Thermosensitive Phase Transition Kinetics of Poly(*N*-isopropylacryl amide-*co*-acrylamide) Microgel Aqueous Dispersions

Qin Wang,[1] Yanbing Zhao,[2] Huibi Xu,[1] Xiangliang Yang,[2] Yajiang Yang[1]

[1]*School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, Wuhan 430074, China*
[2]*College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan 430074, China*

Received 23 August 2008; accepted 1 November 2008
DOI 10.1002/app.29642
Published online 19 March 2009 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Thermosensitive poly(*N*-isopropylacrylamide-*co*-acrylamide) microgel particles were prepared through precipitation polymerization. The diameters of the microgel particles were in the range of 220–270 nm and showed a monodispersion. The lower critical solution temperatures (LCST) of the microgel dispersions were measured by dynamic light scattering and turbidimetric analysis. The results indicated that the LCST increased with an increase of acrylamide (AAm) content in the copolymer composition. The kinetics of the thermosensitive phase transitions of the microgel particles were investigated by time-course UV–vis spectroscopy. The results indicated that the higher the content of AAm in copolymer composition, the more time is required for equilibrium deswelling and the less time required for equilibrium swelling. In addition, the time required for equilibrium deswelling decreased with an increase of the content of the microgel particles in dispersions. By contrast, the time required for equilibrium swelling increased slightly. Thus, a suitable LCST and time required for equilibrium of phase transition can be achieved by adjusting the molar ratio of the comonomers in the microgels and the content of the microgel particles in dispersions. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 113: 321–326, 2009

Key words: kinetics; thermosensitive; microgel dispersion; phase transition

INTRODUCTION

Microgel particles are crosslinked polymer gels and well dispersed in aqueous media, which possess an average diameter in the range of 1–1000 nm (also called as nanogels in literature).[1,2] Thermosensitive microgel particles have the property of a temperature-dependent swelling or shrinking behavior and undergo a significant phase transition near a certain temperature usually called the lower critical solution temperature (LCST).[3] Poly(*N*-isopropylacrylamide) (PNIPAAm) microgel particles have been recently received great attention, because the LCST of PNIPAAm microgel particles in water is close to the temperature of human body and can be easily manipulated by changing the contents of hydrophilic or hydrophobic comonomers.[3–5] Thermosensitive microgel particles show a tremendous potential application in biomedical fields, such as drug delivery,[5–7] chemical sensors,[8] medical diagnostics,[9] etc.

In comparison with conventional bulk thermosensitive hydrogels, a prominent characteristic of thermosensitive microgel particles is that microgel particles respond faster to a change of the surrounding temperature because of their small sizes.[10] An important question is how to modulate the LCST being close to the human body temperature and the kinetics of the phase transition of thermosensitive microgel particles to satisfy various requirements in biomedical application. However, the sizes of microgel particles are too small to examine their swelling or deswelling kinetics by directly measuring volumes or weights as usually done for conventional thermosensitive hydrogels.[11,12] Therefore, an indirect method for a kinetic investigation is to measure the breadths of thermal effect peaks by using a differential scanning calorimeter (DSC) under conditions that the phase transition of microgel particles occurs.[13] Alternatively, another method is to measure the gradient of diameter versus temperature curves by static and dynamic laser light scattering.[14] It is often hard to obtain the time-relative phase transition kinetics by these measurements.

In this work, thermosensitive poly(*N*-isopropylacrylamide-*co*-acrylamide) microgel particles (designated

The authors thank the Analytic and Testing Center of HUST for the measurements of TEM.

Correspondence to: Y. Yang (yjyang@mail.hust.edu.cn).

Contract grant sponsor: National Key Fundamental Research Development Plan of China; contract grant number: 2006CB705606.

TABLE I
Feed Composition and Size Characteristics of PNIA Microgels

Sample	Feed composition (g)				Diameter (nm, 20°C)	Diameter (nm, 50°C)	PDI (20°C)
	NIPAAm	AAm	MBAAm	SDS			
M-0	2.26	0	0.03	0.03	226	86	0.016
M-5	2.15	0.07			236	89	0.018
M-10	2.04	0.14			261	90	0.015
M-15	1.92	0.21			268	108	0.054

as PNIA microgel particles) were prepared by free radical copolymerization, in which, acrylamide (AAm) was used as a hydrophilic comonomer to modulate the LCST of the microgel aqueous dispersions. Time-course UV–vis spectroscopy was employed to investigate the phase transition kinetics of the microgel aqueous dispersions. This investigation could be significant for the application of thermosensitive microgel particles as drug delivery systems.

