell thermo-RMPH with different polymer content and apparent  $D_H$  were prepared, as evidenced by SEC, DLS and TGA. These particles presented switchable diameters upon temperature change and proved to be good candidates for theranostic applications. In terms of SI-ATRP, Gelbrich *et al.*<sup>79</sup> modified the surface of IONPs by an ATRP initiator containing a carboxylic acid moiety (2-bromo-2-methylpropionic acid) to initiate the polymerization of OEGMA and methoxyethyl methacrylate (MEMA). They obtained nanometric core-shell particles, which exhibited a reversible thermoflocculation.

Similarly, but targeting pH-responsive core-shell NP, Ajkidkarn *et al.*<sup>80</sup> modified the surface of iron oxide nanocubes with  $\alpha$ -bromoisobutyric acid. The functionalized MNP were used for the SI-ATRP of DMAEMA and pH-RMPH composites formed, useful for drug delivery applications.

Alternatively, He *et al.*<sup>78</sup> grafted a dendritic ATRP initiator bearing four carboxylic acid anchoring groups onto magnetite (Fe<sub>3</sub>O<sub>4</sub>) MNPs. The Fe<sub>3</sub>O<sub>4</sub>@initiator was then used for the SI-ATRP of pH-sensitive DMAEMA monomer as the first polymer block. Then, this pH-sensitive polymer was chain-extended by a second, hydrophilic block (POEGMA) and water-soluble Fe<sub>3</sub>O<sub>4</sub>@PDMAEMA-*b*-POEGMA hybrid nanoparticles were obtained. As evidenced by SEC analyses, the polymer chains cleaved from the MNPs presented a monomodal molar mass distribution and a low dispersity, confirming the controlled character of the polymerization. DLS measurements revealed that particles with an average hydrodynamic diameter ( $D_H$ ) close to 26 nm and narrow size distribution (low polydispersity indices, PDI) were obtained. Furthermore, the authors showed that the hybrids exhibited a dual pH- and thermoresponsiveness. After DOX loading, the hybrids were able to release their payload on demand.

As discussed previously, catechols are other valuable anchoring groups. The research group of Pellegrino has reported the use of a catechol-functionalized RAFT agent and ATRP initiators to functionalize the surface of cubic and spherical IONPs. These functional groups were then used for SI polymerizations to prepare pH- or thermo-RMPH based on poly(*N*-vinylpyrrolidone-*co*-poly(oligo(ethylene glycol) methyl ether acrylate) (P(NVP-*co*-PEGA))<sup>94</sup>, P(NIPAM-*co*-PEGA)<sup>94</sup> or P(DEGMEMA-*co*-OEGMA)<sup>95</sup> copolymers, by both ATRP and RAFT polymerizations. These works demonstrated the possibility to encapsulate and release DOX in a triggered manner, suggesting their potential in heat-mediated chemotherapy. Overall, the use of SI-controlled polymerization ensured the formation of a polymer shell that was uniform in thickness, prevented MNPs' aggregation without impacting the heating performance of the MNPs. In a related work, Krishnan *et al.*<sup>96</sup> reported recently the SI-ATRP of NIPAM from magnetite (Fe<sub>3</sub>O<sub>4</sub>) MNPs. Interestingly, as evidenced by TEM and DLS, all hybrids were clusters of individual particles, which remained stable in solution at room temperature. The hybrids were successfully used as support for biocatalysts, of which the catalytic activity could be turned on or off as a function of temperature.

Interestingly, Kurzhals *et al.*<sup>61</sup> employed the same initiating and anchoring group (NDPA) to compare two synthetic pathways: *grafting onto* (discussed in section 3.1.3) and *grafting from* to achieve PNIPAM-coated thermoresponsive MNP by ATRP. As discussed previously, *grafting of* NDPA end-functionalized PNIPAM on IONPs led to well-dispersed spherical core-shell stimuli-RMPH. In contrast, the *grafting from* strategy using ATRP-initiator-grafted MNPs, obtained through ligand exchange between NDPA initiator and OA-MNPs in dimethylformamide (DMF), led to complex core-shell particles containing clusters of MNP in their cores as evidenced by TEM. This is presumably due to the difficulty to homogeneously disperse the initiator-coated MNPs in DMF, which was the solvent of polymerization. Nevertheless, the core-shell particles were stable, and compared to the *grafting to* approach, polymers of higher molar mass could be produced. Indeed, *grafting of* high molar mass polymers onto the MNP is difficult to achieve by the *grafting onto* technique because of the steric hindrance.

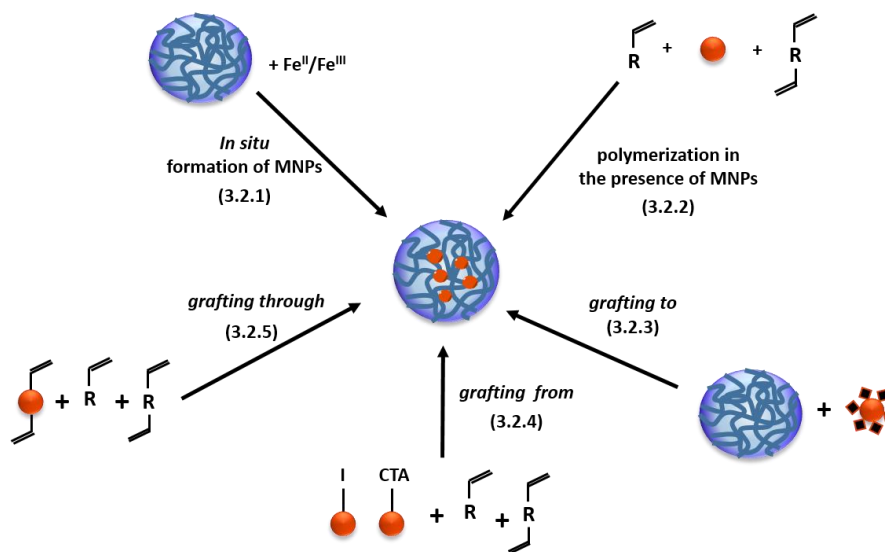
Overall, the *grafting from* approach seems quite versatile, since a rather large variety of anchoring groups can be used to link the initiating moieties on the MNPs surface. While ligand exchange seems a more straightforward approach with less synthetic steps involved, the silanization approach constitutes a more versatile, controlled and robust chemical platform for successive functionalization (not limited to polymers).

### 3.2. Hybrid Nanogels, Microgels

Hybrid nanogels (NGs) or microgels (MGs) are defined herein as crosslinked polymer networks of nanometric or micrometric dimension that contain MNPs. Their size can be close to that of core-shell hybrid particles, however, in contrast to the former class, the shell of the hybrids are not individual chains,

but a covalently crosslinked three-dimensional (3D) polymer network obtained through the systematic use of difunctional monomers, so-called crosslinkers.<sup>97</sup>

The incorporation of the MNPs within NGs and MGs can be done by the same synthetic strategies mentioned before (section 3.1), i.e. (i) the *in situ* generation of MNPs in the pre-formed polymeric network (section 3.2.1), (ii) the *in situ* incorporation of MNPs during the synthesis of the polymeric network (section 3.2.2) or (iii) the incorporation of preformed MNPs in a preformed crosslinked polymer network (section 3.2.3). Alternatively, (iv) the functionalization of MNPs with initiating sites (*grafting from*, section 3.2.4.) or polymerizable units (*grafting through*, section 3.2.5.) are other common strategies. **Figure 8** sums up different synthetic strategies employed to prepare stimuli-responsive hybrid NGs/MGs.



