Monodisperse Magnetic Polymeric Composite Particles for Biomedical Applications

*Shulai Lu, Jose Ramos, Jacqueline Forcada**

Summary: Magnetic polymeric composite particles (MPCPs) were prepared by miniemulsion polymerization of styrene in the presence of hydrophobic magnetic nanoparticles with hexadecane (HD) as hydrophobe, 2,2′-azobisisobutyronitrile (AIBN), and sodium dodecyl sulfate (SDS) as an emulsifier or sodium *p*-styrenesulfonate (NaSS) as an ionic comonomer. The hydrophobic magnetite particles with an average of about 10 nm were prepared by acidification of the water-based magnetite ferrofluid, previously synthesized by a chemical coprecipitation method. The results show that miniemulsion polymerization is an effective method for encapsulation of magnetite into a hydrophobic polymer. Exposed magnetite particles and pure polymer particles can be avoided by selection of appropriate preparation conditions.

Keywords: composite polymer particles; encapsulation; magnetic properties; miniemulsion polymerization

Introduction

Currently, there is an immense interest in the preparation of magnetic polymeric composite particles (MPCPs) for their application in biomedical, bioengineering, and biotechnology fields,[1–3] such as cell separation, immunoassays, nucleic acid purification and DNA separation, enzyme immobilization, magnetic resonance imaging, hyperthermia, and so on. This interest is due to high magnetic susceptibility of MPCPs to an external magnetic field; in addition, they are easily further functionalized and surface-modified by the attachment of various bioactive molecules.[4]

MPCPs should fulfill certain conditions to be suitable for biomedical applications:[5] no sedimentation, uniform size and size distribution, high and uniform magnetic content, superparamagnetic behavior, no toxicity, no iron leaking, etc. In general, the polymerization for encapsulation of magnetite may produce three possible types of particles in the resulting magnetic latex - magnetic polymeric composite particles (MPCPs, with magnetite encapsulated inside), pure polymer particles (PPPs, without magnetite inside) and exposed (free) magnetite particles (BMPs, without polymer coating). The existence of PPPs is not desirable because the magnetic properties of the composite particles are reduced. Nor is existence of BMPs desired because they cannot be further functionalized due to the lack of polymer on their exposed surfaces. In addition, the particle size distribution (PSD) should be as narrow as possible so that MPCPs can respond to external magnetic field as uniformly as possible. Therefore, the challenge in almost the all strategies in preparation of MPCPs is to minimize or even eliminate the formation of PPPs and BMPs. A more difficult challenge is to obtain MPCPs with very narrow PSD. These important issues, however, have not been reported and discussed in detail in the literature.

This work aims to review some conclusions derived from the analysis of the

Grupo de Ingeniería Química, Facultad de Ciencias Químicas, The University of the Basque Country, Apdo. 1072, 20080 San Sebastián, Spain
Fax: (+34) 943 015370;
E-mail: jacqueline.forcada@ehu.es

results obtained in the preparation of MPCPs by miniemulsion polymerization using sodium dodecyl sulfate (SDS) as an emulsifier[6] and by emulsifier-free miniemulsion polymerization using sodium *p*-styrenesulfonate (NaSS) as an ionic comonomer.[7]

Preparation of Hydrophobic Magnetite Ferrofluid

Superparamagnetic particles are of great interest because they do not retain any magnetism after removal of the magnetic field. To ensure that magnetite nanoparticles exhibit superparamagnetic behavior, hydrophilic magnetite particles smaller than 15 nm were prepared by stoichiometric chemical co-precipitation of ferrous and ferric salts.[6] In this way, a water-based magnetite ferrofluid was obtained.

In addition, oleic acid (OA) was used as a stabilizer to keep single magnetite particles having a size of 10-15 nm, and to prevent the formation of large aggregates. The results indicated that oleic acid performed as an effective stabilizer. As oleic acid is hydrophobic and insoluble in water, acetone was used as co-solvent. In the course of the co-precipitation, oleic acid reacted with ammonium hydroxide to form ammonium oleate.[6] In this way, the magnetite particles produced were coated with ammonium oleate and not with oleic acid: so the magnetite ferrofluid obtained was water-based.