EXPERIMENTAL

Materials

N-Isopropylacrylamide (NIPAAm, Across, Geel, Belgium) and *N*,*N*′-methylenebisacrylamide (MBAAm, Tianjin Kermel, China) as a crosslinker were recrystallized from *n*-hexane and methanol, respectively. Sodium dodecyl sulfate (SDS) and other reagents were of analytic grade and used as received. Milli-Q ultrapure water was used throughout all experiments.

Preparation of PNIA microgel particles

PNIA microgel particles with varied monomer compositions were prepared using the precipitation polymerization method described elsewhere.[15] Feed composition for polymerization is shown in Table I. Briefly, desired quantities of the monomers and surfactant were dissolved in 161 mL of water in a 250-mL three-necked round-bottomed flask equipped with a condenser and a gas inlet under continuous magnetic stirring. The aqueous solution was purged with nitrogen for about 30 min and then heated to 70°C. Potassium persulfate (0.09 g) was added to initiate polymerization. The polymerization was performed under a nitrogen atmosphere for 4.5 h at 70°C. The resultant PNIA microgel dispersion was further dialyzed against ultrapure water for 2 weeks to remove possible unreacted monomers and surfactant. A small amount of dialyzed dispersion was taken for size analysis. The microgel dispersion was subsequently lyophilized to collect xerogel for further measurements. In the preparation of microgel particles, the molar ratio of NIPAAm and AAm was 100 : 0, 95 : 5, 90 : 10, and 85 : 15, respectively (the samples were designated as M–0, M–5, M–10, and M–15).

Dynamic light scattering

The hydrodynamic diameters of microgel particles were measured at various temperatures ranging from 20 to 50°C by dynamic light scattering (DLS) (Nano-ZS 90, Malvern, Worcestershire, UK) equipped with a He-Ne laser ($\lambda = 633$ nm). All the samples were diluted with water and maintained at a designed temperature for 5 min before testing. The deswelling ratio (α) of the microgel particles is defined as follows:[16]

$$\alpha = V_T/V_{\text{swollen}} = (D_T/D_{\text{swollen}})^3 = (D_T/D_{20})^3 \quad (1)$$

Herein, V_T and V_{swollen} are the volumes of microgel particles at a certain temperature and at a swollen state, respectively. D_T and D_{20} are the average diameters of the microgel particles at T and 20°C, respectively.

Turbidimetric analysis

The transmittances of the microgel aqueous dispersions, depending on the temperature, were determined at 500 nm by using a UV–vis spectrophotometer (Spectra Max Plus, Molecular Devices, USA). The temperature was in the range of 20–45°C and kept at a designed temperature during 5 min before testing.

Transmission electron microscopy

The morphologies of the microgel particles were investigated by transmission electron microscopy (TEM, Tecnai G2 20, FEI, Netherlands). A drop of the microgel aqueous dispersions was spread onto the surface of a 400-mesh copper grid and allowed to dry for 24 h at 12 and 37°C, respectively. The samples were stained with 1% of phosphormolybdic acid aqueous solution. The accelerating voltage was 200 kV.

Time-course UV–vis spectroscopy

The swelling/deswelling kinetics of the microgel particles was investigated by measuring the

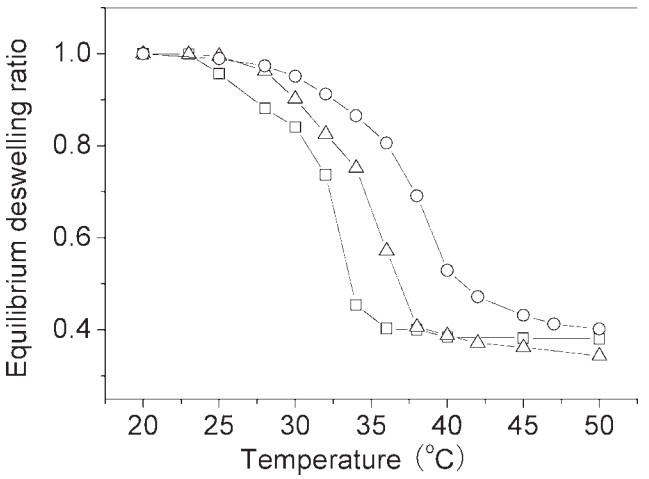


Figure 1 Influence of temperature on the equilibrium deswelling ratio of microgel dispersions; □: M-0; Δ: M-10; ○: M-15. The concentration of the microgel particles in the aqueous media was 1 mg/mL.

