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## ARTICLE TYPE

# Novel nanoaggregates with peripheric superparamagnetic iron oxide nanoparticles and organic cores through self-assembly of tailor-made block copolymers†

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The formation of tailor-made magnetic nanostructures is explored by self-assembly of block copolymers in the presence of superparamagnetic iron oxide nanoparticles (SPION). Depending on the nature of SPION-polymer interactions, the structures range from small-sized nanodispersions, large nanoaggregates, to nanovesicles. The latter represent a novel arrangement into well-defined magnetic vesicles.

In recent years, the use of magnetic nanoparticles has gained significant attention for different fields of application.<sup>[1]</sup> Particularly, the use of superparamagnetic iron oxide nanoparticles (SPION), and their nanoaggregates, in biomedical applications for magnetic resonance imaging or controlled drug delivery has shown a great potential.<sup>[2]</sup> One of the most important issues associated with SPION is the instability caused by air oxidation, which is more marked in the case of smaller particles, and has an effect in their stability as colloidal suspensions.<sup>[1]</sup> Therefore, several strategies have been explored to provide SPION with electrostatic or repulsion stabilization, including the use of small organic and inorganic molecules for structural stabilization or coating the particles with polymers, which determine the major surface interactions of the SPION.<sup>[3]</sup>

The possibility of forming hybrid nanostructures by self-assembly of well-defined amphiphilic block copolymers in the presence of inorganic species<sup>[4]</sup> is seen as a powerful tool to prepare SPION-based nanostructures of controlled morphology and, therefore, of different magnetic performance.<sup>[5]</sup> Since most of SPION mediated syntheses are carried out in organic solvents, particle stabilization is often provided by hydrophobic tail groups<sup>[2c]</sup> (e.g., oleic-based coatings), allowing to achieve very small SPION with controlled size (a critical issue in the application of bottom-up self-assembly strategies) and excellent stability.<sup>[6]</sup> The dispersion of oleic-coated SPION in aqueous media by block copolymers self-assembly has been carried out by using a SPION-anchoring block with a hydrophobic nature, such as poly( $\epsilon$ -caprolactone)<sup>[7]</sup>, poly(styrene)<sup>[8]</sup> or poly(4-n-dodecyloxybenzalacetal)<sup>[9]</sup>. In this case, the main interactions with the SPION original coating are Van der Waals forces. In this research work, it is shown that tailor-made magnetic nanostructures can be prepared by controlling the nature of interactions between the anchoring block and the SPION in their co-micellization process with diblock copolymers.

Recently, we have reported the use of poly(ethylene glycol)-block-poly(4-vinyl pyridine) (mPEG-b-P4VP) as a versatile block copolymer to form core-shell nanostructures based on either hydrophilic or hydrophobic-coated SPION,<sup>[10]</sup> due to the transition metal complexation ability of the pyridyl groups (from P4VP segments) with the iron oxide moieties.<sup>[11]</sup> At pH above the pKa of P4VP, this segment becomes hydrophobic<sup>[12]</sup> and, thus, P4VP's Van der Waals interactions need also to be considered in the stabilization of hydrophobic-coated SPION. In order to understand the role played by the metal complexation in the block copolymer-SPION interactions, a poly(ethylene glycol)-b-polystyrene (mPEG-b-PS) block copolymer (without this specific interaction) was prepared and used for self-assembly in the presence of oleic-coated SPION. Also, to evaluate the type of SPION-aggregates obtained in the presence of block copolymers containing an iron oxide complexing block with a hydrophilic nature, a poly(ethylene glycol)-b-poly(2-(dimethylamino)ethyl methacrylate) (mPEG-b-PDMAEMA) block copolymer was prepared and complexed with oleic-coated SPION.

The block copolymers were prepared by Atom Transfer Radical Polymerization (ATRP)<sup>[13]</sup> to afford copolymers with controlled composition and narrow molecular weight distributions. Table 1 presents the estimated number-average molecular weight ( $M_n$ ) of the block copolymers based on NMR signals ( $M_{n,NMR}$ ), considering the known mPEG molecular weight and the molar ratio of the second block to mPEG units taken as the integrals' ratio of "f" and "b" signals, divided by the respective number of protons (Figure S1 in the Supporting Information). Polydispersity ( $M_w/M_n$ ) values were obtained from GPC analysis (see GPC traces in Figure S2 in the Supporting Information), as well as an estimated  $M_n$  based on a calibration with poly(methyl methacrylate) standards ( $M_{n,GPC}$ ).

