Synthesis of Polystyrene Nanocapsules by Redox Interface-Initiated Inversed Microemulsion Polymerization for Drug Release

Weijun Liu, Guanghong He, Zhicai He

Department of Polymer Science and Engineering, School of Pharmaceutical and Chemical Engineering, Taizhou University, Linhai, Zhejiang 317000, People's Republic of China

Received 29 December 2008; accepted 18 July 2009
DOI 10.1002/app.31144
Published online 7 October 2009 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Polystyrene nanocapsules with a diameter of 140 nm and a water-soluble sodium salicylate core were prepared by redox interface-initiated emulsion polymerization (RIEP) in an inversed microemulsion with cumene hydroperoxide/iron(II) sulfate as the redox initiation couple. The morphology of the nanocapsules was characterized by transmission electron microscopy and field emission scanning electron microscopy. Dynamic light scattering was used to determine the nanocapsule size and polydispersity (0.14–0.20). The release of sodium salicylate from the nanocapsules was monitored by ultraviolet–visible spectroscopy. All of the results indicate that the fabrication of core–shell nanocapsules with the water-soluble active chemical as the core via RIEP was successful. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 115: 1630–1634, 2010

Key words: core-shell polymers; dynamic light scattering; emulsion polymerization; monomers; polystyrene

INTRODUCTION

Recently, great efforts have been devoted to the development of nanoparticulate drug carriers, such as nanoparticles, nanocapsules, micelles, liposomes, and conjugates.[1–3] One major obstacle of nanoparticulate systems for drug delivery is their extensive uptake by the reticuloendothelial systems.[2,4,5] As a solution for preventing reticuloendothelial system uptake, the surface of the nanoparticulates was sterically stabilized by hydrophilic poly(ethylene glycol), and so-called stealth particles were developed.[6] Among various nanoparticulate drug carriers, nanocapsules provide attractive characteristics in that they can prevent reticuloendothelial system uptake of the drug carriers *in vivo*, and hence, they can circulate in the blood for a long period of time. This advantage comes from the structure of the nanocapsule: The hydrophilic portions of an amphiphilic block copolymer form the outer shell and are exposed to body fluid, and hence, the nanocapsules can be protected from phagocytic cells and plasma proteins in the blood.[7] Another important biological advantage of nanocapsules is their enhanced permeability and retention effect, or passive targeting: nanocapsules can slowly accumulate in malignant or inflamed tissues because of the elevated levels of vascular permeability factors in such cells.[8–11]

Nanocapsules with core–shell structures are always a hotspot in the materials field because their structures are known to have many potential applications. Usually, the shell of nanocapsules with core–shell structures is composed of polymers, including natural polymers and synthetic polymers. The core can be solid,[12] liquid,[13] gas, or void.[14] Polymeric nanocapsules with a liquid core can be used as controlled delivery systems for drugs, dyes, and enzymes and for the protection of light-sensitive components. Common approaches for the preparation of polymeric nanocapsules include block copolymer assembly,[15] seeded polymerization with the dynamic swelling method,[16] and interface-initiated polymerization of emulsions.[17] Most methods involve a multistage and time-consuming strategy. For example, polymer particles with a core–shell structure are prepared through multistage emulsion polymerization followed by the removal of the corona through purposefully designed swelling. However, there are few reports on the preparation of nanocapsules containing liquid cores via redox interface-initiated microemulsion polymerization at room temperature.

In this article, we describe the preparation of core–shell polystyrene (PSt) nanocapsules containing water-soluble sodium salicylate (SS) liquid cores through the redox interface-initiated emulsion polymerization (RIEP) of styrene (St) in an inversed

Correspondence to: W. Liu (lwj3600@mail.ustc.edu.cn).
Contract grant sponsor: Natural Science Foundation of Zhejiang Province.

microemulsion. Redox initiation pairs have been used extensively in the emulsion polymerization of vinyl monomers.[18–21] Radicals can be produced rapidly compared with thermally decomposed initiators such as persulfate. Among the redox initiation pairs, the couples composed of one water-soluble component and one oil-soluble component exhibit different characteristics; that is, radicals are formed mostly at the water–oil interface. In previous studies, we took advantage of these interface-initiated emulsion polymerizations to prepare different core–shell particles, such as PSt/PNVP core–shell particles, PSt hollow particles[22] through one-stage emulsion polymerizations, and CdS–PSt hybrid materials.[23] Several pairs of such redox initiators have been used by different researchers, and they include cumene hydroperoxide (CHPO)/iron(II) sulfate (FS), CHPO/tetraethylenepentamine, and *tert*-butyl hydroperoxide with different water-soluble reductants.[24–26] The main target of this study was to prepare SS-loaded nanocapsules by this RIEP technique and illuminate their potential to easily encapsulate other water-soluble other active chemicals with polymers. Indeed, the encapsulated SS could be released through the PSt shell of the nanocapsules.