**Figure 8.** General overview on the different synthetic approaches to design hybrid NG and MG.

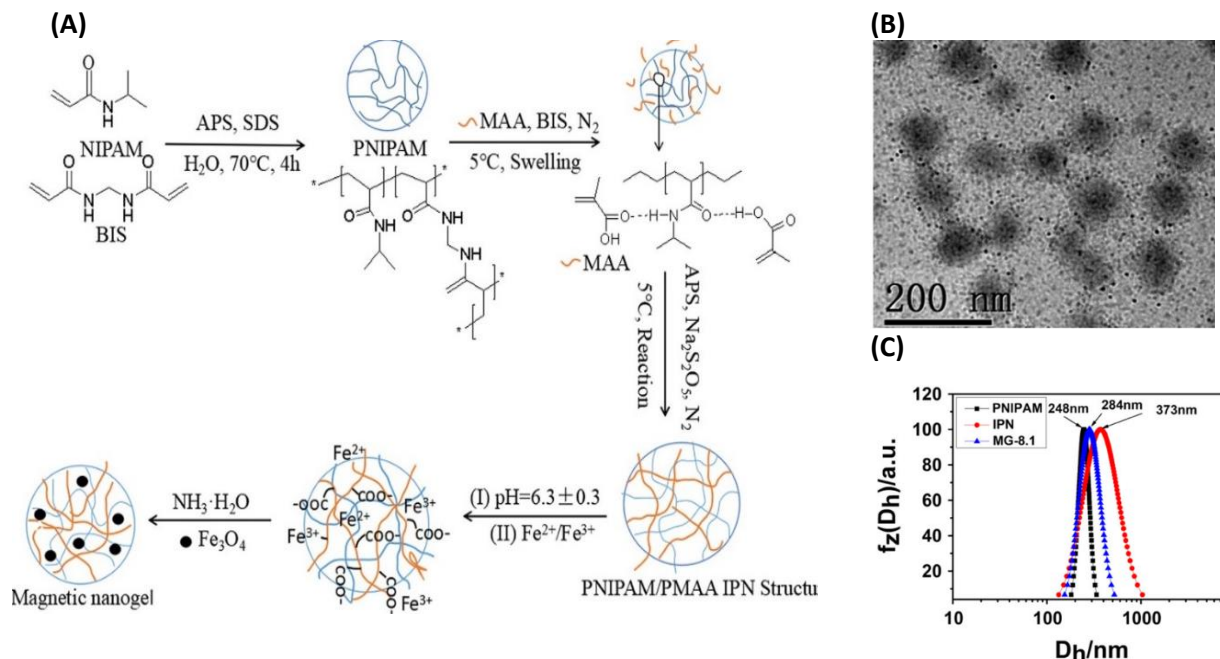
Among such magnetic hybrids, there is a specific type of NGs (or MGs) called magnetic protein imprinted polymers hybrids (MPIP). MPIPs are highly crosslinked polymer networks imprinted by a specific (macro)molecule/protein during their synthesis that are able to selectively recognize it out of a complex mixture.<sup>98</sup>

### 3.2.1. *In situ* formation of magnetic nanoparticles within preformed nanogels or microgels

Based on the same strategy discussed in section 3.1.1, the MNPs are formed *in situ* within an existing polymer network (NG or MG), generally through the co-precipitation of  $\text{Fe}^{2+}$  and  $\text{Fe}^{3+}$  ions in basic conditions.<sup>99–103</sup>

As an example for a complex magnetic hybrid NG system, Yao *et al.*<sup>100</sup> synthesized thermo- and pH-responsive interpenetrated network (IPN) NGs of which the structure is illustrated in **Figure 9A**. In a first step, they prepared a classical PNIPAM-based NG, through the dispersion polymerization of NIPAM in the presence of *N,N'*-methylene bis(acrylamide) (BIS) as a crosslinker. Then, the resulting NGs were swollen in a solution of methacrylic acid (MAA) and BIS, and a second polymerization step was performed to yield the IPN NGs. Finally, the MNPs were produced within the IPN by the co-precipitation of  $\text{Fe}^{2+}$  and  $\text{Fe}^{3+}$  salts. As explained previously, the carboxylic acid groups of PMAA can coordinate the metal cation and thereby assist the formation of nanometric magnetic particles within the preformed IPN. After incorporation of the MNPs, as evidenced by TEM (**Figure 9B**) and DLS (**Figure 9C**), the resulting NGs were spherical in shape

and possessed a reduced diameter compared to the IPN's diameter before MNPs incorporation. As stated by the authors, this can be explained by the interaction between the iron oxide and the polymer networks. The main interest of such hybrid IPNs NGs relies in the fact that the two polymer matrices are independently sensitive to pH and temperature.



**Figure 9.** (A) Preparation of thermo-RMPH by *in situ* reduction of ferrous (Fe<sup>II</sup>) and ferric salts (Fe<sup>III</sup>) within preformed IPN NGs, (B) TEM images of the magnetic NGs, (C) particle size and size distribution of PNIPAM, IPN NGs and 8.1 wt% magnetic NGs at 25°C and pH around 7.4, adapted from reference.<sup>100</sup> Wiley, *Polymers for advanced technologies*, 2019, 30, 312-319.

Many other examples of NGs have been devised containing AA or MAA units that are prone to complex with iron cations. For instance, NGs composed of P(NIPAM-*co*-HEMA-*co*-MAA)<sup>101</sup> or P(NIPAM-*co*-AA-*co*-HEA)<sup>103</sup> have been prepared, where, at sufficiently high pH, the (M)AA units can coordinate to the iron salts and thereafter to the newly-formed MNPs surface. It should be mentioned that the MNP act then as additional crosslinking point in the polymer network.

### 3.2.2. Polymerization in the presence of magnetic nanoparticles: simple embedding or ligand exchange

The most common strategy used to prepare hybrid NGs is the *in situ* incorporation of preformed MNPs during monomer polymerization to create the polymer network. As such, the copolymerization of various monomers and crosslinkers were performed in the presence of MNPs, either in organic (OAc- or OAm-stabilized MNPs) or aqueous media (mainly CA-stabilized MNPs). This method has proved to be efficient robust, and allowed the synthesis of various temperature-, pH- and photo-RMPH NGs.<sup>104–113</sup>

For instance, Wei *et al.*<sup>104</sup> reported the synthesis of photo-RMPH by ATRP-mediated crosslinking copolymerization of 4-[(4-methacryloyloxy)phenylazo] benzenesulfonic acid (MAPA-SA) (a photo-responsive azobenzene-containing monomer) and ethylene glycol dimethacrylate (EGDMA) as crosslinker in the presence of OA-stabilized MNPs. The additional presence of paracetamol during the polymerization process allowed the preparation of photo-responsive molecular imprinted NGs (MPIP). SEM and TEM analyses confirmed the formation of MPIP with a rough surface. Paracetamol could be loaded into the NGs

when the azobenzene moieties were in *trans* configuration. After loading, paracetamol could be released via irradiation at 365 nm, which triggers the photo-isomerization into *cis*-azobenzene, as evidenced by differential pulse voltammetry (DPV). Similarly, Ghosh *et al.*<sup>107</sup> synthesized thermoresponsive NGs through the emulsion copolymerization of PEGMA, DEGMEMA and EGDMA in the presence of bare MNPs and sodium dodecyl sulfate (SDS) as a surfactant. Such approach yielded 315 nm large spherical NGs, presenting an LCST behavior with a  $T_c$  of 35°C. The authors further showed that the NG could encapsulate drugs and release them upon application of an alternating current (AC) magnetic field.

Additionally, whenever negative charges are present within the NGs/MGs, different authors evidenced that these charges provided additional electrostatic stabilization to the embedded MNPs. Therefore, Jiang *et al.*<sup>108</sup> synthesized pH- and thermo-RMPH by adding CA-stabilized MNPs in the copolymerization of NIPAM, BIS and AA, initiated by potassium persulfate (KPS) via a 2-step dispersion polymerization process in water. After dialysis, fluorescent lactoferrin (Cy5.5-Lf) was covalently linked to the 90 nm-sized NGs for imaging purposes. The resulting hybrid, fully characterized by the usual techniques, was proven to be an efficient drug delivery system with efficient cell-internalization. Likewise, Medeiros *et al.*<sup>109</sup> synthesized poly(*N*-vinylcaprolactam-co-itaconic acid)-based magnetic NGs using BIS as the crosslinker. The NGs were obtained via dispersion polymerization in water in the presence of OAc-stabilized MNPs. Spherical nanometric hybrids (190-nm in diameter) composed of a magnetic core and a stimuli-responsive shell were obtained. Thanks to the presence of the partially ionized groups of the itaconic acid, the RMPH were stable over time at pH 4.5. The hybrids exhibited pH- and temperature responsiveness, useful for drug delivery applications.