transmittance ($\lambda = 500$ nm) with variable time on an UV–vis spectrophotometer (UV-2550, Shimadzu, Japan) employing a recycling thermobath (TB-85, Shimadzu) to maintain the test temperature constant. The machine was set at a kinetic mode. Briefly, the microgel dispersion (3 mL) was placed in a quartz cuvette of 1-cm path length and kept for 5 min at a desired temperature, which was slightly higher than the LCST. The spectrum was recorded and provided the deswelling kinetics of the microgel particles. The swelling kinetics was obtained by reversing the temperature procedure. The measured time was 300 s for the swelling/deswelling cycle.

RESULTS AND DISCUSSION

Characterization of the PNIA microgel particles

The feed composition for polymerization of PNIA microgel particles, average hydrodynamic diameter, and polydispersity index (PDI) of the size distribution of the obtained PNIA microgel particles measured by DLS are listed in Table I. The sizes of the PNIA microgel particles are in the range of 220–270 nm, and the distributions are nearly monodisperse at 20°C.

Figure 1 shows the equilibrium deswelling ratios of the microgel particles at various temperatures. The equilibrium deswelling ratios of the microgel particles with different contents of AAm decreased slightly with an increase of the temperature, but an abrupt change occurred in a narrow range of temperature. The temperature responding to the turning point of the curve is usually defined as the LCST. Figure 1 shows that the LCST of the microgel particles dispersion can be tuned between 32 and 38°C

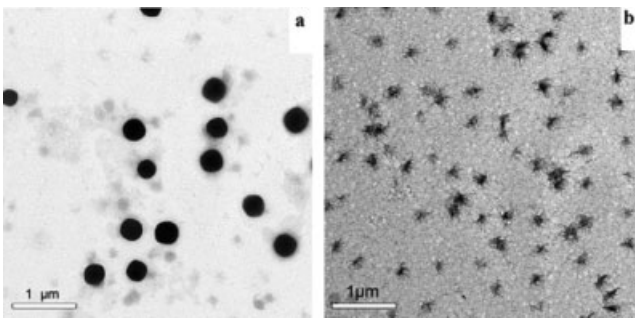


Figure 2 TEM images of M-5 microgel particles dispersed in aqueous media at (a) 12°C and (b) 37°C.

by changing the content of AAm. When the contents of AAm were in the range of 0–15 mol % in PNIA, the corresponding LCST of the samples M–0, M–5, M–10, and M–15 is 32, 34 (shown in Fig. 3), 36, and 38°C, respectively. Furthermore, when the content of AAm was increased, the range of temperatures required to achieve deswelling equilibrium became broad, implying that the thermosensitivity of the PNIA microgel particles decreased.

The deswelling behavior of the microgel particles with an increase of temperature was further investigated by TEM. Figure 2 shows the morphologies of the M–5 microgel dispersions at 12 and 37°C. Obviously, the microgel particles are typical spherite with approximate diameters of 270 nm at 12°C, but the microgel particles collapse into irregular shapes with approximate diameters of 170 nm at 37°C, probably due to the heterogeneous structures of thermosensitive microgel particles. In general, the swelling phenomenon of microgel particles below the LCST is caused by the formation of hydrogen