On the other hand, hydrophobic magnetite particles were prepared by acidification of hydrophilic magnetite particles. As a consequence, ammonium oleate was transformed into oleic acid (OA) with a strong acid.[6] In this way, an oil-based Fe_3O_4 ferrofluid (Fe_3O_4-St) was obtained with 10% in weight content with respect to styrene (St). The transformation of the hydrophilic to hydrophobic character of magnetite particles is fundamental for their encapsulation inside the polymer particles.

Preparation of Magnetic Polymeric Composite Particles by Miniemulsion Polymerization

The effect of the amount of SDS on the production of MPCPs was studied by the preparation of MPCPs with different amounts of SDS, with other experimental conditions kept unchanged (Table 1)

TEM microphotographs of the synthesized MPCPs are shown in Figure 1. As can be seen, the amount of SDS had a notable effect on the magnetite encapsulation degree, particle size (D_N), polydispersity index (PDI) and particle size distribution (PSD) of MPCPs (Figure 2). With 2% SDS, the magnetite encapsulation degree was very high, and some BMPs and few PPPs were observed. At 3% SDS the encapsulation of magnetite was successful and neither BMPs nor PPPs were observed. When the amount of SDS was 4%, the magnetite encapsulation degree was lower than with 2% or 3%, because the number of BMPs increased. With 5% SDS, the magnetite encapsulation degree was much lower than with the 2% and 3%, and large quantities of BMPs were observed.

In Figure 1, it can also be seen that the particle size of the MPCPs decreased when the amount of SDS increased. The trend of particle size depending on amount of SDS was similar to that of a conventional emulsion polymerization; as expected the PSDs of the MPCPs became broader with increasing amounts of SDS (Figure 2).

Thus, it can be concluded that decreasing the amount of SDS improves the

Table 1.
Recipes using SDS as an emulsifier[a].

Latex	SDS (%)
SDS-1	2.0
SDS-2	3.0
SDS-3	4.0
SDS-4	5.0

Reaction conditions: T = 70 °C; 49 rpm; reaction time 21 h; DDI Water = 63.0 g; Fe_3O_4 + St = 7.0 g; AIBN = 4.0%; HD = 12.0%.
[a]All the percentages are based on the total amount of Fe_3O_4 and St.