Chou *et al.*<sup>110</sup> investigated whether reaction of MNP with AA monomer prior to the radical crosslinking copolymerization could have a positive impact on the NG hybrids' structure. The authors revealed through XPS analysis that such a pre-stabilization step, performed before mixing the MNP with NIPAM and BIS and polymerization, favored the incorporation of MNPs. Indeed, using this 2-step method, compared to a one-pot 1-step a higher embedding efficiency of MNPs was achieved (as assessed by TGA measurements), presumably thanks to a better dispersibility of the MNP. In addition, TEM imaging revealed that smaller NGs were produced with diameters between 150 and 240 nm (with the 2-step method), while larger diameters (between 270 and 550 nm) were obtained with the 1-step method.

Generally, the synthesis of the NP by dispersion polymerization in the presence of preformed MNP is quite popular, as it allows to incorporate MNPs within NGs and MGs with good yield. Furthermore, it is evidenced in the literature that such approach allows the incorporation of several MNPs per NG/MG, which in turn makes possible to enhance the NG/MG hybrids' diameter and thereby increase their response towards AMF/EMF stimuli.

### 3.2.3. Grafting to: Post-synthesis complexation of magnetic nanoparticles within nanogels/microgels

The coordination of preformed MNPs within preformed NGs or MGs containing (M)AA units is one of the strategies that allows to use bare MNPs without developing specific surface chemistries. For example, Cazares-Cortes *et al.*<sup>114</sup> prepared thermoresponsive NGs by free radical polymerization of DEGMEMA, OEGMA, MAA and oligo(ethylene glycol diacrylate) (OEGDA). The bare MNPs were integrated by diffusion into the NGs at acidic pH (pH 2-3), and the complexation between carboxylic acid of the NGs and MNPs was triggered by increasing the pH to 6. TGA analyses and TEM imaging confirmed the presence and homogeneous incorporation of the MNPs within the spherical NGs. However, stability issues were encountered when NGs incorporating more than 50 wt% of MNPs were targeted. The ability of these pH-RMPH NGs to encapsulate and release DOX in a controlled fashion was evaluated.



Similarly, MNPs stabilized by alkyl chains could be efficiently incorporated into hydrophilic 3D polymer structures through *in situ* ligand exchange between the stabilizing groups of the MNPs and the functional groups present within the NG/MG. Nandwana *et al.*<sup>115</sup> illustrated this approach by mixing OAc- and OAm-coated MNPs in chloroform solution with an ethanolic solution of P(NIPAM-*co*-BIS-*co*-AA) NGs. After removal of chloroform, milliQ water was added and pH was adjusted to 7 in order to trigger the ligand exchange. Such NGs, characterized by means of TEM and DLS, presented spherical shape with diameters around 200 nm. Interestingly, the presence of the MNPs on the outside/surface of the NGs was confirmed using energy-dispersive X-ray (EDX) and elemental mapping. The obtained hybrids were stable and used as multimodal diagnostic imaging devices and drug delivery systems.

#### 3.2.4. Grafting from

The *grafting from* approach, discussed in section 3.1.4 for linear polymers, can also be applied to the synthesis of NG stimuli-RMPH.

As a representative example, Frimpong *et al.*<sup>116</sup> prepared thermoresponsive NGs by a two-step *grafting from* method. First, OAc- or CA-coated MNPs underwent ligand exchange to form bromoalkyl- and bromosilane-coated MNPs, in organic or aqueous media respectively. The resulting surface-functionalized MNPs were then used as initiators for the SI-ATRP of NIPAM and PEGDMA (a crosslinker,  $M_n = 400$  g/mol). The formation of a crosslinked polymer shell was confirmed using FTIR and TGA measurements. Depending on the initiator grafting density on the MNPs, hybrids with diameters ranging from 60 to 300 nm were obtained as evidenced by TEM imaging. DLS studies were performed in order to monitor the change of the particle size with temperature. The authors evidenced the LCST-type shrinking of the NGs above a  $T_c$  close to 30°C.

Alternatively, Li *et al.*<sup>117</sup> modified MNPs using TEOS and APTES' silanization to obtain amine-functionalized MNPs. The aminated MNPs were reacted with 4-cyano-4-ethyl-trithiopentanoic acid (CEPA, a CTA) through amide bond formation. The obtained MNPs functionalized by the CTA were then used in the radical crosslinking copolymerization of NIPAM, acrylamide (AAm) and *N,N*-bis(acryloyl)cystamine (BAC), as crosslinker. The hybrids exhibited diameters between 240 and 360 nm and a LCST-type  $T_c$  of 38°C determined by TEM imaging and DLS measurements respectively. The authors showed that they were able to encapsulate and release DOX or Curcumine on demand through temperature or redox control. Indeed, upon glutathione (GSH) addition, the disulfide (present in cystamine) can be cleaved through a redox mechanism, induce the destruction of the NGs and thereby the release of its payload.

Overall, the *grafting from* pathway allow to produce NGs and MGs in a controlled fashion. The swelling or shrinking of the polymer matrix was shown as a response to several stimuli, triggering the release of a payload ideally without leakage of the magnetic particles.

#### 3.2.5. Grafting through

This technique relies on the functionalization of MNPs with vinyl functional groups so that they virtually “copolymerize” with a conventional vinylic monomer. As they are decorated by several vinyl groups, the MNPs can behave as crosslinkers. In the literature, such vinyl-MNPs are widely used in the free-radical dispersion copolymerization of NIPAM, along with BIS as crosslinker, to yield thermoresponsive NGs and MGs.<sup>118</sup> Other co-monomers such as (meth)acrylic acid ((M)AA)<sup>119–122</sup>, allyl amine (AlAm)<sup>123</sup>, *N*-ethylmaleamic acid (NEMA)<sup>124</sup>, *N*-(hydroxymethyl)acrylamide (NHMA)<sup>125</sup> can also be inserted to impart additional pH-responsive properties. The most common method used to achieve such surface modification of MNPs is the silanization technique, as already described in section 3.1.3.

For instance, Zhao *et al.*<sup>126</sup> modified the surface of magnetite NPs with TEOS followed by the silanization of the free alkyl siloxanes groups with vinyl functions. Then, the methacrylate-bearing MNPs were copolymerized with allyl glycidyl ether (AGE) and diisopropylaminoethylmethacrylate (DIPAEMA) to prepare pH-responsive NGs. The presence of the polymer was confirmed using TGA and FTIR measurements, while TEM imaging and DLS analysis proved the formation of NGs with spherical uniform shape and an increased diameter compared to the Fe<sub>3</sub>O<sub>4</sub> MNPs. The epoxide moieties of AGE enabled the post-polymerization functionalization of the system, while the presence of DIPAEMA units provided pH-sensitivity.

Alternatively, Xie *et al.*<sup>127</sup> prepared polymerizable MNPs in one single step, using vinyl triethoxysilane (VTEO). They synthesized pH-responsive molecularly imprinted MGs (MPIPs) through the copolymerization of DMAEMA, vinylphenyl boronic acid (VPBA), BIS with VTEO-functionalized MNPs, in the presence of the OVA glycoprotein, using ammonium persulfate (APS) as an initiator. Before removal of the protein, these MPIP were characterized by FTIR, TGA and SEM imaging which confirmed the presence of both the polymer and the MNPs and thus the formation of the hybrid NGs. After removal of the OVA protein, authors showed that the hybrids exhibited pH-responsiveness and were useful for glycoprotein recognition.

### 3.3. Hybrid macrogels

In addition to the NGs and MGs discussed above, magnetic stimuli-responsive gels of macroscopic dimensions can also be prepared via the incorporation of MNPs within a stimuli-responsive crosslinked polymer matrix. The synthetic approaches are similar to the reported ones: (1) MNP can be synthesized within an existing polymer network from precursor salts<sup>128</sup> (cf. section 3.2.1) or (2) be present during the crosslinking polymerization of stimuli-responsive monomers<sup>129–132</sup> (cf section 3.2.2).