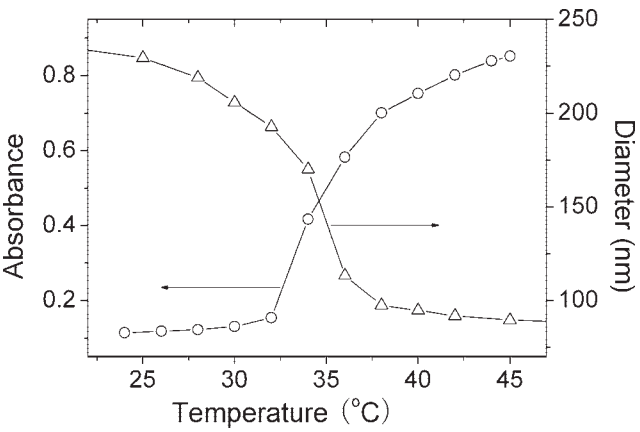
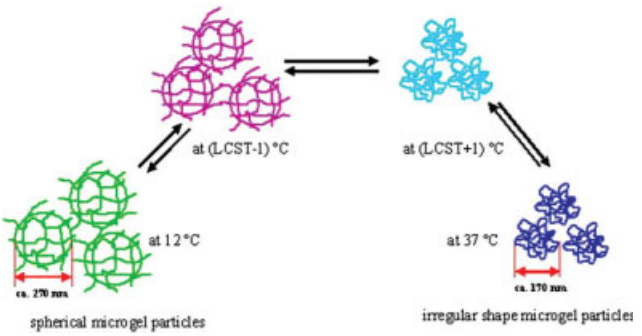


Figure 3 Absorbance and hydrodynamic diameters of M–5 microgel particles dispersed in water as a function of temperature. ○, absorbance (microgel particles concentration 13 mg/mL); Δ, diameter (microgel particles concentration 1 mg/mL).



Scheme 1 Schematic illustration of swelling/deswelling of PNIA microgel particles at the temperature between 12 and 37°C. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

bonds between water, amide, and carbonyls of acylamide groups.[16] The deswelling phenomenon of microgel particles above the LCST is mainly due to the disruption of the hydrogen bonds. Herein, intra/intermolecular chains hydrogen bonding and hydrophobic interactions between isopropyl groups play a dominant role. The process of swelling/deswelling of the PNIA microgel particles is schematically shown in Scheme 1.

The thermosensitive properties of the PNIA microgel particles can also be characterized by turbidimetric analysis.[17] Figure 3 shows the absorbance and hydrodynamic diameters of M–5 microgel dispersions as a function of temperature. The results indicate that the absorbance of the microgel dispersions increases, whereas the hydrodynamic diameters decrease with an increase of temperature. The temperatures responding to the crosspoint of both curves can also be considered as the LCST. When the temperature is below the LCST, the microgel particles are in swollen state with larger diameters. In this case, the difference in refractive index between the microgel–water macrocomplex and bulk water is small, resulting in low turbidity. When the temperature is higher than the LCST, the microgel particles are in deswollen state with smaller diameters. In this case, the water is expelled from the gel network, resulting in a high turbidity. Interestingly, the both curves of turbidity and diameter are almost symmetric as shown in Figure 3, suggesting that the turbidity of microgel dispersion reflects indirectly the change of the sizes of the microgel particles and the phase transition induced by varying the temperature. In addition, similar results were obtained for the sample M–0, M–10, and M–15 (not shown in Fig. 3), i.e., the LCST of PNIA microgel particles increases with an increase of the AAm content. This result is consistent with the results of DLS analysis.

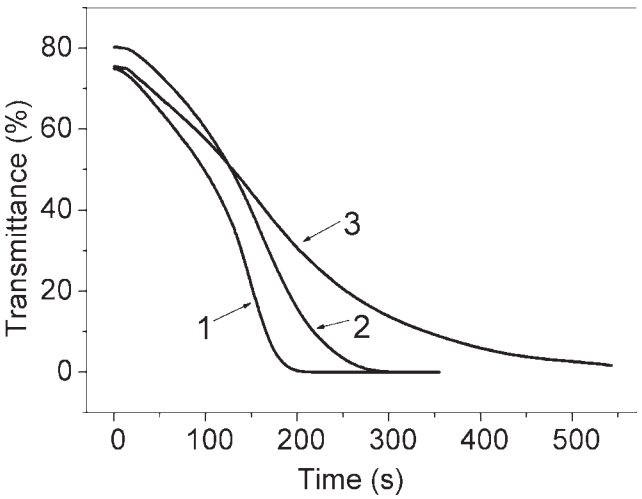


Figure 4 Deswelling kinetics of PNIA microgel dispersions (concentration of microgel particles 13 mg/mL) at (LCST + 1)°C. 1: M–0; 2: M–10; 3: M–15.