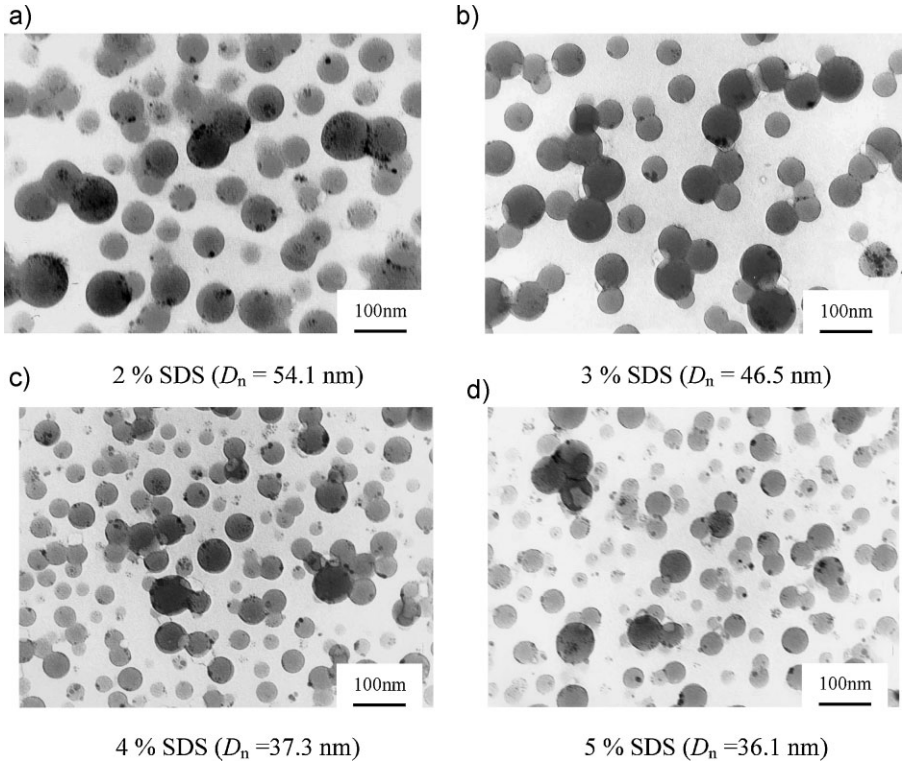

Figure 1.
TEM microphotographs of MPCPs prepared using different amounts of SDS.

encapsulation degree of magnetite and narrows the PSD, and also decreases the number of BMPs and PPPs. The optimum amount of SDS was 2∼3%, based on the sum of the total amounts of styrene and magnetite (St + magnetite).

Preparation of Self-Stabilized Magnetic Polymeric Composite Particles by Emulsifier-Free Miniemulsion Polymerization

The effect of the amount of NaSS on the production of MPCPs was studied by the preparation of MPCPs using different amounts of NaSS, maintaining the other experimental conditions unchanged (Table 2)

TEM microphotographs of the SS-MPCPs synthesized with different amounts of NaSS are shown in Figure 3. As can be seen, the amount of NaSS had a notable effect on the magnetite encapsulation degree, particle size, and PSDs of the SS-MPCPs. From 5% to 15% of NaSS the encapsulation degree was increased, and some BMPs but no PPPs were observed. At 20% of NaSS, the encapsulation of magnetite was successful, and neither BMPs nor PPPs were observed. The absence of PPPs formed during the polymerization process indicated that monomer droplet nucleation was achieved entirely by using an emulsifier-free miniemulsion polymerization technique. Micellar nucleation was avoided completely in the absence of emulsifier, and homogeneous nucleation was also prevented. However, when the concentration of NaSS was 25%, a significant number of PPPs were observed. At this concentration, the amount of oligomers formed in the aqueous

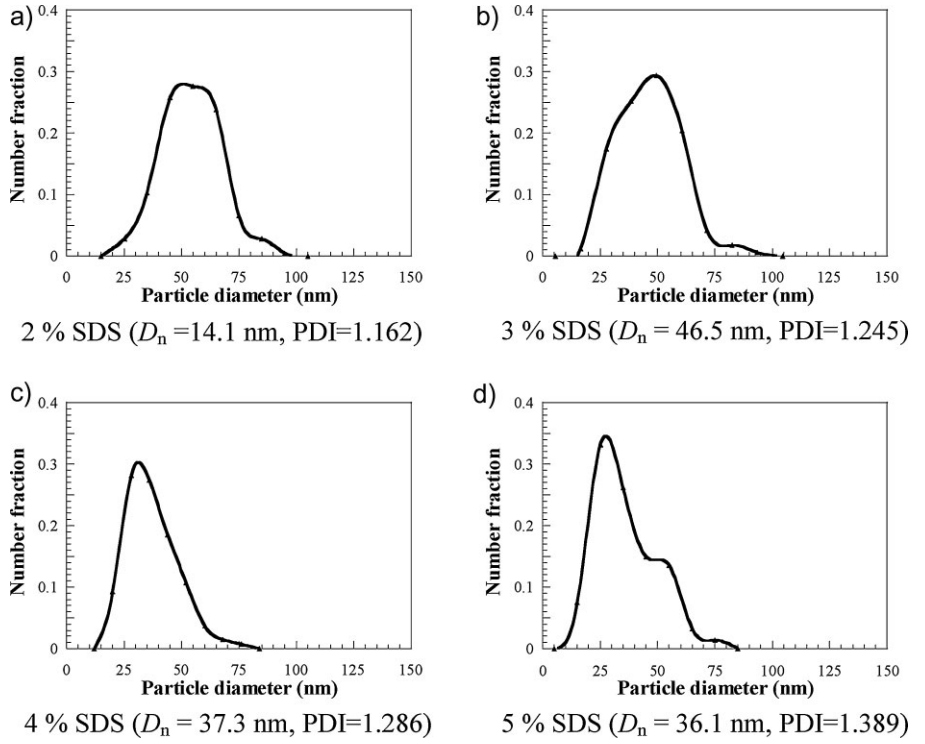

Figure 2.
Particle size distributions of MPCPs prepared using different amounts of SDS.

phase is sufficient to stabilize the particles generated by homogeneous nucleation and pure polymer particles were produced.