EXPERIMENTAL

Materials

St was purchased from Shanghai Chemical Reagent Co. and was washed with NaOH (10 wt %) aqueous solution and then distilled water until pH 7. After it was dried with anhydrous $MgSO_4$, St was distilled *in vacuo* before use. CHPO and divinylbenzene (DVB) were purchased from Sigma–Aldrich. SS, FS, octylphenyl poly(ethylene glycol) ether with $n = 4$ (OP-4), and octylphenyl poly(ethylene glycol) ether with $n = 10$ (OP-10) were purchased from Shanghai Chemical Reagent Co. Other chemicals and solvents were analytical grade and were used without any further purification.

Preparation of the PSt nanocapsules containing SS cores via RIEP

Our typical procedure for the fabrication of PSt nanocapsules containing water-soluble SS liquid cores was as follows. FS (60 mg) and SS (0.4021 g) were dissolved in distilled water (3.5 mL) to obtain the dispersed phase. The nonionic surfactants OP-4 and OP-10 were selected as emulsifiers, and hexane was used as the continuous oil phase. In a typical experiment, OP-4 (3.084 g) and OP-10 (2.743 g) were dissolved in hexane (50 mL) to form the continuous phase. The SS aqueous solution was dropped into the continuous phase, and the obtained mixture was sonified to obtain an inversed microemulison. Then, the emulsion was heated to 35°C while it was purged with nitrogen for 1 h. The oil-soluble components of St (1.5 or 2.0 g), the crosslinking reagent DVB (10 mg), and CHPO (100 mg) were dissolved in hexane (10 mL). The obtained solution was added dropwise into the inversed microemulsion for 2 h. The polymerization was continued for another 12 h to ensure the complete conversion of the monomers. Solid nanocapsules containing SS were obtained after they were destabilized with ethanol, washed with hexane (to remove the surfactants) and ethanol, centrifuged, and dried *in vacuo* at room temperature.

Release of SS from the nanocapsules

The release of SS from the nanocapsules was carried out by the dispersal of the centrifuged nanocapsules (0.4 g) in deionized water (30 mL). The mixture was placed in a dialysis membrane bag with a molecular cutoff of 10 kDa; the bag was tied and immersed in 300 mL of water. The system was kept at 40°C with continuous magnetic stirring. At different intervals from 10 to 200 min, 5 mL of deionized water without any nanocapsules was withdrawn from the dialysis bag for analysis of the amount of released drug with ultraviolet–visible (UV–vis) spectroscopy at 295.0 nm. At each sampling, another 5 mL of deionized water was added to retain the volume of the release system constant. Thus, the dependence of drug release on time and the total amount of encapsulated SS within the nanocapsules were evaluated. The sampling influence on the concentration of SS was corrected with a mathematical method with eq. (1):

$$C_n = C'_n + \sum C_{n-1} V_s/300 (n > 1) \quad (1)$$

where C_n is the corrected concentration, C'_n is the measured concentration at the nth time, n is the order of sampling, and V_s is the sampling volume.[27]

Instrumentation

For the observation by transmission electron microscopy (TEM), the obtained microemulsions were thinned to 1000× with hexane, and one drop of the thinned latex was attached to a copper grid. After the natural evaporation of the solvent, the morphology of the PSt nanocapsules containing SS in the core was observed under a Hitachi model H-800 TEM instrument at an accelerating voltage of 200 kV. As for the morphology observation under field-emission scanning electron microscopy (FESEM; JEOL JSM-6700) at an acceleration voltage of 10 kV, the solid nanocapsules were attached to a piece of adhesive tape, and the samples were coated

TABLE I
Interface-Initiated Polymerization of St in an Inversed Microemulsion

Nanocapsule	DVB (mg)	St (g)	Size as measured by TEM (nm)		R_g (nm)	R_h/PDI (nm)
			Average radius	Thickness		
A	10	1.5	62	22	70	74/0.14
B	10	2.0	74	31	82	86/0.20

