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COMMUNICATION

Synthesis of double-responsive magnetic latex particles via seeded emulsion polymerization using macroRAFT block copolymers as stabilizers

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We report an efficient method to synthesize stimuli-responsive magnetic latexes with high magnetic response. An amphiphilic poly(2-dimethylaminoethyl methacrylate)-*b*-polystyrene (PDMAEMA-*b*-PS) block copolymer was first synthesized by RAFT solution polymerization, and subsequently employed to stabilize iron oxide clusters. The resulting superparamagnetic clusters were then used as seeds in styrene emulsion polymerization generating magnetic latex particles with a strong response to a magnetic field, and decorated with double-responsive PDMAEMA segments.

The incorporation of magnetic particles into polymer latexes has attracted increasing interest over the last 30 years owing to the wide potential of the resulting composite particles in removal of toxic contaminants, as magnetic support for catalysis, in targeted drug delivery, cancer diagnosis and therapy, and for magnetic separation or magnetic resonance imaging (MRI).¹ Such particles are commonly synthesized via (mini)emulsion polymerization of hydrophobic monomers in the presence of superparamagnetic iron oxide (IO) nanoparticles.^{1,2} This approach nevertheless suffers from drawbacks, such as phase separation between the inorganic particles and the polymer, concomitant nucleation of polymer particles free of IO, and/or low IO content in the final magnetic particles, limitations that obviously negatively impact their performances.³ Efficient strategies able to overcome these drawbacks have however been reported in the literature.^{4–7} These rely on the preparation of IO clusters prior to their encapsulation by (mini)emulsion polymerization (*i.e.* clusters of IO nanoparticles are used, not the IO nanoparticles themselves). The successful formation of well-defined IO clusters indeed guarantees that a high amount of magnetic material is incorporated into the composite particles, endowing them with a fast magnetic response. In a typical clustering procedure, organically-modified IO nanoparticles are first dispersed in a non-polar solvent, such as toluene or

octane. This organic phase is then dispersed in an aqueous surfactant solution using a high-energy emulsification device, forming sub-micron size droplets loaded with IO. In a last step, either the IO-loaded droplets themselves^{6,7} or the IO clusters suspension obtained after solvent evaporation,^{4,5} are used as seeds in emulsion polymerization resulting in the formation of hybrid particles with high IO contents (up to 80 wt%).⁷

On the other hand, the development of nano-objects with controlled surface reactive groups is the focus of many studies due to the potential applications of such functional nanoparticles, especially in the field of nanomedicine.⁸ One successful strategy to design polymeric nanoparticles with well-defined surface functionalization relies on the use of reversible addition–fragmentation chain transfer (RAFT) polymerization.⁹ The versatility of the RAFT technique over a wide range of functionalities together with the ability to access well-defined macromolecular architectures, notably in dispersed media, make it now possible to engineer a variety of functional particles.¹⁰ Furthermore, when stimuli-responsive polymer chains are used to decorate the particle surface, the resulting materials can exhibit CO₂,¹¹ thermo- and/or pH-responsive properties¹² allowing their use in biomedicine.¹² The combination of RAFT and (mini)emulsion polymerization to prepare magnetic latex particles has already been reported in the literature.^{13–15} In particular, our group recently described the successful preparation of magnetic latex particles exhibiting fully encapsulated morphology and stabilized by poly(acrylic acid) segments using the RAFT-assisted encapsulating emulsion polymerization process.¹⁴ However, to the best of our knowledge, the combined usage of RAFT polymerization and IO clusters formation is an appealing research direction that has never been investigated so far.