In Figure 4 PSDs, particle sizes, and PDIs of the different SS-MPCPs synthesized are shown. As can be seen, particle sizes and PDIs decreased, and PSDs became narrower when the amount of NaSS increased up to 20%. Furthermore, the PSD of SS-MPCPs-20 was relative narrow and its PDI (1.081) was close to monodispersity in size (PDI < 1.05) according to Tsaur et al.[8] However, at 25% of NaSS, the particle size of the SS-MPCPs decreased, but the PSD was very broad (PDI 1.920), showing a clear bimodality. This was due to the generation of a high amount of small PPPs by the homogeneous nucleation mechanism (see Figures 3e and 4e).

In addition, in the TEM micrographs (Figure 3) and in the PSDs (Figure 4) of all the SS-MPCPs prepared, the existence of a few large composite particles in all latexes can be observed.

The distribution of magnetite inside composite particles is an important factor, which can influence the magnetic characteristics of composite particles. As can be seen in the micrographs shown in Figure 3, the magnetite particles in all the SS-MPCPs

Table 2.
Recipes using NaSS as an ionic comonomer[a].

Latex	NaSS (%)
SS-MPCPs-5	5.0
SS-MPCPs-10	10.0
SS-MPCPs-15	15.0
SS-MPCPs-20	20.0
SS-MPCPs-25	25.0

Reaction conditions: T = 70 °C; 49 rpm; reaction time 21 h; DDI Water = 63.0 g; Fe_3O_4 + St = 7.0 g; AIBN = 4.0%; HD = 15.0%.
[a]All the percentages are based on the total amount of Fe_3O_4 and St.