Thermosensitive phase transition kinetics of PNIA microgel particles dispersions

The time-course UV–vis spectroscopy is usually employed to study the kinetics of enzyme reactions[18] and the phase transition kinetics of conventional thermosensitive copolymers based on *N*-isopropylacrylamide.[19,20]

Figure 4 shows the transmittances of M–0, M–10, and M–15 microgel dispersions as a function of time. The measurements were carried out at (LCST + 1)°C after the samples were equilibrated for 5 min at 20°C. As mentioned earlier, the turbidity of microgel dispersions reveals deswelling behavior of microgel particles. Herein, the transmittances of

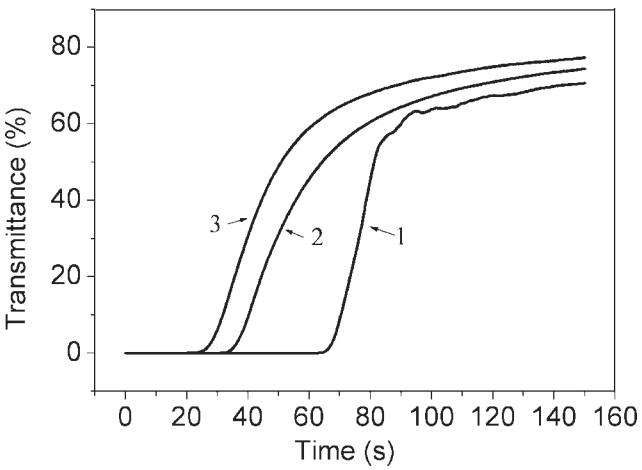


Figure 5 Swelling kinetics of PNIA microgel dispersions (microgel particles concentration 13 mg/mL). The testing temperature range was from 42 to 12°C. 1: M–0; 2: M–10; 3: M–15.

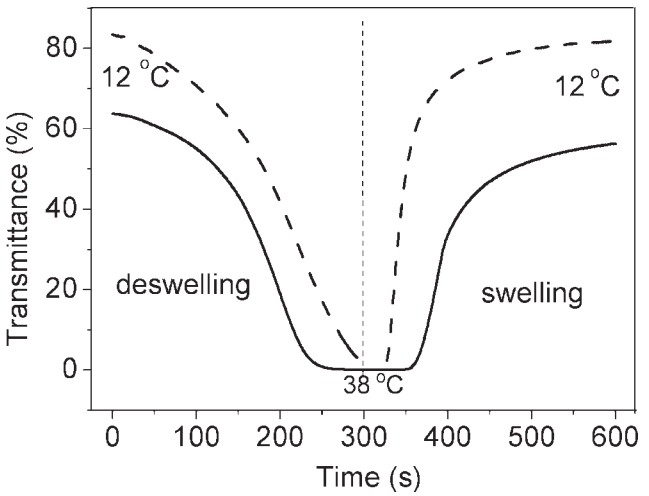


Figure 6 Influence of concentration of microgel M–10 dispersions on the deswelling kinetics at the temperature ranging from 12 to 38°C and swelling kinetics at the temperature ranging from 38 to 12°C; Solid: 77 mg/mL; dash: 13 mg/mL.

three samples decreased rapidly with an increase of time until the deswelling equilibrium was reached, i.e., an invariable turbidity means microgel particles have reached deswelling equilibrium. The time required for equilibrium deswelling was about 200, 290, and 480 s, respectively. In other words, the higher the content of AAm in the microgel, the more time is required for the equilibrium deswelling. This may be ascribed to the hydrophilicity of AAm. The increase of polymer hydrophilicity leads to the enhancement of interaction between water and hydrophilic groups in the polymer. Thus, the diffusion of water from the microgel–water macrocomplex is more difficult at the testing temperature. The result is in accord with that for the conventional bulk hydrogels.[12]

However, when the measurements were carried out at 12°C after the samples were equilibrated for 5 min at 42°C, the swelling kinetics of the microgel particles were obtained as shown in Figure 5. The times required for equilibrium swelling of M–0, M–10, and M–15 were about 90, 70, and 50 s, respectively. Apparently, it is attributed that the hydrophobicity of NIPAAm is stronger than that of AAm. The more the hydrophobic NIPAAm in the microgel particles, the lower is the LCST of microgel particles, and longer is the time required for equilibrium swelling.