For instance, Wang *et al.*<sup>131</sup> achieved dual pH- and thermo-RMPH macrogels in two steps. First, attapulgite-Fe<sub>3</sub>O<sub>4</sub> NPs (AT-MNPs) were synthesized *via* the co-precipitation technique. Then, the AT-MNPs were incorporated in the macrogel network via the free radical copolymerization of DEGMEMA, OEGMA and AA. The resulting macrogels incorporating AT-MNPs presenting a cylinder shape and characterized notably by means of FTIR and field emission-SEM (FE-SEM), displayed tunable swelling properties upon modification of pH, temperature or under application of an AMF.

### 3.4. Hybrid micelles

In contrast to the previous sections where the (co)polymers used were generally hydrophilic, micelles are composed of amphiphilic block copolymers where only one block is water-soluble. In water, amphiphilic copolymers assemble into core-shell micelles with a hydrophilic corona and a hydrophobic core. The incorporation of MNPs within the micelles' cores can be achieved by either physical entrapment (embedding method, see section 3.4.1) or through the combination of ligand exchange and the *grafting to* method (see section 3.4.2).

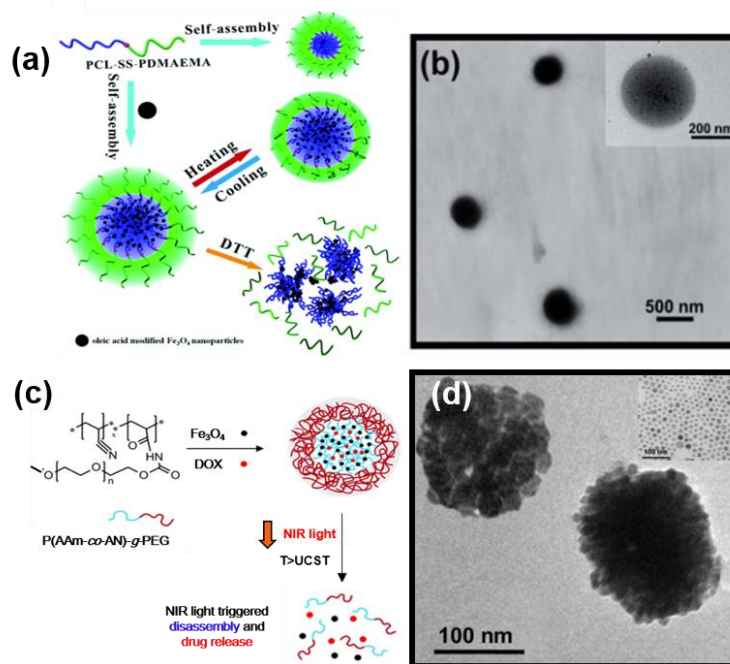
The most common method to prepare amphiphilic block copolymer micelles is the *solvent-evaporation method*.<sup>133</sup> Following the same strategy, hybrid micelles can also be produced: therefore, a mixture of the colloidal MNPs and the block copolymer dissolved in organic solvent (usually a volatile one, such as THF) is added dropwise into water. As water is a selective solvent of one of the blocks of the copolymer, the self-assembly into core-shell micelles is spontaneously triggered. The formed hybrid micelles are then recovered in aqueous solution after dialysis against water.

A specific type of hybrid micelle is so called core-crosslinked hybrid micelle (CCHM), *i.e.* micelles of which the core is crosslinked, which will be described in section 3.4.3.

### 3.4.1. Embedding through physical entrapment

The physical entrapment of various MNPs, such as maghemite ( $\gamma\text{-Fe}_2\text{O}_3$ ), magnetite ( $\text{Fe}_3\text{O}_4$ ) or even magnesium-zinc-iron MNPs (also named MZF), via the *solvent-evaporation method* has been extensively reported in the literature, using amphiphilic diblock<sup>134</sup>, triblock<sup>135</sup> or even star-like<sup>136,137</sup> copolymers. In the cited examples, poly( $\epsilon$ -caprolactone) (PCL) was used as a hydrophobic degradable block, whereas the thermoresponsive hydrophilic block was comprised of NIPAM and AAm<sup>134</sup> or DEGMEMA and OEGMA<sup>136,137</sup> units. These thermo-RMPH micelles showed an LCST-like behavior and spherical shape with diameters ranging from 70 nm to 250 nm depending on the copolymer structure. All systems were able to encapsulate and release DOX upon application of an external AMF inducing magnetic hyperthermia. Using a similar approach, Wang *et al.*<sup>138</sup> also prepared LCST-type thermoresponsive hybrid micelles using an amphiphilic helical diblock copolymer derived from poly(phenyl isocyanide) (PPI) modified by either an aliphatic chain (constituting the hydrophobic block) or three triethylene glycol branches (for the hydrophilic block). The resulting hybrids were also able to encapsulate and release DOX on demand through the application of an AMF.

Eventually, Zou and Yuan<sup>139</sup> prepared redox- and thermoresponsive hybrid micelles. They used amphiphilic poly( $\epsilon$ -caprolactone)-*block*-poly(dimethylaminoethylmethacrylate) (PCL-*b*-PDMAEMA) diblock copolymers possessing a redox-responsive S-S linkage between both blocks (**Figure 10a**). Spherical nanoobjects displaying a mean diameter around 460 nm were formed as evidenced by DLS measurements and TEM imaging (**Figure 10b**) The authors showed that the release of DOX could be controlled by the addition of DL, dithiothreitol (DTT) and the increase of the temperature above 50°C.



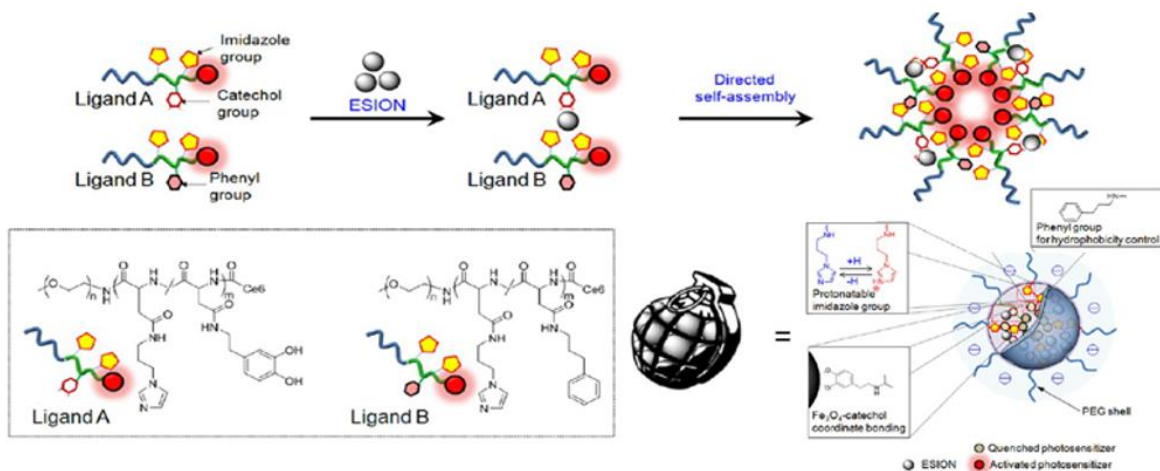
**Figure 10.** (a) Design of the PCL-SS-PDMAEMA@Fe<sub>3</sub>O<sub>4</sub> hybrid micelles and temperature- and redox-responsive behavior, (b) TEM images of the stimuli-RMPH at 25 °C (Reproduced from reference<sup>139</sup> with permission of the Royal Society of Chemistry); (c) Schematic illustration of UCST-type thermo- and light-RMPH, (d) TEM images of Fe<sub>3</sub>O<sub>4</sub> nanoparticles (insert) and Fe<sub>3</sub>O<sub>4</sub>@P(AAm-co-AN)-g-PEG hybrid micelles (Adapted from reference<sup>140</sup> with permission of the Royal Society of Chemistry)

In addition to LCST polymers, diblock copolymers comprising a UCST block have also been synthesized. For instance, Wu *et al.*<sup>140</sup> and Li *et al.*<sup>141</sup> designed UCST-responsive hybrids from a poly(acrylamide-co-acrylonitrile) (P(AAm-co-AN)) copolymer grafted with either methoxy PEG succinimidyl carbonate (mPEG-SC) chains<sup>140</sup> (**Figure 10c**) or PEG end-functionalized with A54<sup>141</sup>, a hepatic tumor cell targeting peptide.