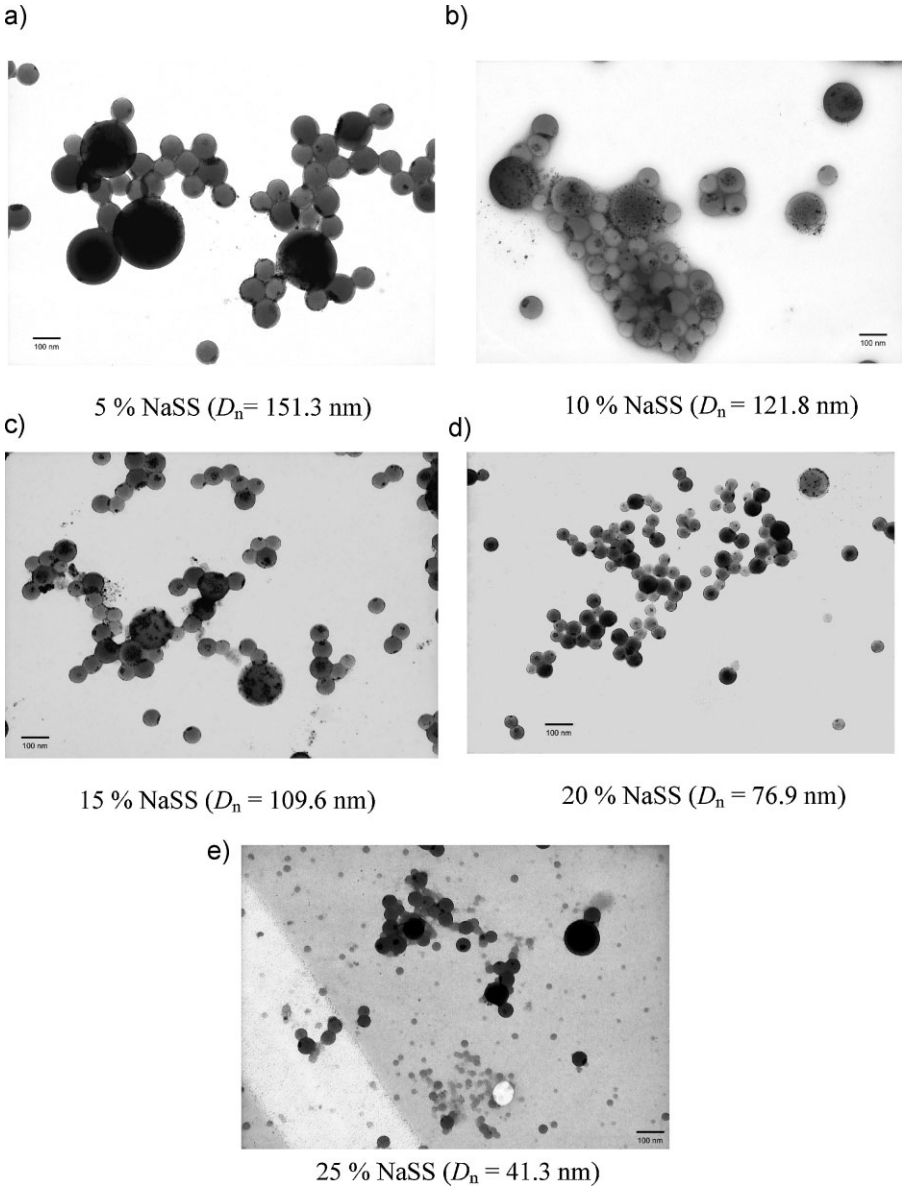

Figure 3.
TEM microphotographs of SS-MPCPs prepared with different amounts of NaSS.

synthesized are mainly in the core of the composite particles. However, in the MPCPs prepared using SDS as emulsifier (see Figure 1), the magnetite particles were almost all located in the outer layer of the composite particles, and this distribution was non-uniform.

Due to the ionic character of NaSS, the copolymerization of St with NaSS increases the hydrophilicity of the polymer formed and enhances the hydrophobicity of oleic acid-coating magnetite particles. Thus, magnetite particles are mainly in the core of SS-MPCPs.