Figure 6 shows the effect of microgel particle concentrations (solid content) on the swelling/deswelling kinetics of M–10 dispersions. The deswelling and swelling process were characterized by transmittance measurement at the temperature ranging from 12 to 38°C and from 38 to 12°C, respectively. The results indicated that the time required for equilibrium deswelling was about 240 s for the sample with high solid content (77 mg/mL) and about 300 s for the sample with low solid content (13 mg/mL). However, the swelling rate of microgel particles in a low solid content system was quicker than that in a high solid content system. A possible explanation involves the gelation of high solid content system when the temperature increased, resulting in the decrease of transmittance of system.[21] When the temperature decreased, the sample with low solid content rapidly swelled because of the low content of hydrophobic groups in the system. In addition, the curves of swelling/deswelling are almost symmetric, suggesting that the phase transition of the microgel dispersions is reversible.

CONCLUSION

A series of thermosensitive poly(*N*-isopropylacrylamide-*co*-acrylamide) microgel particles was prepared by free radical copolymerization. The LCSTs and deswelling/swelling kinetics of the microgel particles were investigated by dynamic light scattering and turbidimetric analysis. The LCSTs of the microgel particles can be tuned up by changing the amount of AAm in the copolymer composition. The kinetics of the thermosensitive phase transitions of the microgel dispersions depend on the AAm content as well as the microgel particles content in the dispersions. The time required for equilibrium deswelling increased and the time required for equilibrium swelling decreased with an increase of the AAm content in the copolymers. The time required for equilibrium deswelling decreased and the time required for equilibrium swelling increased with an increase of the microgel particle content of the dispersions.

References

1. Ogawa, K.; Nakayama, A.; Kokufuta, E. Langmuir 2003, 19, 3178.
2. Baker, W. O. Ind Eng Chem 1949, 41, 511.
3. Pelton, R. H. Adv Colloid Interface Sci 2000, 85, 1.
4. Kuckling, D.; Vo, C. D.; Adler, H. J. P.; Volkel, A.; Colfen, H. Macromolecules 2006, 39, 1585.
5. Vinogradov, S. V.; Bronich, T. K.; Kabanov, A. V. Adv Drug Delivery Rev 2002, 54, 135.
6. Sahiner, N.; Alb, A. M.; Graves, R.; Mandal, T.; McPherson, G.; Reed, W.; John, V. T. Polymer 2007, 48, 704.
7. Lopez, V. C.; Hadgraft, J.; Snowden, M. J. Int J Pharm 2005, 92, 137.
8. Holtz, J. H.; Holtz, J. S. W.; Munro, C. H.; Sanford, A. A. Anal Chem 1998, 70, 780.
9. Pichot, C.; Taniguchi, T.; Delair, T.; Elaïssari, A. J Dispersion Sci Technol 2003, 24, 423.
10. Tanaka, T.; Fillmore, D. J. J Chem Phys 1979, 70, 1214.

11. Bromberg, L.; Temchenko, M.; Hatton, T. A. Langmuir 2002, 18, 4944.
12. Yildiz, B.; Isik, B.; Kis, M. Eur Polym J 2002, 38, 1343.
13. Gan, D. J.; Lyon, L. A. J Am Chem Soc 2001, 123, 7511.
14. Wu, C.; Zhou, S. Q.; Au-yeung, S. C. F.; Jiang, S. H. Die Angew Makromol Chem 1996, 240, 123.
15. Pelton, R. H.; Chibante, P. Colloids Surf 1986, 20, 247.
16. Saunders, B. R.; Crowther, H. M.; Morris, G. E.; Mears, S. J.; Cosgrove, T.; Vincent, B. Colloids Surf A: Physicochem Eng Aspects 1999, 149, 57.
17. Woodward, N. C.; Chowdhry, B. Z.; Snowden, M. J.; Leharne, S. A.; Griffiths, P. C.; Winnington, A. L. Langmuir 2003, 19, 3202.
18. Toti, P.; Petri, A.; Gambicorti, G.; Gambicorti, T.; Osman, A. M.; Bauer, C. Biophys Chem 2005, 113, 105.
19. Liu, X. M.; Wang, L. S.; Wang, L.; Huang, J. C.; He, C. B. Biomaterials 2004, 25, 5659.
20. Bradley, M.; Ramos, J.; Vincent, B. Langmuir 2005, 21, 1209.
21. Wang, Q.; Zhao, Y.; Yang, Y.; Xu, H.; Yang, X. Colloid Polym Sci 2007, 285, 515.