Using Fe<sub>3</sub>O<sub>4</sub> nanoparticles, both light-RMPH were formed through the *solvent-evaporation method*. Spherical nanoparticles were obtained<sup>140</sup> (**Figure 10d**) (with a diameter of 170 ± 56 nm) and exhibited a UCST-type transition of 43°C. They were successfully used for the encapsulation and on-demand release of DOX using NIR as a trigger.

### 3.4.2. Grafting to

While the *solvent-evaporation method* forms hybrid core-shell micelles by simple physical entrapment, the *grafting to* approach is based on specific interactions between the MNPs and the hydrophobic block (as already discussed in section 3.1.3 and 3.2.3). In the literature, amphiphilic diblock copolymers comprising a hydrophilic PEG block and a hydrophobic pseudo-polypeptide block modified with DPA (catechol) moieties were able to interact with MNPs through ligand exchange.<sup>142,143</sup> For instance, Ling *et al.*<sup>142</sup> reported the ring-opening polymerization of benzyl-L-aspartate-*N*-carboxyanhydride (Bz-L-Asp-NCA) from a PEG-NH<sub>2</sub> macroinitiator to achieve block copolymers that were successively functionalized by the fluorophore Ce6. Thereafter, the pseudo-polypeptide block was modified with different molecules, namely 3-phenyl propyl amine (3PPA), imidazole (Im) and DPA to impart hydrophobicity, pH-responsiveness and MNPs-ligation to the copolymer (**Figure 11**). The hybrids were obtained in 2 steps: First, a ligand exchange reaction was performed in organic solvent between OAc-stabilized MNPs (which measured only 3 nm in diameter) and the DPA-modified block copolymers (ligands A and B, in **Figure 11**). Second, the core-shell hybrids were formed by the *solvent-evaporation method* using DMSO as the organic solvent. So-called nano-grenades of 100 nm in diameter were formed that enabled allowed the dual-modal detection of small tumors thanks to the presence of both a fluorophore and MNPs.



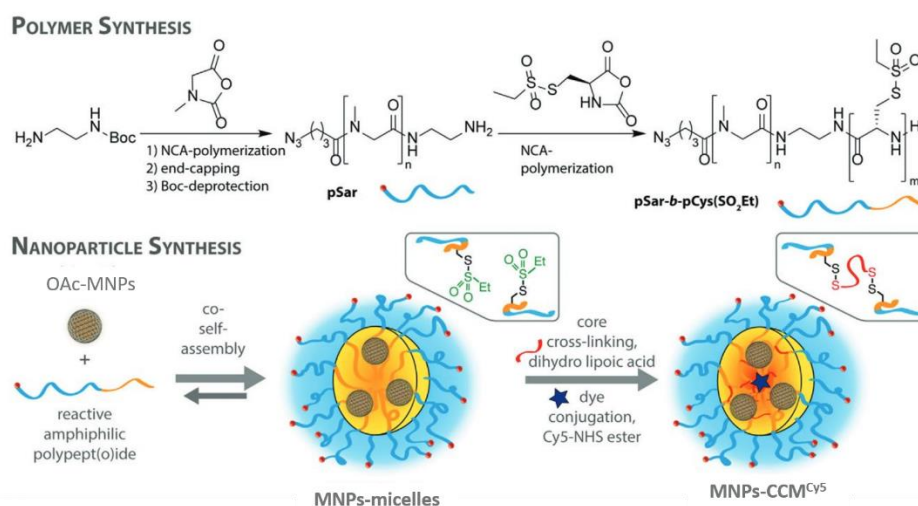
**Figure 11.** Schematic representation of the pH-sensitive, ligand-assisted self-assembly of extremely small iron oxide nanoparticles (ESION), (adapted with permission from JACS, 2014, 136, 5647-5655, © 2014, American Chemical Society<sup>142</sup>);

### 3.4.3. Core-crosslinked hybrid micelles

This class of hybrid micelles differs from the previous one by the fact that the hydrophobic cores -in which the MNPs are entrapped- are crosslinked. Thanks to the covalent crosslinking, the hybrids are more stable to dilution or shear, which is beneficial for biomedical applications.<sup>144</sup>

For instance, Guimaraes *et al.*<sup>145,146</sup> described the synthesis of pH-responsive spherical core-crosslinked hybrid micelles (CCHM), which was achieved in two steps. First, they synthesized amphiphilic block copolymers, namely PDMAEMA-*b*-PS or PAA-*b*-PS. These copolymers were then used to prepare spherical

magnetic hybrid clusters using the *solvent-evaporation method* and FA-stabilized IONPs as MNP. The formed complexes then served as seeds for the emulsion polymerization of styrene in water with divinylbenzene (DVB) as a crosslinker. TEM revealed the formation of spherical particles displaying a rather large magnetic core domain constituted of several MNPs surrounded by a polymer shell, of which the thickness could be modulated by the polymer content. The responsive properties of the resulting spherical CCHM, with PDMAEMA or PAA as hydrophilic shell were evaluated. It was evidenced that the modification of pH induced great morphology changes, suitable for biomedical application. Bauer et al.<sup>147</sup> described an example of redox-responsive CCHM. First, they synthesized an amphiphilic block copolymer composed of poly(sarcosine)-*block*-poly(S-ethylsulfonyl-L-cysteine) (pSar-*b*-pCys(SO<sub>2</sub>Et)) (**Figure 12**). After self-assembly, the core was crosslinked with dihydrolipoic acid through disulfide bond formation. Interestingly, this crosslinker also possesses affinity to MNPs ensuring thereby the MNPs' stability within the hybrids. Eventually, a dye, Cyanine5 (Cy5) was also conjugated to the CCHM to allow their detection by fluorescence emission.



**Figure 12.** Synthesis of diblock copolymers possessing ethylsulfonyl cysteine groups that allow the preparation of MNPs-CCHM via disulfide bridge formation. Adapted from reference <sup>147</sup> with the permission of Wiley-VCH GmbH.

The resulting hybrids were spherical in shape with diameters below 100 nm. They were studied *in vitro* and *in vivo*, showing notably their ability to trigger a desired pro-inflammatory reaction, in response to glutathione addition triggering the release of the MNPs inside the cells.

The above examples show that the *solvent-evaporation method* combined with embedding or ligand exchange/*grafting to* techniques allows the production of stimuli-RMPH. However, compared to MNP-core/polymer-shell hybrids (see section 3.1), this approach requires the use of organic solvent and an additional formulation step, which may represent a severe hurdle for biomedical applications.