The polymerizations were carried out in OP-4 (3.084 g) and an OP-10 (2.743 g)/hexane solution (50 mL) with CHPO (100 mg) as the initiation oxidant, FS (60 mg) as the initiation reductant, and SS (0.4021 g) in water (3.5 mL).

with gold *in vacuo*. For laser light scattering, the obtained microemulsions were thinned with deionized water. Then, the thinned latex was passed through a Millipore filter (0.45 m) to remove any dust. The hydrodynamic radius (R_h), gyration radius (R_g), and polydispersity index (PDI) of the nanocapsules were determined on a modified commercial laser light-scattering spectrometer (ALV/SP-125) equipped with an ALV-5000 multi-τ digital time correlator and a He–Ne laser (632.8 nm). UV–vis analysis was performed on a Shimadzu UV-2100 spectrophotometer at room temperature.

RESULTS AND DISCUSSION

Preparation and confirmation of the PSt nanocapsules containing SS

PSt nanocapsules containing SS in the core were prepared though RIEP of St in inversed microemulsion, as summarized in Table I. The core–shell hollow morphology of the nanocapsules containing liquid cores was clearly observed under TEM as shown in Figures 1(a) and 1(b), which are for nanocapsules A and B, respectively. In those images, PSt appears as black loops. The nanocapsules were hollow because of the removal of water, and the cores appeared white to gray. By counting 100 nanocapsules, we obtained the average radius and shell thickness and listed them in Table I. Both the size and shell thickness of the nanocapsules increased with increasing amount of St. Figure 1(c) shows the FESEM image of the dried nanocapsules containing SS. A hollow structure with a broken shell was observed, and most of the dried nanocapsules appeared irregular in shape. This may have been caused by the collapse of the PSt shell during the dryness.

The hydrodynamic radius distributions [$f(R_h)$] of PSt nanocapsules containing liquid cores are shown in Figure 2, and the data are listed in Table I. The PDI of nanocapsules A and B were 0.14 and 0.20; this indicated a little broadened distribution of those nanocapsules with R_h values of 74 and 86 nm, respectively. Their R_g values were very close to their R_h values; that is, the R_h/R_g ratios were about unity

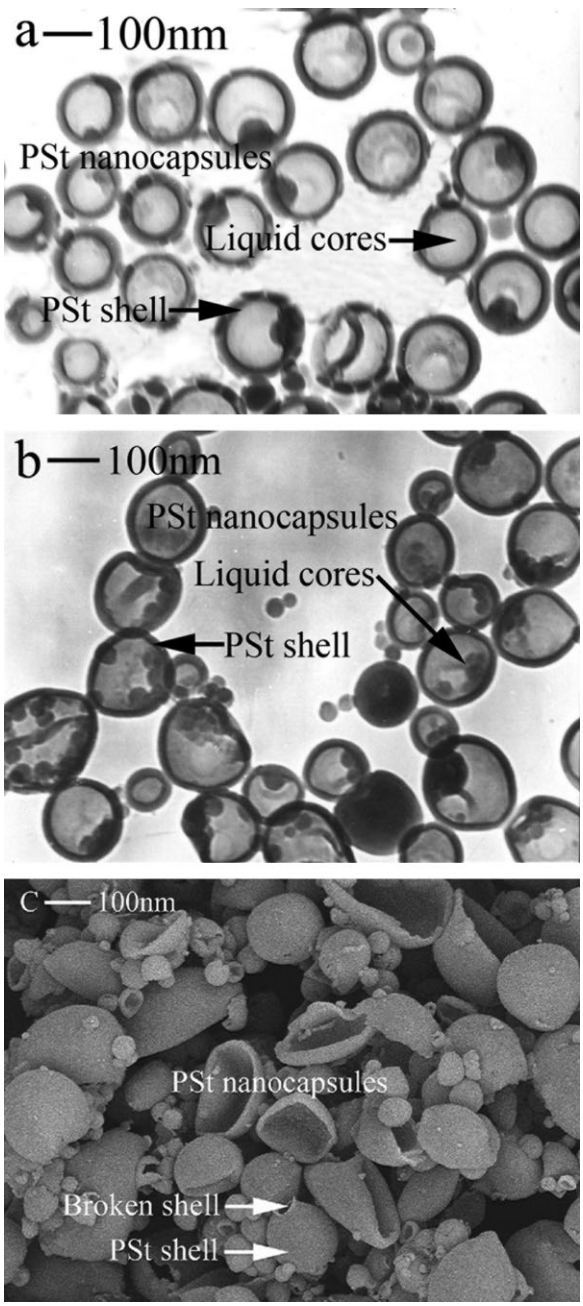


Figure 1 (a) TEM image of nanocapsule A, (b) TEM image of nanocapsule B, and (c) FESEM image of nanocapsule A.