**Table 1.**  $M_n$  and polydispersity ( $M_w/M_n$ ) values of synthesized block copolymers

Block copolymer	$M_{n,NMR}$ (g/mol)	$M_{n,GPC}$ (g/mol)	$M_w/M_n$
mPEG <sub>113</sub> -b-P4VP <sub>44</sub>	9,704	19,646	1.16
mPEG <sub>113</sub> -b-PS <sub>54</sub>	15,663	24,387	1.21
mPEG <sub>113</sub> -b-PDMAEMA <sub>55</sub>	19,298	16,800	1.16

The influence of hydrophobic coating nature of the SPION was assessed using two different coatings. One type of SPION was functionalized with a mixture of oleic acid, oleylamine, and 1,2-

hexadecanediol<sup>[14]</sup> to afford SPION with a longer oleic-coating (LOSPION); whereas another type of SPION was prepared using only oleylamine<sup>[15]</sup> to obtain SPION having a shorter oleic-coating (SOSPION). (see X-ray diffractograms, TGA traces and TEM micrographs in Figure S3, Supporting Information). The SPION aqueous dispersions, obtained by self-assembly of the different block copolymers, were prepared at pH = 9.0 to avoid the protonation of the nitrogen in the P4VP and PDMAEMA segments.<sup>[12, 16]</sup> Table 2 presents the hydrodynamic sizes that were obtained, based on Dynamic Light Scattering (DLS) analysis, for the three block copolymers and for the two types of hydrophobic-coated SPION.

**Table 2.** Hydrodynamic diameter of nanostructures and respective polydispersity values, as determined by DLS, for SPION aggregates formed by self-assembly with different block copolymers at concentrations of 1.0 mg/mL for the block copolymer and 0.1 mg/mL for the SPION.

Block copolymer	LOSPION		SOSPION	
	D <sub>H</sub> (nm)	PDI	D <sub>H</sub> (nm)	PDI
mPEG <sub>113</sub> -b-P4VP <sub>44</sub>	183.5	0.231	257.5	0.572 <sup>[a]</sup>
mPEG <sub>113</sub> -b-PS <sub>55</sub>	117.2	0.218	139.6	0.330
mPEG <sub>113</sub> -b-PDMAEMA <sub>54</sub>	161.7	0.179	151.9	0.123

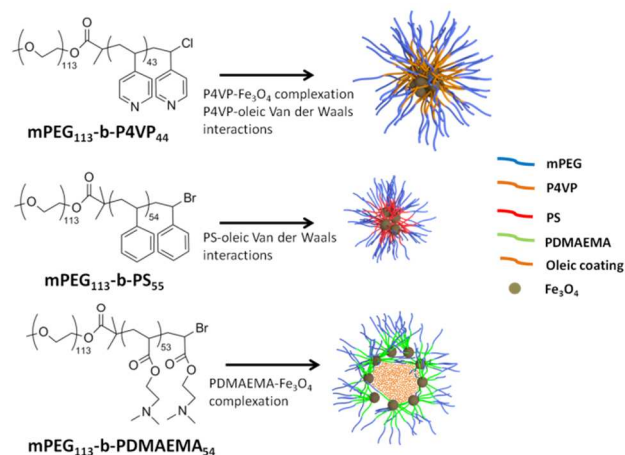
[a] unstable aggregates

The DLS results suggest that stable nanostructures with good degree of structural control were obtained for the different SPION's dispersions. The only exception was found to be on the aggregates prepared with the mPEG-b-P4VP block copolymer in the presence of the SPION coated with oleylamine (SOSPION), which formed large agglomerates with tendency to precipitate. As we previously reported,<sup>[10]</sup> large aggregation effects can occur when the P4VP to SPION ratio is not high enough to stabilize the SPION into the self-assembled mPEG-b-P4VP structures. The increased agglomeration effect with SOSPION, when compared to micellar structures obtained with LOSPION, may be ascribed to the formation of very large cores due to a stronger P4VP-iron oxide interaction caused by a shorter oleic coating of SPION. When a longer oleic-coating is used, the interactions between the SPION's coating surface and the hydrophobic segment of copolymer can play a more significant stabilizing role. As suggested by the hydrodynamic sizes measured by DLS, smaller structures are formed when the mPEG-b-PS block copolymer is used. In spite of the hydrophilic nature of PDMAEMA, for the mPEG-b-PDMAEMA block copolymer, the self-assembled nanostructures were within the same size range as those obtained with hydrophobic anchoring blocks (PS and P4VP). However, due to completely different nature of polymer-SPION

interactions, one should expect different morphologies to be obtained.