To avoid time-consuming extra steps and the use of organic solvents and to overcome inherent limitations in up-scaling, the polymerization-induced self-assembly (PISA)<sup>148–151</sup> technology appears an interesting alternative. Indeed, this technique allows the simultaneous synthesis and self-assembly of amphiphilic block copolymers into nano-objects, directly in water, without any purification step required and at high solid content (generally about 20 wt%). Additionally, not only spherical nano-objects, but also worms<sup>152</sup> or vesicles<sup>153</sup> can be prepared. Karagoz *et al.*<sup>153</sup> were the first ones who used this approach to prepare MNP hybrids for magnetic resonance imaging (MRI). First, they synthesized PEGMA-*b*-PMAA-*b*-PS vesicles via PISA in methanolic dispersion polymerization conditions. In a second step, the MNPs were generated through the alkaline co-precipitation of Fe(II) and Fe(III) salts within the vesicles, where the carboxylic acid moieties of the PMAA block served as ligands for the IONPs formed *in situ*. Nguyen et al.<sup>152</sup>

synthesized fiber-like micelles composed of poly(acrylic acid-*co*-butyl acrylate)-*block*-polystyrene-*block*-poly(acrylic acid-*co*-butyl acrylate) (P(AA-*co*-BA)-*b*-PS-*b*-P(AA-*co*-BA)) triblock copolymers using a similar RAFT-mediated emulsion polymerization PISA process. The hybrids were created thanks to a *grafting to* approach via interactions between the negatively charged carboxylates present on the fiber surfaces and the preformed IONPs. Though none of these aforementioned PISA-hybrids included stimuli-responsive polymers so far, we believe that the PISA process is a powerful tool to engineer various hybrid morphologies. In addition, it should be possible to combine PISA with MNP using stimuli-responsive polymers to generate stimuli-RMPH with tunable morphologies.<sup>154,155</sup>

### 3.5. Polymeric magnetic membranes

Membranes have been defined as “structure[s], having lateral dimensions much greater than [their] thickness, through which transfer may occur under a variety of driving forces”.<sup>156</sup> When MNPs are incorporated within such 3D networks through covalent or physical interactions so-called polymeric magnetic membranes (PMM) are formed.<sup>3,157</sup>

It is possible to design PMM in which pores or channels open and close upon application of an external stimulus. Therefore, composite membranes composed of a (generally) non-responsive polymer matrix in which distinctive domains of a thermoresponsive polymer are embedded have been devised. The permeability of such membranes can then be controlled by the temperature. As shown in **Figure 13**, PMMs can be formed by embedding the polymeric NGs (or MGs) and free MNPs either in separate domains (**Fig. 13.1**; section 3.5.1), or by embedding magnetic hybrid NG/MGs (**Fig. 13.2**; section 3.5.2), within a crosslinked polymer matrix. In the following, we will describe several representative examples for each category, and describe some potential applications of PMM.

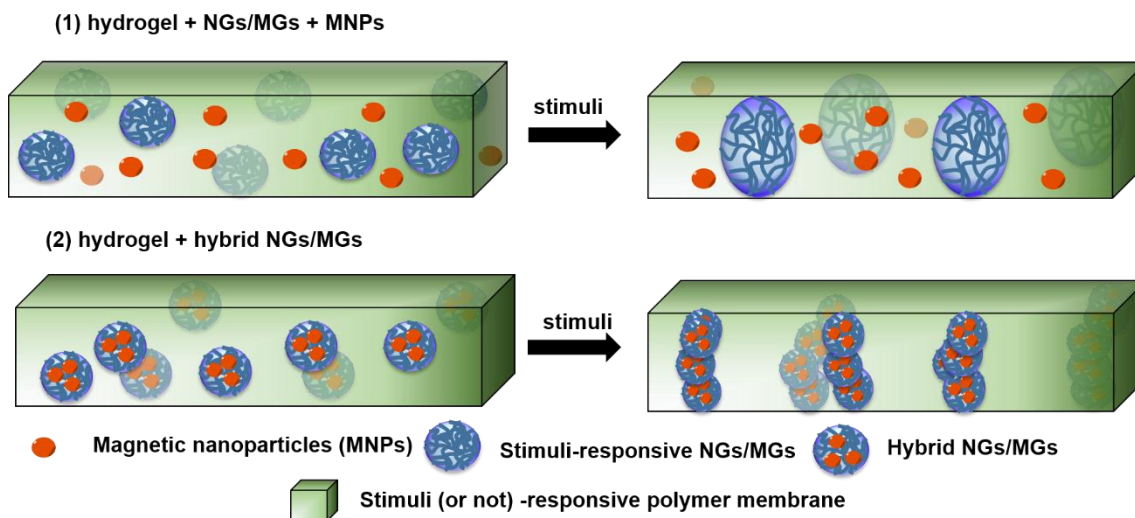


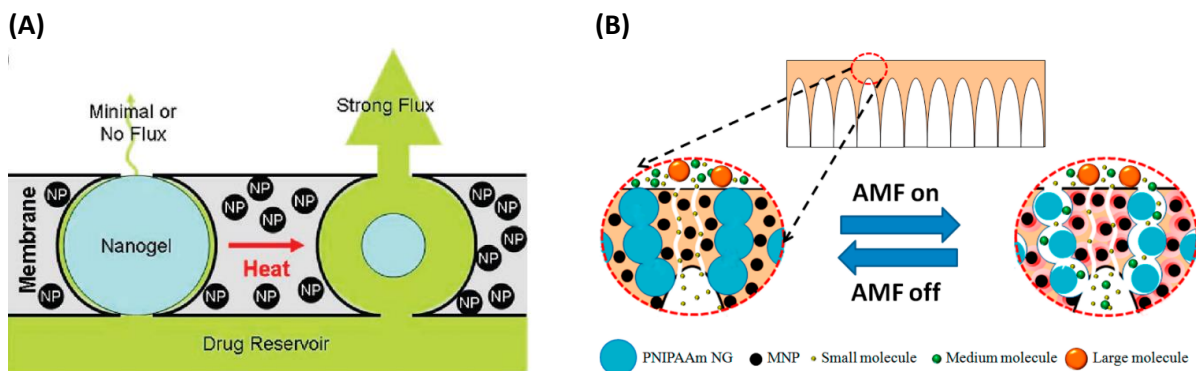
Figure 13. Overview of the different classes of polymeric magnetic membranes (PMM)

#### 3.5.1. Combination of thermoresponsive nanogels/microgels and magnetic nanoparticles within a polymer matrix

Campbell *et al.*<sup>158</sup> reported the synthesis of thermoresponsive PMM in two steps. First, thermosensitive MGs were prepared by the free radical polymerization of NIPAM, AAm, *N*-isopropylmethacrylamide (NIPMAM) and BIS in water. The resulting MGs solutions were then added into two distinct polymer

solutions: The first one contained hydrazide-functionalized PNIPAM chains (hydrazide-PNIPAM) and MNPs coated by hydrazide-PNIPAM, while the second one contained dextran-chains bearing aldehyde groups, a model drug and PEG-stabilized MNPs. After mixing both polymer solutions containing the MGs, gelation occurred because of the reaction between hydrazide and aldehyde moieties. The magnetic properties of both the MNPs and the resulting complex PMM were determined using Superconducting Quantum Interface Device (SQUID). Interestingly, upon application of an external AMF, the MNPs acted as local nanoheaters, inducing a volume phase transition of the MGs and the polymer matrix, thereby triggering drug release. Hoare *et al.*<sup>159</sup> also prepared thermosensitive PMMs with sieving properties by mixing thermosensitive NGs, MNPs, poly(vinyl alcohol) (PVA) and glutaraldehyde to form a complex PMM as presented in **Figure 14A**. The membrane composition was determined using XPS, along with XRD experiments, while TEM imaging allowed to visualize the ferrofluid distribution within the PMM. The authors showed that upon temperature increase above  $T_c$  (with  $T_c(\text{PNIPAM}) \sim 34^\circ\text{C}$ ) the NGs within the crosslinked PVA matrix shrank. The NGs act therefore as temperature-controlled valves that are able to tune the permeability of the membrane and thereby the extent of drug release.

Lin *et al.*<sup>160</sup> described another strategy to prepare thermoresponsive PMM. They incorporated PNIPAM-based NGs and amine-functionalized MNPs within a poly(ether sulfone) (PES) matrix to create biocompatible composite membrane disk filters. Elemental analysis (EA) and TGA confirmed the high loading of the membrane with NGs and MNPs, while ATR-FTIR and thermoresponsive contact angle measurements confirmed the presence of the NGs and the MNPs on the PMM surfaces. Similar to the previous examples, upon application of an AMF, the MNPs acting as local nanoheaters induced the shrinking of the PNIPAM NGs, thus creating channels within the PMM, which increased significantly the membrane's permeability (**Figure 14B**).