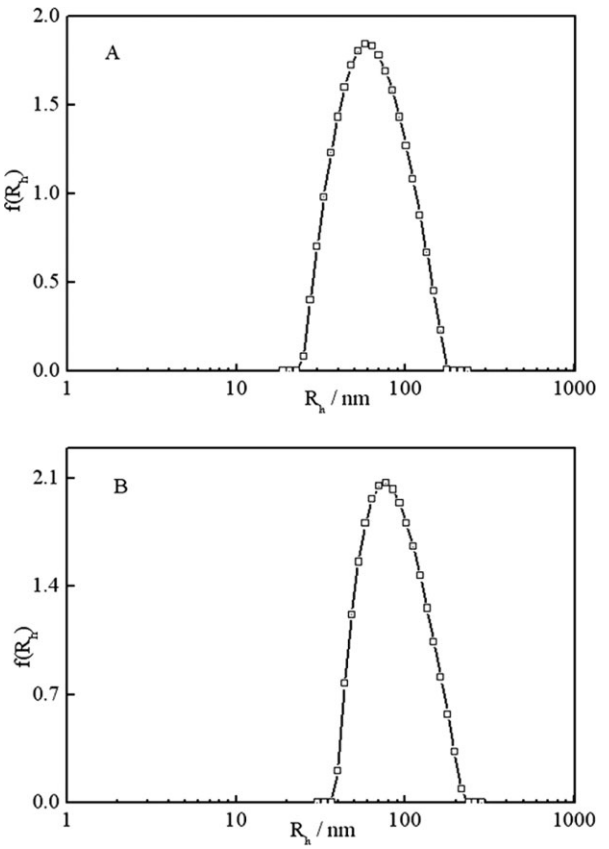


Figure 2 $f(R_h)$ of (A) nanocapsules A and (B) B in aqueous solutions (temperature = 25°C, angle = 90°; the nanocapsules were dispersed in distilled water).

for both nanocapsules A and B. These results suggest that the hollow structure of the PSt nanocapsules contained liquid cores.

Release of SS from the nanocapsules

One of the most important applications of hollow spheres is as drug carriers. PSt hollow microspheres have peerless advantage in being used as drug carriers because they are biologically inert. Herein, SS was chosen as a model drug because it was easily detected by UV–vis spectrophotometry. Figure 3 shows the release profiles of SS from the PSt hollow nanocapsules for various time intervals in deionized water at 40°C. Figure 3(A) shows the variation of the UV–vis spectrum of the withdrawn solution of nanocapsule A with sampling duration. Figure 3(B) summarizes the absorbance (wavelength = 295 nm) dependences of the SS released from both nanocapsules A and B on the release time. Figure 3(C) shows that the concentration of SS in the release medium as a function of time could be monitored by the calibration of the absorbance–concentration dependence with SS aqueous solutions with known concentrations. On the basis of the release characteristics from both nanocapsules A and B, SS in the nanocapsules could be released through a PSt shell in deionized water. The increase of the absorbance suggested an increase in the amount of SS released from the nanocapsules from 10 to 200 min. Furthermore, by comparison with the SS release characteristics from nanocapsules A and B, we concluded that the release of SS from the nanocapsules could be controlled by the thickness of the PSt shell.

