Available online at www.sciencedirect.com
ScienceDirect
Journal of Magnetism and Magnetic Materials 310 (2007) 2850–2852
Journal of magnetism and magnetic materials
www.elsevier.com/locate/jmmm

Preparation and characterization of thermal-sensitive ferrofluids for drug delivery application

Ting-Yu Liu, Shang-Hsiu Hu, Sheng-Hsiang Hu, Szu-Ping Tsai, San-Yuan Chen*

Department of Materials Sciences and Engineering, National Chiao Tung University, Hsinchu 300, Taiwan, ROC

Available online 1 December 2006

Abstract

Novel thermal-sensitive ferrofluids (F127-ferrofluids) consisting of core–shell-type magnetic nanoparticles dispersed in Pluronic F127-containing aqueous solution were prepared. The core (magnet)–shell (Pluronic F127) nanoparticles were synthesized by in situ co-precipitation process, which were characterized using transmission electron microscope, X-ray diffraction and vibrating sample magnetometer. The F127-ferrofluids gelled above the lower critical solution temperatures (LCST) of approximately 23–28 °C, which were higher than that of pure Pluronic F127-fluids (21–25 °C). The increase in the LCST of the F127 ferrofluids may be attributed to a result of a physical interaction between the F127 molecules and the core–shell magnetic nanoparticles.

Keyword: Ferrofluid; Core–shell; Magnetic nanoparticle; Pluronic F127; Thermal sensitive; Drug delivery

1. Introduction

Recently, ferrofluids are widely used in the fields of biology and biomedicine such as enzyme and protein immobilization, genes, radiopharmaceuticals, magnetic resonance imaging (MRI), diagnostics, immunoassays, RNA and DNA purification, separation, and targeting drug delivery devices [1,2]. In order to develop functional nanosized magnetite particles, a stable dispersion of the magnetic nanoparticles in organic or aqueous media is critically required with an aid of using effective surface modification. A delicate balance of hydrophilicity/hydrophobicity in the polymer structure is responsible for manipulating a lower critical solution temperature (LCST) phenomenon. A series of tri-block copolymers composed of poly (ethylene oxide)–poly (propylene oxide)–poly (ethylene oxide) (Pluronics) are a kind of temperature-sensitive polymers that demonstrate reversible solution transition behaviors in aqueous solutions [3,4]. Consequently, the novel thermo-sensitive ferrofluids that combine Pluronics-based polymers (Pluronics F127) with magnetite nanoparticles can lead to a temperature-responsive drug carrier system, because the magnetite itself provides a source of heat in the alternating magnetic field [5].

2. Experiment

The stable thermo-sensitive ferrofluids were synthesized using the method of in situ co-precipitation of Fe (II) and Fe (III) salts in the presence of Pluronic F127 (F127, Sigma). In this process, 0.05 g of F127, 1.35 g of $FeCl_3 \cdot 6H_2O$ (5 mmol, Riedel-deHaën), and 0.498 g of $FeCl_2 \cdot 4H_2O$ (2.5 mmole, Fluka) were dissolved in 50 ml of water under vigorous stirring at 60 °C. Then, the ammonia solution (33%, Riedel-deHaën) was quickly added to the reactor and stirred until pH reached 10, followed by hydrothermal treatment at 80 °C for 30 min. After washing five times, filtering, and freeze-drying, core (magnet)–shell (F127) nanomagnetic particles (NMPs) were successfully prepared. Finally, the 1 g of core–shell NMPs were dispersed in the 10 ml of 40% (w/v) F127 aqueous solution (pure F127 fluids, dissolved at 4 °C beforehand) by sonication at 4 °C for 6 h. The well-dispersed thermo-sensitive ferrofluids were thus fabricated. Besides, Fe_3O_4 NMPs (diameter ca. 5–10 nm) fabricated by

*Corresponding author. Tel.: +886 3 5731818; fax: +886 3 5725490.
E-mail address: sychen@cc.nctu.edu.tw (S.-Y. Chen).

0304-8853/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jmmm.2006.11.129

the in situ co-precipitation process were used as referenced materials [1].