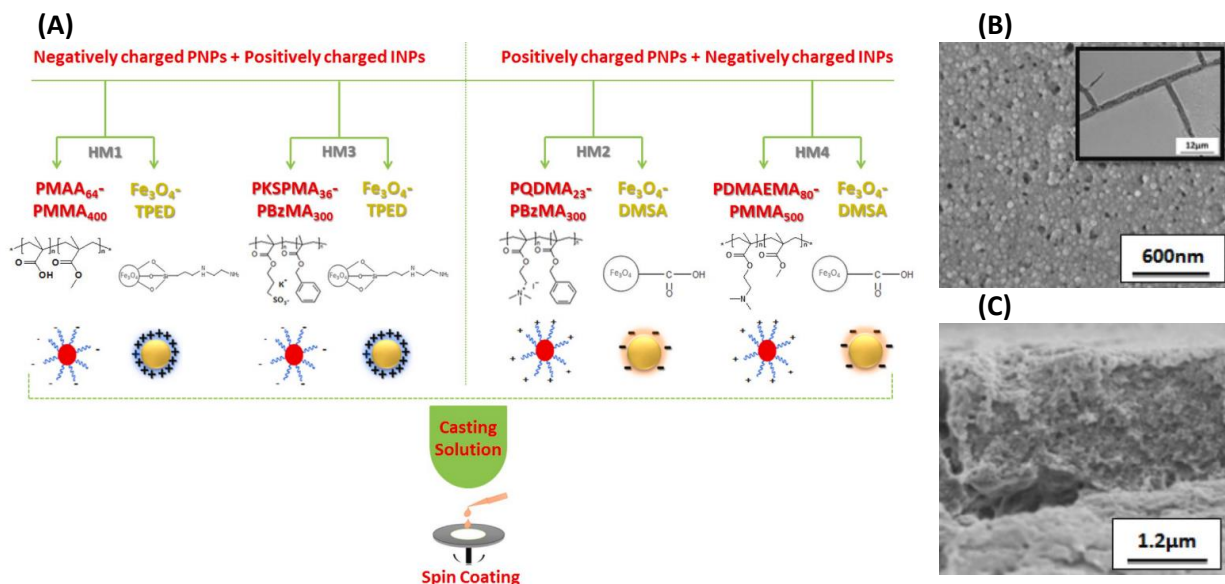
**Figure 14.** (A) PMMs comprising PNIPAM NGs and MNPs within a PVA/glutaraldehyde matrix (reproduced with permission from Nano Letters, 2009, 10, 3651-3657, ©2009, American Chemical Society<sup>159</sup>) and (B) PMMs comprising PNIPAM NGs and MNPs entrapped within a PES matrix (reproduced with permission from ACS Appl. Mater. Interfaces 2016, 8, 29001–29014 ©2016, American Chemical Society.<sup>160</sup>)

### 3.5.2. Embedding of magnetic hybrid nanogels and microgels within a polymer matrix

Csetneki *et al.*<sup>161</sup> synthesized PMM by embedding hybrid NGs within a PVA matrix. The NGs were prepared in two steps. First, MNPs were coated by PS via the polymerization of styrene in the presence of magnetite ( $\text{Fe}_3\text{O}_4$ ) particles (embedding approach). Then, NIPAM, BIS and KPS were used to produce a crosslinked shell around the PS-coated MNPs (cf. section 3.2.2). The resulting magnetic NG were in turn integrated into a PVA matrix. Upon application of an EMF, the magnetic NG aligned within the PVA matrix to form nanochannels which modified the permeability of the membrane.<sup>161</sup>

### 3.5.3. Thin-film magnetic membranes

A particular class of PMMs are thin-film magnetic membranes (TFMM) which have been widely described by Upadhyaya, Farooq *et al.*<sup>162–165</sup>. They are usually prepared through tape-casting or spin-casting by depositing a mixture of positively or negatively charged MNPs and oppositely charged pH-responsive diblock copolymers<sup>163,164</sup> or NPs<sup>162,164,165</sup> that can have various morphologies (spheres, fibers, vesicles). As illustrated in **Figure 15**,<sup>165</sup> the formation of TFMMs relies thus on the electrostatic interaction between the oppositely charged inorganic MNPs and polymeric NPs. Filtration tests demonstrated a good mechanical stability of the TFMM. Their permeability was systematically evaluated at different pH.



**Figure 15.** (A) Schematic representation of nanostructured TFMM prepared from oppositely charged MNPs and NPs. SEM images of the (B) top-surface and (C) cross-section of the hybrid membranes HM4. The insert is an image of the top surface with lower magnification (reproduced with permission from reference <sup>165</sup>)

In general, the three described approaches allow the preparation of stimuli-RMPH membranes (PMMs) with interesting features and properties for molecular sieving application and on-demand drug delivery.

### 3.6. Additional morphologies

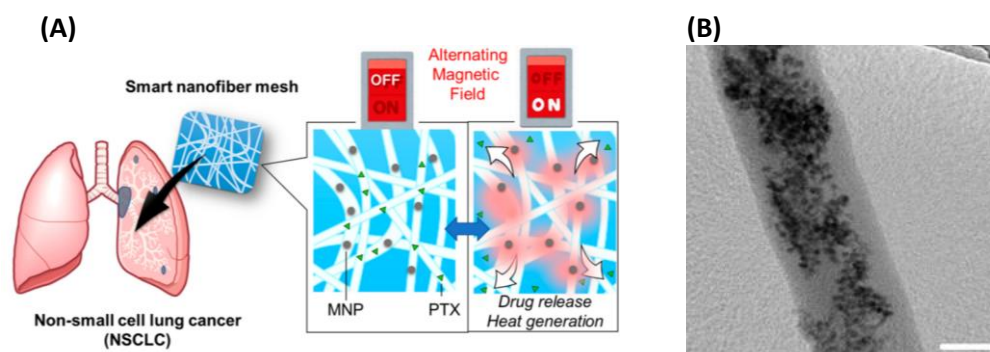
In this last section, we have gathered particular, additional hybrid morphologies that do not fit in the former sections. Among those, one can cite highly anisotropic hybrids, which exhibit a high aspect ratio, and shape-changing hydrogel bilayers, also called microgrippers, which are exemplified below.

#### 3.6.1. Magnetic fiber-like polymeric particles

Magnetic fiber-like polymeric particles are elongated, anisotropic or cylindrical polymeric nanoparticles (with one dimension much larger than the other two dimensions) that comprise MNPs within their structure. So far, mainly electrospun magnetic fibers have been prepared by combining stimuli-responsive polymers, such as PNIPAM, and MNPs. To achieve their efficient entrapment within the fibers, MNPs are always mixed with the stimuli-responsive polymer before the electrospinning. The electrospinning conditions (time, temperature, humidity, voltage, solvent) are generally studied and then optimized to avoid bead formation and produce uniform fibers. For example, Chen *et al.*<sup>166</sup> reported the preparation of



thermo-RMPH fibers by mixing APTES-modified-MNPs with PNIPAM at a weight ratio of 1 to 0.5 prior to electrospinning. PNIPAM electrospun nanofibers with a diameter around 800 nm were obtained. Their surface proved to be magneto-thermo-responsive, switching from hydrophilic to hydrophobic upon temperature modification (induced by AMF). Similarly, Kim *et al.*<sup>167</sup> and Niiyama *et al.*<sup>168</sup> reported the synthesis of fiber meshes composed of crosslinked P(NIPAM-co-NHEAM) (NHEAM = *N*-hydroxyethylacrylamide) electrospun nanofibers, with MNPs and a model drug entrapped within the polymer matrix (**Figure 16**). The hybrids were characterized by SEM, EDX, TEM and TGA measurements. Upon the application of an AMF, the entrapped MNPs acted as local nanoheaters, inducing a transition of the crosslinked PNIPAM fibers from hydrophilic to hydrophobic matrixes. Such transition induced the collapsing of the fibers thereby releasing the encapsulated drug, in this case, paclitaxel (PTX), as evidenced by UV-VIS measurements. Such magnetic hybrid fibers proved therefore to be efficient drug-delivery vehicles for therapeutic applications.