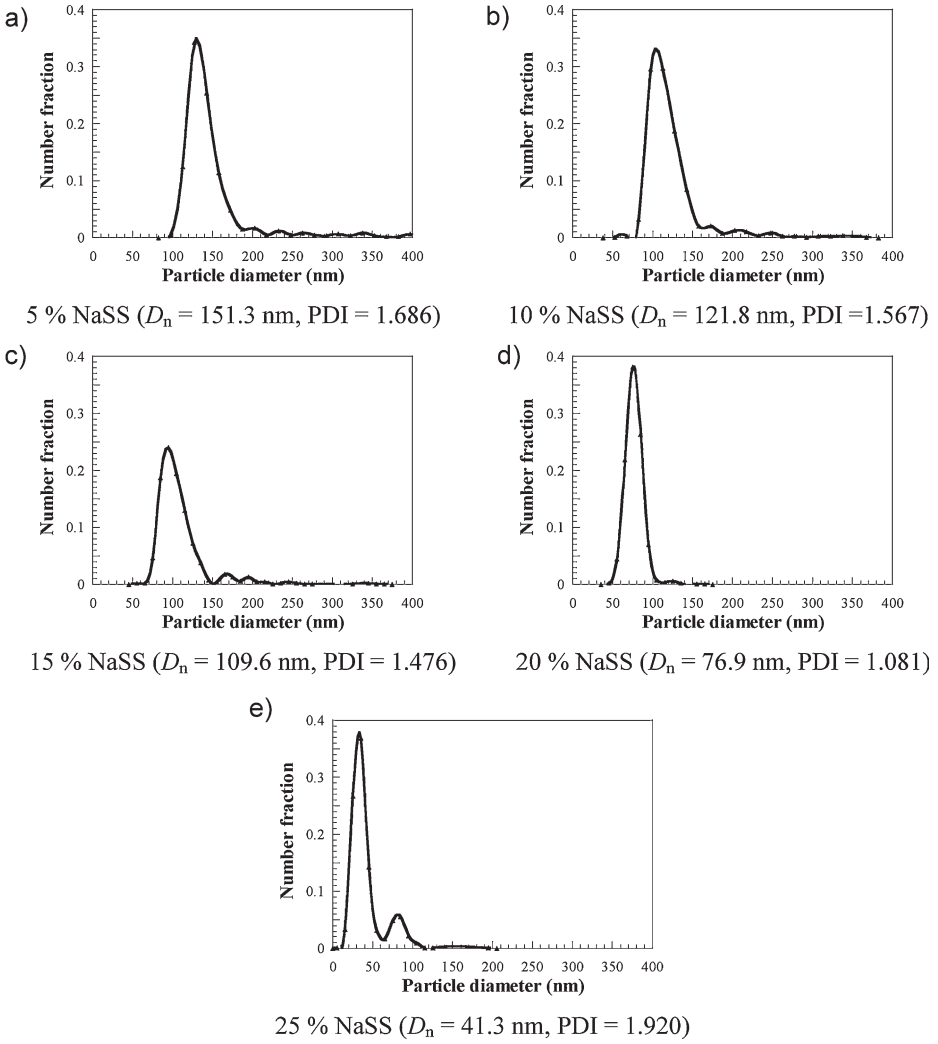

Figure 4.
PSDs of SS-MPCPs prepared with different amounts of NaSS.

On the other hand, as was commented before, there are a few large composite particles in the magnetic latexes. As can be seen in Figure 3, the distribution of magnetite particles inside the largest composite particles is completely different from that of the smallest ones. This means that the formation of this kind of particles is due to aggregation of some particles. Besides, it can be seen that the number of magnetite particles encapsulated inside each magnetic particle is not the same.

Conclusion

Miniemulsion polymerization is an effective method of encapsulation of magnetite in a hydrophobic polymer. Exposed magnetite particles and pure polymer particles can be avoided completely by selecting the appropriate preparation conditions.

SDS works as a high-efficiency emulsifier in the preparation of MPCPs by miniemulsion polymerization; decreasing the amount of SDS improves the magnetite

encapsulation degree, narrowing the PSD, and decreasing the amount of BMPs and PPPs at the same time. The optimum percentage of SDS, based on the total amount of styrene and magnetite, was 2∼3%.

On the other hand, NaSS works as a highly efficiencient stabilizer in the preparation of SS-MPCPs by emulsifier-free miniemulsion polymerization. Increasing the amount of NaSS improves the magnetite encapsulation degree, decreases the particle size, narrows the PSD, and reduces the number of BMPs and PPPs. The optimum percentage of NaSS, based on the total amount of St and magnetite, is 20%. At higher concentrations of NaSS, high amounts of PPPs were observed.

The magnetite particles in the SS-MPCPs were mainly in the core of the composite magnetic particles, the number of magnetite particles encapsulated inside each magnetic particle being different.

Acknowledgements: The authors thank the Spanish Ministerio de Ciencia e Innovación/ Programa Nacional de Materiales (MAT 2006-12918-CO5-03) for financial support.

[1] J. Ugelstad, P. Stenstad, L. Kilaas, W. S. Prestvik, R. Herje, A. Bererge, E. Hornes, *Blood Purif.* **1993**, *11*, 349.
[2] A. Elaïssari, R. Veyret, B. Mandrand, J. Chatterjee, *Surfactant Science Series, Colloidal Biomolecules, Biomaterials, and Biomedical Applications* **2004**, *116*, 1.
[3] M. Arruebo, R. Fernandez-Pacheco, M. R. Ibarra, J. Santamaria, *Nanotoday* **2007**, *2*, 22.
[4] X. Q. Liu, Y. P. Guan, Z. Y. Ma, H. Z. Liu, *Langmuir* **2004**, *20*, 10278.
[5] K. Landfester, L. P. Ramirez, *J. Phys.: Condens. Matter.* **2003**, *15*, S1345.
[6] S. Lu, J. Forcada, *J. Polym. Sc i., Part A: Polym. Chem.* **2006**, *44*, 4187.
[7] S. Lu, J. Ramos, J. Forcada, *Langmuir* **2007**, *23*, 12893.