Figure 1 presents TEM images of the self-assembled block copolymers in the presence of LOSPION. The images show a diversity of self-assembled nanostructures obtained when different anchoring polymers are used, ranging from large SPION nanoaggregates, small sized SPION-nanodispersions to polymersome-like structures, having SPION mainly located at the shell layer of the nanoaggregates.

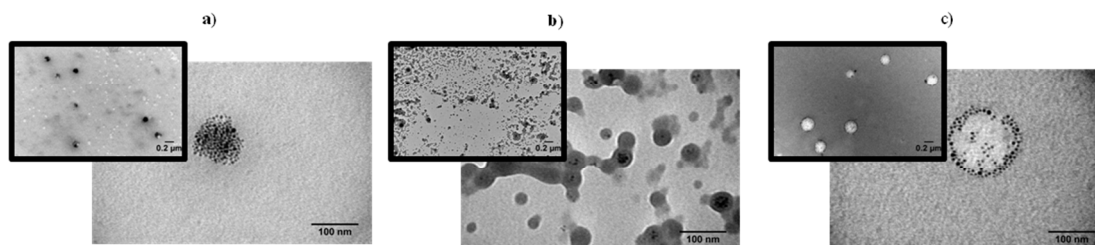
Scheme 1 provides proposed structures for the three block copolymers self-assembled in the presence of oleic-coated SPION, showing the dependence of the type of nanostructures that are formed with the nature of interaction between the anchoring block and oleic-coated SPION.



**Scheme 1.** Representation of SPION hybrid nanostructures formed by self-assembly of diblock copolymers in the presence of oleic-coated SPION.

As discussed in our previous publication,<sup>[10]</sup> the pyridyl group coordination with iron oxide moieties of SPION enables the formation of clusters of SPION in aqueous dispersed core-shell structures that are sterically stabilized by the presence mPEG block. As shown in Figure 1, the strong interaction of P4VP with iron combined with its hydrophobic character at self-assembly conditions, allows the formation of highly SPION-loaded micelles.

When the mPEG-b-PS block copolymer is used, smaller self-assembled structures that contain only a few SPION inside the micellar structures are formed. The formation of these smaller nanostructures can be ascribed to the restricted interaction of the PS segments with SPION, which is limited to the interaction of the anchoring polymer with the coated SPION surface through PS-oleic acid Van der Waals forces. It should be noted that the formation of these small core-shell hybrid magnetic structures is

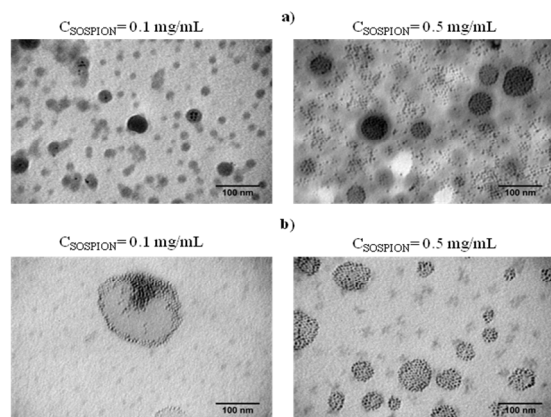


**Figure 1** - TEM micrographs of LOSPION self-assembled in the presence of a) mPEG<sub>113</sub>-b-P4VP<sub>44</sub>, b) mPEG<sub>113</sub>-b-PS<sub>55</sub>, and c) mPEG<sub>113</sub>-b-PDMAEMA<sub>54</sub> block copolymers at a concentration of 1.0 mg/mL for the block copolymer and of the 0.1 mg/mL LOSPION. Images were taken at magnification x300,000 (main image) and at x50,000 (image at upper left).



in agreement with those obtained with a polystyrene-*b*-poly(acrylic acid) block copolymers.<sup>[8]</sup> In fact as only Van der Waals forces are present, the interaction for each individual coated SPION with the hydrophobic aromatic ring is limited, which can be useful to prepare nanodispersions of SPION.