**Figure 16.** (A) Schematic representation of on-off switchable temperature-responsive fiber mesh for cancer thermo-chemotherapy. The mesh contains PTX and MNPs. The mesh releases heat and drug when activated by AMF, (B) TEM image of the MNPs-nanofibers, the scale bar is 200 nm (reproduced from reference <sup>168</sup>)

While electrospinning is clearly interesting to provide long fibers, the need to use organic volatile solvents, such as 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), and the tedious optimization of the electrospinning parameters (voltage, distance between needle and target, nature of solvent, flow rate) render this method quite tedious.

### 3.6.2. Grippers

As defined by Kobayashi *et al.*<sup>169–171</sup> polymeric microgrippers “offer the possibility to pick and place fragile biological cargo in hard-to-reach conduits. They have potential applications in drug delivery, minimally invasive surgery, and biomedical engineering”. In their most recent paper<sup>171</sup>, the authors reported the synthesis of biodegradable dual-responsive grippers by photo-patterning of a high-swelling thermo-responsive hydrogel layer situated on top of a low-swelling gel layer comprising MNPs. To prepare them, a multilayer photolithography process in two steps was used. First, MNPs were mixed in a chamber with AAm and BAC (the degradable crosslinker) before UV-light exposure under a chromium photomask to control the site of polymerization. To add fluorescent properties, a small quantity of a fluorescent monomer, methacryloxyethyl thiocarbamoyl Rhodamine B was added to the monomer mixture. After photo-patterning and rinsing, a low-swelling patterned gel membrane was formed. The next step consisted in the crosslinking UV-polymerization of a solution of OEGMA and bis(2-methacryloyl)oxyethyl disulfide (DSDMA) in order to generate the high swelling layer, as illustrated in **Figure 17**.

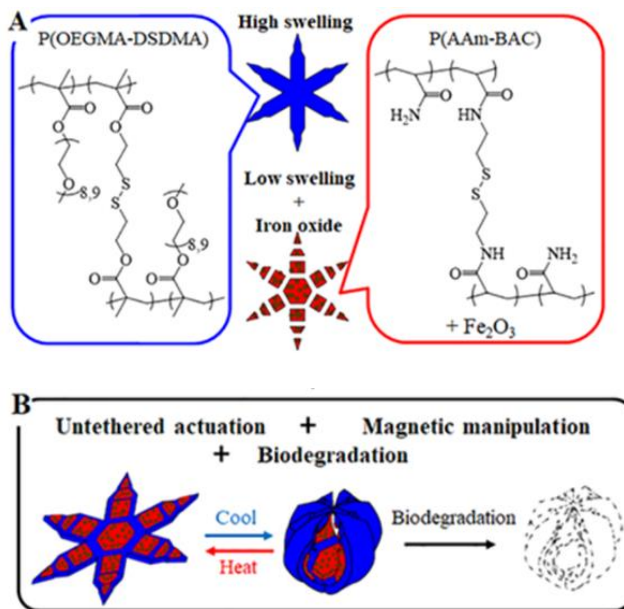


Figure 17. Schematic representation of the molecular composition, structure, and operation of the magneto-thermoresponsive grippers. (A) The grippers are composed of a bilayer of two hydrogels: a reversible high-swelling P(OEGMA-DSDMA) gel, and a low-swelling P(AAm-co-BAC) gel containing IONPs. (B) Illustration of the multifunctional nature of the soft grippers, including thermo-responsive actuation, magnetic manipulation, and biodegradation (adapted with permission from ACS Applied Material Interfaces, 2019, 11(1), 151-159, ©2018, American Chemical Society.<sup>171</sup>)

The authors evidenced that a low concentration of DSDMA crosslinker and a high concentration of BAC crosslinker allowed the formation of grippers, which combined magneto-thermoresponsiveness and degradability (thanks to the cleavage of the crosslinkers' disulfide bonds): the devices were able to open and close, upon heating and cooling. It was also shown that it was possible to operate the grippers remotely through the application of a magnetic field. Finally, the degradability into soluble biocompatible chains was evidenced by addition of glutathione or vitamin C, proving the interest of such compounds as medical devices.

#### 4. Conclusion and Perspectives

Stimuli-RMPH are promising materials finding applications in a large number of domains. Their size, structure, shape and constituting compounds must be selected in view of their application, and scientists have devised a large variety of strategies to produce them. In the last two decades, various architectures and morphologies have been prepared ranging from common magnetic core-shell polymer particles, to nanogels and microgels, micelles, and membranes to exotic structures like grippers or magnetic fibers.

In this review, we have summarized and detailed the most common synthetic strategies that have been reported in the literature. A first strategy relies on the *in-situ* synthesis of MNPs within a preformed polymer network that possesses functional groups able to coordinate iron salts, that are precursors of the MNP. The second one relies on the incorporation of bare MNPs through physical embedding during polymerization. The third strategy is based on the *grafting to* approach, through which MNPs can be incorporated into various nano-objects by exploiting their ability to interact via specific chemical groups, such as carboxylic acid, phosphonic acid and catechol moieties, present along the polymer backbone or as chain-ends. Additionally, the *grafting from* and *grafting through* techniques have also been employed after adequate modification of the MNPs. For *grafting from*, the surface of MNPs is first modified with

polymerization-initiating sites, whereas for *grafting through* MNPs are modified by polymerizable functional groups and can thus act as crosslinkers within the polymer structure. **Table 1** summarizes the synthetic approaches reported in the literature and the corresponding morphologies, which can be produced. It notably shows that a specific morphology can often be obtained through several synthetic approaches.

**Table 1. Overview of the synthetic methods and the corresponding RPMH morphologies**

Method/ Synthetic Approach	Reported Hybrid Morphologies
<i>In situ</i> creation of MNPs through complexation of iron salts	Core-shell, NG, MG, macrogel
Physical entrapment during polymerization (embedding of bare MNPs)	Core-shell, hybrid micelle, NG, MG, macrogel, grippers, PMM, fibers
<i>Grafting onto</i>	Core-shell, micelle, NG, MG, PMM
<i>Grafting from</i> (MNPs functionalized by initiators or CTA)	Core-shell, NG, MG
<i>Grafting through</i> (MNPs with polymerizable groups)	Core-shell, NG, MG

Even though a large variety of structures, morphologies and materials has been reported, the preparation of stimuli-RMPH with specific, reversible and reproducible properties remains challenging and generally involves several synthesis steps. Additionally, in most cases, the incorporation of MNPs within polymeric materials is not straightforward, and the syntheses often employ organic solvents, which can be a serious hurdle when biomedical applications are targeted. Therefore, new approaches to synthesize stimuli-RMPH using less toxic and greener synthesis strategies have to be devised. An interesting method, which has been briefly mentioned above (section 3.3.3) could actually answer these concerns. Indeed, recent research shows that the PISA technology allows the straightforward synthesis of magnetic responsive hybrid materials directly in water and with high yields. Hitherto, there are only few examples reporting the use of PISA to synthesize magneto-responsive polymer hybrids<sup>152,153,172,173</sup>. To this end, the authors generally combined the classical PISA process with (i) the aforementioned *grafting from* technique<sup>172</sup>, (ii) the *in situ* creation of MNPs within vesicles<sup>153</sup> or (ii) their post-synthesis complexation<sup>152,173</sup> via electrostatic interactions between positively charged MNPs and negatively charged spherical, rod-like<sup>173</sup> or fiber-like micelles<sup>152</sup>. However, to the best of our knowledge, apart from solely magneto-responsive hybrids mentioned previously, to date multi-stimuli-RMPH that combine stimuli-responsive polymers and MNPs obtained through the PISA process are not yet explored in the literature and should be further explored.

Finally, it seems that in most of the reported works spherical IONPs were mainly used, while other MNP morphologies, such as cubic IONPs, or anisotropic, rod-like or octahedron NPs, have only seldom been reported, despite the variety of morphologies that can be formed with MNPs.<sup>174</sup> However, since the shape of MNPs can alter their magnetic response<sup>175</sup>, the development of stimuli-RMPH with MNPs of other morphologies should be of great interest.

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