3. Results and discussion

TEM photos (JEOL-2000FX) in Fig. 1(a) show the core–shell structure of the magnet-F127 NMPs. The average thickness of the F127 layers is about 1–2 nm, and the magnet diameter is about 5–7 nm.

Moreover, it was found in the XRD (Rigaku) pattern (Fig. 1(b)) that six diffraction peaks at $2\theta = 30.1^\circ$, 35.6°, 43.3°, 53.5°, 57.2°, 62.9° are the characteristic peak of Fe_3O_4 crystal. Hence, the resulting magnet NMPs can be defined as Fe_3O_4 NMPs. An additional diffraction peak at ca. $2\theta = 32.3^\circ$ was detected in the NMPs, which is a characteristic peak of Fe_2O_3 crystal, indicating a small amount of Fe_2O_3 phase was associated with the core–shell NMPs but the superparamagnetic behavior of the core–shell NMPs was not affected. Furthermore, the spectrum of pure F127 showed two characteristic peaks at $2\theta = 18.8^\circ$ and 23.1°, indicating that the F127 displays high degree of crystallization. However, the core–shell NMPs exhibit a broad diffraction pattern at 21°, which is believed to be an ultra-thin layer of F127 that is difficult to re-crystallize to fully develop a matured F127 lattice. In addition, Fig. 1(c) shows that Fe_3O_4 NMPs display a higher magnetization (M_s) (60.9 emu/g) than that of the core–shell NMPs i.e., M_s (28.4 emu/g). The incorporation of the F127 may cause damages in some domains of the nanocrystalline Fe_3O_4 resulting in a lower M_s. Nevertheless, it further evidenced that the F127 is truly deposited around the surface of the Fe_3O_4 nanoparticles.

Fig. 2 shows the DSC (Perkin-Elmer, Diamond DSC) spectra upon heating and cooling cycles (5 °C/min) for both pure F127 fluids and F127 ferrofluids with a process of the gelation and liquefaction, respectively. An endothermic peak of pure F127 fluids and F127 ferrofluids in the heating cycle was detected which is due to the aggregation transition (gel formation) of these two fluids in aqueous suspension. Such aggregation is caused by the temperature sensitivity of the PPO segments of the Pluronic that being anchored to the gel network. Much like the uncrosslinked Pluronic, polymers can form intra- and inter-molecular micelle-like aggregates due to the hydrophobic interaction [3]. The gelation started at 21.8 °C and maximized at 32.5 °C for pure F127 fluids, and it commenced at 22.8 °C and maximized at 35.6 °C for F127 ferrofluids. It is more difficult to identify where LCST is spreading with a broad peak. In this case, the exothermic peak in the cooling cycle can be used to identify the LCST, due to its sharper peak. The liquefaction started at 24.9 °C and maximized at 21.4 °C for pure F127 fluids, but commenced at 28.5 °C and maximized at 23.5 °C for the F127 ferrofluids. Therefore, LCST of the pure F127 fluids can be defined in the range of 21–25 °C, which is agreed with literature data [4]. However, it is lower than the LCST of the F127 ferrofluids, 23–28 °C. The reason that LCST shift for the F127 ferrofluids was due to the presence of the core–shell NMPs, which may play a role of cross-linker, resulting in an increased LCST. Similar results can be found in PNIPAAm/clay systems [6].

In addition, a drug can be dispersed homogenously in F127 ferrofluids below the region of LCST, and then encapsulated into F127 ferrogel above LCST, and higher drug encapsulation efficiency was obtained. Moreover, it