For the mPEG-*b*-PDMAEMA block copolymers, because, at pH 9.0, the PDMAEMA lower critical solution temperature (LCST) (~45°C)<sup>[16]</sup> is significantly greater than the ambient temperature, one could expect that, due to the double hydrophilic nature of the block copolymer, the self-assembly with hydrophobic SPION would not occur. However, even though PDMAEMA remains hydrophilic at the self-assembly conditions (Figure S4, Supporting Information), the co-micellization of mPEG-*b*-PDMAEMA with LOSPION occurs, as shown in Figure 1. The appearance of these polymersome structures can be possibly explained by the formation of an PDMAEMA-SPION shell layer through complexation between the iron and the polymer nitrogen atoms, while still interacting with the oleic acid moieties originally from the SPION. The PEG block of the copolymer stabilizes the corona structure and the core of this self-assembled structure is expectedly to be formed by the hydrophobic oleic compounds that were used to form the SPION structures (see further discussion of Figure 4).



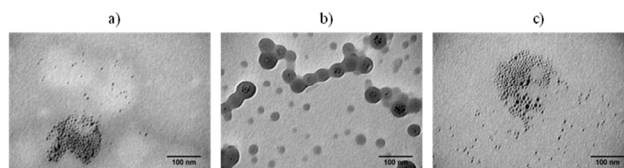
**Figure 2.** TEM micrographs of SOSPION self-assembled in the presence of 1.0 mg/mL of the block copolymer a) mPEG<sub>113</sub>-*b*-PS<sub>55</sub> and b) mPEG<sub>113</sub>-*b*-PDMAEMA<sub>54</sub> at SPION concentration of 0.1 mg/mL and 0.5 mg/mL. Images were taken at magnification x300,000.

As previously indicated by DLS measurements (see Table 2), a change in the type of oleic-coating of SPION has no significant effect on the size of the structures formed by the self-assembly of mPEG-*b*-PS and mPEG-PDMAEMA block copolymers. Figure 2 shows that, although the nanostructures formed by mPEG-*b*-PS in the presence of SOSPION seem to be reasonably similar to those obtained in the presence of LOSPION, those obtained with mPEG-*b*-PDMAEMA show a tendency towards an increased loading of SPION into the polymersome core. The core filling seem to take place preferably at one side of the polymersome, which can be attributed to an increasing SPION interaction, possibly promoted by the increasing complexation with PDMAEMA segments.

When the SOSPION concentration is increased the self-assembled structure is filled by more SPION, losing its polymersomic morphology into a structure that resembles much more to a micelle. This effect is attributed to the lower availability of PDMAEMA segments to complex with iron oxide moieties and, therefore, to a lower exchange of polymer segments

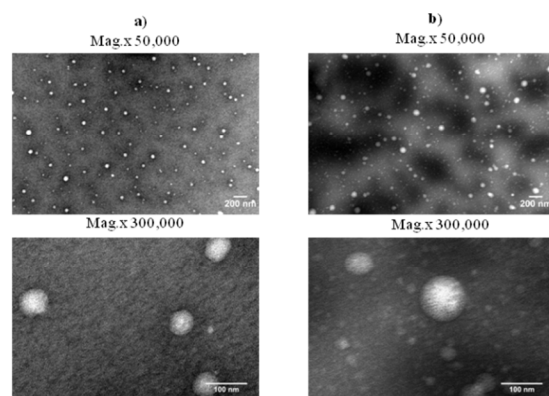
with oleylamine physically attached to the SPION surface. In the case of mPEG-PS copolymer, when a higher concentration of SPION is used for the preparation hybrid nanostructures, significantly larger micelle structures are obtained. This result shows that the size of the hybrid SPION nanostructures, and thus expectedly their magnetic performance, may also be tailored by the block copolymer to SPION ratio.

Also, the use of polymeric segments which can be protonated at low pH values, provides a responsive character to the self-assembled structures. As shown in Figure 3, when the pH of the aqueous solutions is decreased to 4.0 (below the pKa of the P4VP<sup>[12]</sup> and of the PDMAEMA<sup>[16]</sup>), the previously formed self-assembly structures based on mPEG-*b*-P4VP and mPEG-*b*-PDMAEMA are disrupted. This effect is attributed to the protonation of the nitrogen atoms of the polymer structure and, consequently, a significant change in polymer polarity and at the same time a loss of the complexation capacity with iron of these two polymers. Since the structure of PS is not affected by the pH change, the hybrid SPION self-assembled structures based on mPEG-*b*-PS retain the same morphology.