In this work we report the synthesis of magnetic latex particles decorated with double-stimuli responsive PDMAEMA segments.^{16–18} An amphiphilic PDMAEMA-*b*-PS block copolymer was first synthesized via RAFT polymerization (Fig. 1A), and used as stabilizer for the formation of IO clusters (Fig. 1B). The resulting self-assembled clusters were then used as seeds in styrene emulsion polymerization leading to the

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Figure 1 – Schematic representation of (A) synthesis of PDMAEMA-*b*-PS-TTC amphiphilic block copolymer and (B) IO cluster formation and synthesis of magnetic latex particles.

formation of magnetic latex particles decorated with double-responsive polymer segments. Finally, the thermal, pH and magnetic responsive properties of the particles were investigated.

The PDMAEMA-*b*-PS amphiphilic block copolymer was synthesized in a two-step RAFT solution polymerization (Fig. 1A, see SI for detailed experimental procedure). A preliminary kinetic study was first performed aiming at the preparation of a PDMAEMA hydrophilic block with twice the number of units initially targeted (*i.e.*, 80 DMAEMA units, MR1, Table SI1 and Fig. SI1). Then, a scale-up experiment was performed and a batch of macroRAFT agent was obtained by quenching the polymerization at 56% conversion (MR2 in Table SI1) maintaining a high degree of livingness for the polymer chains.¹⁹ After the chain extension of this macroRAFT with styrene, an amphiphilic macroRAFT composed of 45 DMAEMA and 9 styrene units (MR3, ¹H NMR in Fig. SI2) was obtained. DMF-SEC analysis (Fig. SI3) shows a shift of the monomodal main peak towards higher molar masses, indicating successful preparation of the targeted block copolymer.

As mentioned above, the use of IO clusters has been demonstrated to be an efficient alternative for the preparation of composite particles with high IO contents. In order to prepare such IO clusters, PDMAEMA-*b*-PS-TTC was employed as a stabilizer in an emulsification/solvent evaporation protocol (Fig. 1B) similar to that previously reported by Paquet *et al.*^{5,20} Commercial fatty acid-modified IO nanoparticles (FA@IONPs, commercial name: EMG1200 from Ferrotec®) were first dispersed in toluene to form an organic ferrofluid. In parallel, an aqueous solution of the stabilizer PDMAEMA-*b*-PS-TTC (2.5 10⁻⁴ M and pH 4) was also prepared. The two phases were then mixed and sonicated from 2 to 10 min (plot of droplet size vs sonication time shown in Fig. SI4) resulting in a colloiddally stable system after 4 min of sonication. After solvent evaporation, a cluster suspension with $Z_{av} = 180$ nm (PDI = 0.05) and a high yield of formation ($f = 86\%$ - see SI for detailed calculation) was obtained. The TEM images of Figs 2A

and SI5 reveal the formation of well-defined clusters exhibiting a spherical morphology. Obviously, various parameters can influence cluster formation such as the initial pH, the sonication power or the macroRAFT composition and concentration. The effect of all these parameters will be addressed in a future publication.

Seeded-emulsion polymerization of styrene using the PDMAEMA-*b*-PS-stabilized IO clusters as seeds was next carried out at pH 5 (natural pH of the dispersion) as schematically represented in Fig. 1B. The experiment performed using the crude IO cluster suspension (without any previous purification, Exp 1, Table SI2) and targeting 10% of polymer content (PC) resulted in the formation of only 37 wt% of magnetic latex particles (ω_{mag} , fraction of particles that was effectively collected by magnetic separation after 30 s, see SI for detailed calculation) with a relatively low iron oxide content ($IOC^{TGA} = 22\%$, Exp 1, Table SI2). Such a low fraction of magnetic particles can be associated with the formation of a large amount of free polymer particles (*i.e.*, devoid of inorganic particles) from secondary nucleation and/or of hybrid particles with low IO content that are not attracted to the magnet (TEM images of the particles before magnetic separation are shown in Fig. SI6). Secondary nucleation may be attributed to the presence of macroRAFT in the continuous phase, presumably organized as micelles, which can be swollen by monomer, and thus become competitive nucleation sites. In order to avoid secondary nucleation, the cluster suspension was purified via magnetic wash (10 min exposure to the magnetic field), followed by redispersion in water. A second emulsion polymerization was carried out using the purified clusters (Exp 2, Table SI2) and, in addition, a lower polymer content (PC = 5%) was targeted to increase the final iron oxide content. As expected, the magnetic fraction and the iron oxide content increased significantly ($\omega_{mag} = 69$ wt% with $IOC^{TGA} = 32\%$, Exp 2, Table SI2 and Fig. SI7) indicating that the extent of secondary nucleation was significantly reduced, the