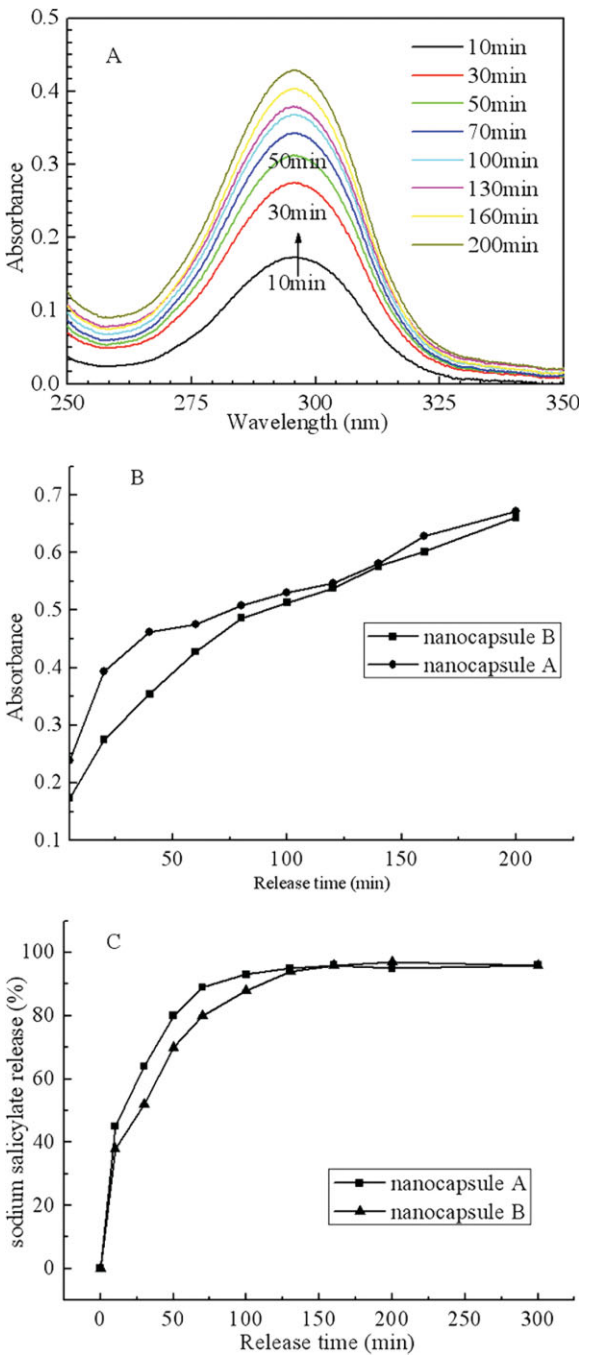
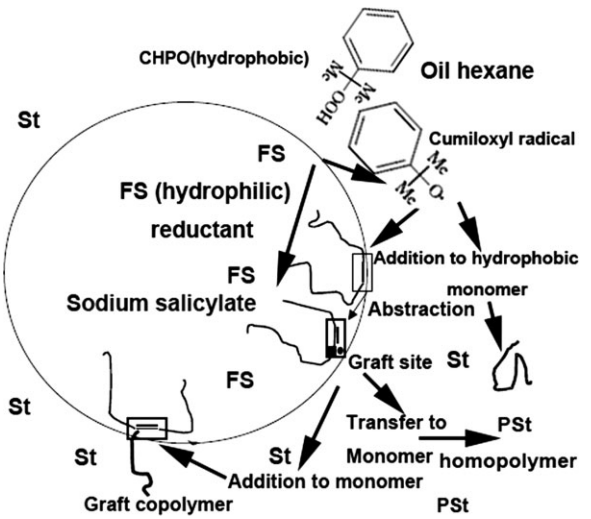


Figure 3 (A) UV–vis diagrams of SS released from nanocapsule A, (B) absorbance dependence of SS released from nanocapsules A and B on time, and (C) release profiles of SS from PSt hollow microspheres at 40°C. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]



Scheme 1 Schematic preparation of the PSt nanocapsules containing liquid-core microspheres through interface-initiated polymerization.

Mechanism for the formation of the PSt nanocapsules containing SS (Scheme 1)

PSt nanocapsules containing liquid cores were prepared through a one-stage redox interface-initiated polymerization in an inversed emulsion, and the probable mechanism is suggested as follows. In this polymerization initiated by the redox couple, the oil-soluble oxidant component CHPO stayed in the continuous phase of the inversed emulsion, whereas the reductive water-soluble component FS existed in the dispersed phase. Primary radicals were produced mainly at the oil–water interface, where both of them were encountered. The primary radicals initiated the polymerization of St near the interface to form PSt propagating chains. PSt propagating chains might have been anchored to the surfactant monolayer or escaped to the media bulk. In our case, the anchoring could have been caused by the interaction between the chains and the octyl group of octylphenyl poly(ethylene glycol) ether. The anchoring of the PSt chains would have formed PSt-enriched loops at the oil–water interface and absorbed the coming monomer. Propagating radicals seldom had the chance to escape from the interface to initiate the monomers in the oil media. At the same time, DVB as a crosslinking agent made the polymer chains act as a network. In this way, PSt nanocapsules acted with PSt as the shell and SS as the core.