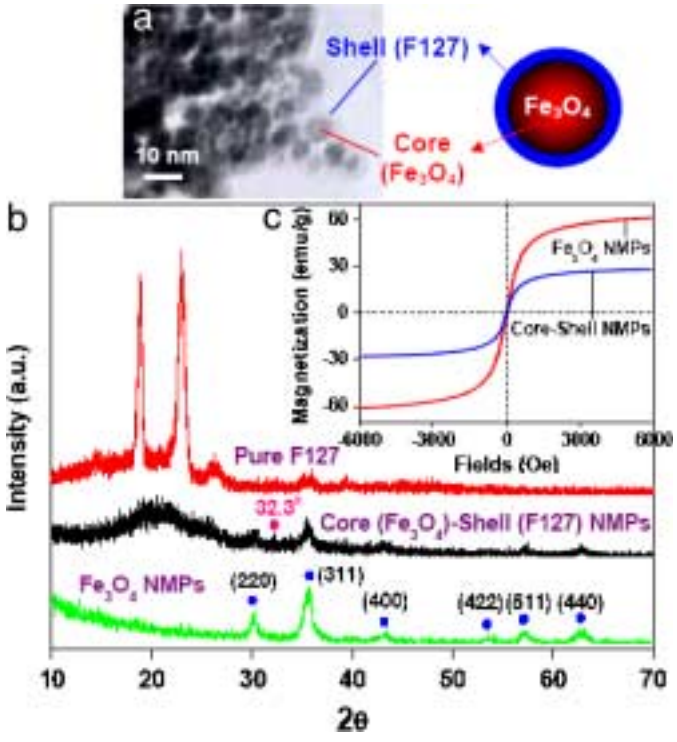

Fig. 1. (a) TEM photo of core–shell NMPs, (b)XRD pattern of core–shell NMPs, and (c) magnetization curve of core–shell NMPs using VSM.

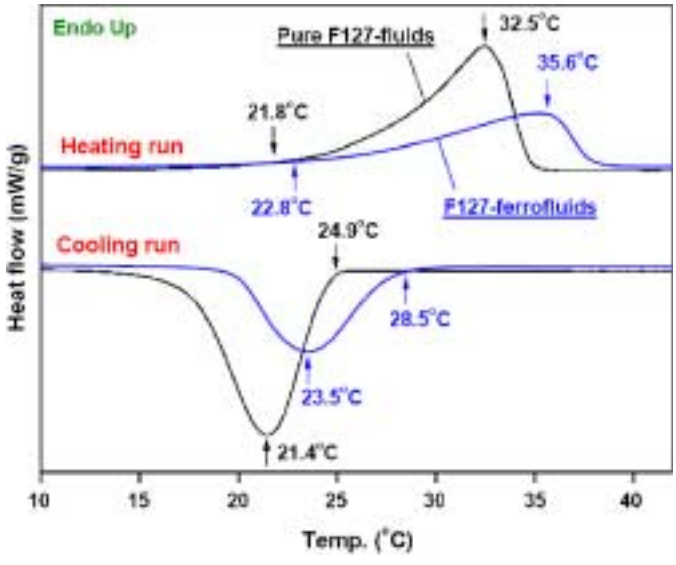

Fig. 2. DSC heating and cooling scans of pure F127 fluids and F127 ferrofluids.

can be anticipated that the temperature increase in the F127 ferrofluids modulated by hyperthermia of magnetic nanoparticles under external alternating magnetic fields [5] allows a phase transformation to a solid-like F127 ferrogels, which can find new applications in medicine. Further investigation in this aspect is in progress and will be reported shortly.

4. Conclusion

Novel thermo-sensitive ferrofluids were successfully synthesized with core–shell NMPs and F127 fluids, and can be modulated by temperature changes to form ferrogels. By its thermo-triggered operations and higher drug encapsulation efficiency, it is potential to use this type of F127 ferrofluids for medical applications, such as an intelligent drug delivery system.

Acknowledgement

The authors gratefully acknowledge the National Science Council of the Republic of China for its financial support through Contract No. NSC-94-2216-E-009-016.

References

[1] S.Y. Mak, D.H. Chen, Macromol. Rapid Commun. 26 (2005) 1567.
[2] M.R. Kim, T.G. Park, J. Control Release 80 (2002) 69.
[3] L. Bromberg, M. Temchenko, G.D. Moeser, T.A. Hatton, Langmuir 20 (2004) 5683.
[4] L. Bromberg, M. Temchenko, T.A. Hatton, Langmuir 19 (2003) 8675.
[5] J.H. Park, K.H. Im, S.H. Lee, D.H. Kim, D.Y. Lee, Y.K. Lee, K.M. Kim, K.N. Kim, J. Magn. Magn. Mater. 293 (2005) 328.
[6] K. Haraguchi, T. Takehisa, S. Fan, Macromolecules 35 (2002) 10162.