Figure 2 – TEM images of (A) IO clusters and (B-D) isolated magnetic latex particles (Exp 2 to 4, Table SI2) after magnetic wash (30 s) to eliminate the free (non-magnetic) polymer particles as schematically illustrated in the SI (Scheme SI1).

nucleation preferentially occurring into the clusters, as illustrated in Fig. 2B. In a third experiment, the polymer content was further decreased to 2.5% (Exp 3, Table SI2) leading to the formation of hybrid particles with an even higher IOC^{TGA} of 47% (Exp 3, Fig. SI7). The increase of the IOC^{TGA} values from 32 to 47% obviously affected the magnetic response. Indeed, Fig. SI8 shows that 85% of the particles were collected for Exp 3 after 30 s under a magnetic field, while it was only 69% for Exp 2. These results are very interesting, in particular for the optimized system (Exp 3), as a fast magnetic response is a crucial aspect in the preparation of efficient magnetic carriers. Nonetheless, for the two systems, the original spherical shape of the clusters was not maintained after polymer encapsulation (Fig. 2B and Fig. 2C for Exp 2 and 3, respectively), *i.e.*, the iron oxide nanoparticles are no longer confined into spherical domains within the hybrid particles. Therefore, with the aim of fixing the cluster morphology during the polymerization, an additional experiment (Exp 4, Table SI2) was carried out with 23 wt% of divinylbenzene (DVB), a crosslinking agent. Hybrid particles with a well-defined core-shell morphology were successfully obtained (Fig. 2D). Furthermore, a high IOC^{TGA} (47%) and a fast response to the magnetic field were observed (Exp 4, Table SI2 and Fig. SI8). The effect of DVB content on the preparation of the magnetic latex particles is currently under investigation and will be reported in greater details in a future publication.

The magnetic properties of the hybrid particles were next investigated. TGA of FA@IONPs (Fig. SI7) indicates that the commercial nanoparticles contain only 17 wt% of organic ligand (identified by the provider as “fatty acid”) resulting in a

high magnetization at saturation (56 emu g^{-1} , Fig. SI9). After cluster formation and purification, the organic content of the obtained clusters was almost the same as that of the FA@IONPs (19 wt%, Fig. SI7) resulting in a similar magnetization at saturation (59 emu g^{-1} , Fig. SI9). This similarity in the results can be related, most probably, to magnetic washes during purification step of the cluster suspension, which lead to partial removal of non-adsorbed fatty acid from FA@IONPs (more details presented in the SI). Most notably, the superparamagnetic properties, characteristics of small FA@IONPs ($< 20 \text{ nm}$),²¹ were retained after cluster formation (Fig. SI9), even though the latter displayed relatively large sizes ($Z_{\text{av}} = 180 \text{ nm}$). The magnetization curve of the composite particles (Exp 2) also exhibited no hysteresis and a reasonably high magnetization at saturation of 27 emu g^{-1} (Fig. SI9), in agreement with the high IO content (32 wt%). This is an important result as superparamagnetism is required for most applications involving magnetic separations. Indeed, as the hybrid particles exhibit no remanent magnetization after removal of the magnetic field, they have no attraction for each other and can be therefore easily redispersed without aggregation.