CONCLUSIONS

We successfully prepared PSt nanocapsules containing an aqueous solution of SS through a one-stage interface-initiated inversed microemulsion polymerization. This interface-initiated polymerization provided an efficient, one-step route for the synthesis of polymer nanocapsules containing liquid cores. The size and shell thickness of the nanocapsules could be controlled by the amount of monomer. The formation feature of primary radicals and the anchoring effect of PSt chains to the interface were suggested to be the reasons for the formation of the nanocapsules with the water-soluble solute cores. A study of the release of SS with the model disclosed that the drug release from the obtained nanocapsules could be controlled by the thickness of the polymer shell.

The authors thank the Central Laboratory of Analysis and Structure Research at the University of Science and Technology of China. They also thank Zhicheng Zhang of the Department of Polymer Science and Engineering at the University of Science and Technology of China.

References

1. Bae, K. H.; Lee, Y. H.; Park, T. G. Biomacromolecules 2007, 8, 650.
2. Dan, P.; Jeffrey, M. K.; Omid, C. F.; Robert, L. Nat Nanotechnol 2007, 2, 751.
3. Yu, C. Y.; Jia, L. H.; Yin, B. C.; Zhuo, R. X. J Phys Chem C 2008, 112, 16774.
4. Zhang, X. G.; Teng, D. Y.; Wu, Z. M.; Wang, X.; Wang, Z.; Yu, D. M.; Li, C. X. J Mater Sci: Mater Med 2008, 19, 3525.
5. Constantinos, M. P.; Dimitris, T.; Zili, S. Mol Pharm 2007, 4, 169.
6. Sean, M. H.; Rachel, R. G.; Jeffrey, M. D. Pharm Res 2007, 24, 2353.
7. Nwekome, G. R.; Shreiner, C. D. Polymer 2008, 49, 1.
8. Franck, G.; Zydowicz, N. S. Colloids Surf A 2008, 331, 133.
9. Xing, F. B.; Cheng, G. X.; Yi, K. J.; Ma, L. R. J Appl Polym Sci 2005, 96, 2225.
10. Carr, R.; Weinstock, I. A.; Aksimentiev, A. Nano Lett 2008, 8, 3916.
11. Kenji, K.; Takahiro, F.; Toru, T.; Shinichi, S.; Chie, K. Polymer 2008, 49, 2832.
12. Mehrdad, H.; Amir, A.; Pedram, R. Adv Drug Delivery Rev 2008, 60, 1638.
13. Zhang, Y.; Yin, L. C.; Qian, F.; Tang, C.; Yin, C. H. Eur Polym J 2008, 44, 1654.
14. Wang, W. S.; Zhen, L.; Xu, C. Y.; Shao, W. Z. J Phys Chem C 2008, 112, 14360.
15. Wan, A. J.; Kou, Y. X. J Nanopart Res 2008, 10, 437.
16. Oh, J. K.; Drumright, R.; Matyjaszewski, K. Prog Polym Sci 2008, 33, 448.
17. Daniel, C.; Michael, S.; Carola, H. R. Macromolecules 2007, 40, 3122.
18. Zeaiter, J.; Romagnoli, J. A.; Barton, G. W.; Gomes, V. G.; Hawkett, B. S.; Gilbert, R. G. Chem Eng Sci 2002, 57, 2955.
19. Essawy, H. A. Colloid Polym Sci 2008, 286, 795.
20. Chiu, T. P.; Don, T. M. J Appl Polym Sci 2008, 109, 3622.
21. Lamb, D. J.; Morrison, B. R.; Gilbert, R. G. Polymer 2005, 46, 285.
22. Liu, W. J.; Zheng, R.; He, Z. C. Polym Bull 2008, 61, 27.
23. He, W. D.; Zheng, C.; Ge, X. W.; Liu, H. R. J Solid State Chem 2006, 179, 1240.
24. Scheerer, P.; Borchery, A.; Krauss, N.; Wessner, H.; Gerth, C.; Kuhn, H. Biochemistry 2007, 46, 9041.
25. Rodríguez, R.; Barandiaran, M. J.; Asua, J. M. Macromolecules 2007, 40, 5735.
26. He, W. D.; Wang, Y. M.; Zhang, Z. C. Polym Int 2006, 55, 520.
27. Gan, Q.; Wang, T. Colloids Surf B 2007, 59, 24.