**Figure 3.** TEM micrographs of LOSPION self-assembled in the presence of a) mPEG<sub>113</sub>-*b*-P4VP<sub>44</sub>, b) mPEG<sub>113</sub>-*b*-PS<sub>55</sub>, and c) mPEG<sub>113</sub>-*b*-PDMAEMA<sub>54</sub> block copolymers in aqueous pH of 4.0 (concentration of 1.0 mg/mL for the block copolymer and of the 0.1 mg/mL LOSPION). Images were taken at magnification x300,000.

In order to evaluate the nature of the PDMAEMA-based magnetic polymersomes' core and the role of the oleic acid, further samples were prepared by self-assembling mPEG<sub>113</sub>-*b*-PDMAEMA<sub>54</sub> only in the presence of oleic acid (without the iron oxide phase). Figure 4 compares the TEM micrographs for the samples prepared with oleic acid with those prepared with LOSPION, using negative staining to highlight the organic nature of the nanostructures' core.



**Figure 4.** TEM micrographs, negatively stained with uranyl acetate, of mPEG<sub>113</sub>-*b*-PDMAEMA<sub>54</sub> block copolymers self-assembled in the presence of a) oleic acid or of b) LOSPION at a concentration of 1.0 mg/mL for the block copolymers and at an equivalent concentration of oleic acid of 0.067 mg/mL.

The TEM suggests that, since mPEG-*b*-PDMAEMA alone cannot form the same micellar structures under the self-assembly

conditions used, the formation of a core-shell structure is attributed to the formation of an oleic core stabilized by the block copolymer. In fact, although oleic acid is hydrophobic, its acidic functionality is expected to interact with the amine groups of PDMAEMA, explaining the aqueous stabilization of the oleic group by the mPEG-b-PDMAEMA block copolymer. When LOSPION are used, similar structures are obtained, providing evidence for the equivalency of the self-assembly process, and the role played by the SPION's oleic stabilizing group in the obtained polymersomic structures. Moreover, negative staining highlights the anchoring of polymeric segments to the iron oxide phase, which are preferably located at the shell layer as shown in Figure 1. One should consider that the formation of a large hydrophobic core in this type of structure opens the possibility of solubilising hydrophobic compounds, such as hydrophobic drugs, and, thus, these vesicle structures may be regarded as particles with great potential for the preparation of magnetic drug delivery systems<sup>[17]</sup>.

On the polymeric side, the peculiarity of self-assembly system based on mPEG-b-PDMAEMA block copolymer, due to PDMAEMA-oleic-coated SPION specific interactions, suggests that the architecture of the polymeric phase may also induce differences in the type of nanostructures that can be obtained. Although, changing the composition and the molecular weight of the block copolymer does not lead to significant differences on the self-assembled nanostructures (Figure S5, Supporting Information). Contrarily, we have found that differences can be observed when PDMAEMA homopolymer or a triblock copolymer having an "ABA"-type topology, PDMAEMA<sub>54</sub>-PEG<sub>136</sub>-PDMAEMA<sub>54</sub>, were used (Figure S6, Supporting Information). Both architectures formed stable oleic-coated SPION dispersions, but the structures were less uniform than those obtained with the mPEG-b-PDMAEMA diblock copolymer. In fact, the suitability of PDMAEMA as a dispersant for oleic-coated SPION is attributed to its direct interaction with both the oleic-coating and the iron oxide moieties. In the case of the PDMAEMA homopolymer, the poorer uniformity of the self-assembled structures can be explained by the lack of steric stabilization in hydrophilic environments provided by the PEG segment, which is absent. When the triblock copolymer was used, the formation of very large polymersome structures, which can even interact with smaller self-assembled structures, can be observed. This result suggests that the existence of two external PDMAEMA blocks may induce the formation of structures of greater complexity than those obtained with the diblock copolymer with PEG stabilized structure.

In conclusion, by varying the anchoring segment of the diblock copolymer, and thus the nature of the polymer-particle interactions, in the presence of oleic-coated SPION, a wide variety of magnetic nanostructures could be obtained, which range from small nanodispersions, nanoaggregates to vesicles when, respectively, PS, P4VP or PDMAEMA blocks were used. This approach represents a very important comprehensive study in a view of preparing tailor-made magnetic nanostructures.

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