We then focused our attention on the responsive properties of the PDMAEMA chains. Indeed, this polymer is a well-known stimuli-responsive polymer, which exhibits a pH-dependent cloud point temperature (T_{CP}).¹⁶⁻¹⁸ Its T_{CP} varies from around 40°C in alkaline conditions to 80°C in neutral conditions, exhibiting no phase transition at acidic pH.¹⁶ As shown in Fig. 3A, the PDMAEMA-TTC phase transition was observed neither in acidic conditions (pH 4) nor in slightly basic conditions (*i.e.*, pH 7.1-7.4). However, when the pH was increased, T_{CP} decreased from 69°C at pH 8 to around 45°C for $\text{pH} \geq 9$. The cloud point temperature of PDMAEMA-TTC at pH 9 was confirmed by DLS resulting in a T_{CP} of 44°C (Fig. SI10). This value is higher than in the literature ($T_{\text{CP}} = 38-42^\circ\text{C}$ ^{16,18} at pH 9 and $T_{\text{CP}} = 35-39^\circ\text{C}$ ^{16,17} at pH 10), which can be ascribed to the lower molar mass of the polymer in our system.¹⁶⁻¹⁸ These results thus confirm the thermo-responsiveness of the PDMAEMA-segments under basic conditions. Finally, the pH-responsive properties of the magnetic latex particles stabilized by PDMAEMA chains (Exp 2, Table SI2) were evaluated by ζ -potential measurements at different pH values. Fig. 3B clearly shows the pH-dependent behavior of the particle surface, which is directly related to the composition of the hydrophilic part of the amphiphilic macroRAFT. By increasing the pH, the DMAEMA units are deprotonated decreasing the contribution of the cationic charges to the stabilization, resulting therefore in a gradual decrease of the ζ -potential. Surprisingly, the ζ -potential of the particles becomes negative for $\text{pH} > 9$. This can reasonably be attributed to the deprotonation of the carboxylic acid chain-end of the stabilizing polymer, originating from the R group of the RAFT agent (a schematic representation of this effect is shown in Fig. 3B and the structure of the RAFT agent presented in Fig. 1A). Previous works^{22,23} have shown that the ζ -potential of polymer particles decorated with PDMAEMA becomes negative under basic conditions corroborating our findings.

Figure 3 – (A) Thermo-responsiveness of PDMAEMA-TTC in water solution for different pH values (MR2, 10 g L⁻¹) evaluated by UV-Vis spectroscopy and (B) pH-responsive properties of the hybrid latex particles (Exp 2) evaluated from ζ -potential measurements.

The authors associated this behavior with the anionic sulfate groups present at the polymer chain ends derived from the persulfate initiator. It is also known that DMAEMA can be partially hydrolyzed in aqueous solution resulting in the formation of methacrylic acid,²⁴ which could also explain the negative ζ -potential observed at pH 10 (Fig. 3B). However, after polymerization, the PDMAEMA polymer is significantly more stable than its monomer²⁴ and it is very unlikely that hydrolysis is occurring in our system.

In conclusion, we have reported a new and successful strategy for the preparation of magnetic IO/polymer particles with well-defined surface functionalization. Our approach relies on the use of an amphiphilic macroRAFT for the formation of stable IO clusters that are subsequently encapsulated within a polymer shell by seeded emulsion polymerization. The macroRAFT not only allows high yield formation of stable clusters but also provides a versatile platform for the design of composite particles with tailored surface properties by appropriate choice of the hydrophilic block. PDMAEMA segments exhibiting a dual pH-temperature responsive behavior were successfully incorporated at the particle surface showing great promise in biological applications where both tunable interactions and high colloidal stability are sought. Besides, this strategy can benefit from the great versatility of the RAFT technique offering very efficient ways to synthesize magnetic latex particles decorated with a wide variety of polymeric segments. Hence, particles with different surface properties could be obtained, highlighting this strategy as a powerful tool for the development of new magnetic carriers.

Conflicts of interest

The authors declare no conflict of interest.

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