A New Strategy for Controlled Drug Release: Synthesis of an Amphiphilic Hydrogel with IPN Structure

Hossein Hosseinzadeh

Department of Chemistry, Payame Noor University, 19395-4697, Tehran, Iran.

The present work focused on the design of drug delivery system (DDS) based on a pH-sensitive amphiphilic hydrogel with interpenetrating polymer networks (IPN) structure. The IPN was constructed with hydrophilic poly(acrylic acid) (PAA) and hydrophobic poly(styrene) (PST) by a free radical polymerization technique. It is found that the presence of hydrophobic network can overcome disadvantageous burst effect of hydrophilic network. This may be a result of hydrophobic aggregation encapsulating ephedrine molecules. The hydrogel prepared possessed a porous structure as determined by scanning electron microscopy. The water absorbency of hydrogels was measured in solutions with pH ranged 1 to 13. The starch-based hydrogel exhibited a pH-responsiveness character so that a swelling-deswelling pulsatile behavior was recorded at pHs 2 and 7. Using drug ephedrine as a model molecule, the *in vitro* controlled drug-release behaviors of these hydrogels were also investigated. These results suggest that a porous hydrogel could potentially be a useful local delivery system to release drugs primarily at a specific site of body.

Key words: Acrylic acid, Styrene, Hydrogel, Drug delivery, Ephedrine.

Recently, drug delivery systems based on natural hydrogels have been extensively explored to achieve the higher concentration of drugs in the specific region or tissue and the controlled release profile for extended time periods.[1-4]

Drug release from solid matrices systems, made of polymer(s) and drug(s), is a basic concept for studies on controlled drug delivery. The most interesting class of polymers in this application is given by hydrogels. Hydrogels are special soft and pliable polymeric materials that can absorb large quantities of water, saline or physiological solutions while the absorbed solutions are not removable even under pressure.[5] Stimuli-responsive smart hydrogels that can respond to environmental physical and chemical stimuli, such as temperature [6], pH,[7] light,[8] magnetic field,[9] and substance species,[10] have attracted great interests in recent years due to their versatile applications such as controlled drug and gene delivery systems,[11-15] chemical-/bio-separations,[16] and sensors and/or actuators.[17] Among those smart hydrogels, pH-responsive hydrogels have been extensively investigated for potential use in site-specific delivery of drugs to specific regions of the gastrointestinal tract and have been prepared for delivery of low molecular weight drugs.

Interpenetrating polymer networks (IPN) composed of hydrophilic and hydrophobic networks should possess amphiphilicity, and should be a family of amphiphilic polymers. This is because IPN is with physically interlocked structure of two polymer networks and there is no chemical

---

* To whom all correspondence should be addressed.
E-mail: h_hoseinzadeh@pnu.ac.ir

bonding between two networks.[18] This leads to the fact that each polymer network can retain its individual properties like its homopolymer; but at the same time, owing to physically interlocked interaction of two networks, if one component swells or shrinks, the other component can be enforced to cooperate by attractive and repulsive interactions of whole network.[19-21] Therefore, when an amphiphilic IPN was swollen, hydrophobic network can form hydrophobic aggregation. The hydrophobic aggregation not only can limit swelling degree of hydrophilic network, but also may encapsulate hydrophobic drug molecules.

In the current study we investigated the synthesis and utility of an amphiphilic hydrogel from polymerization of acrylic acid and styrene monomers, for the controlled release of a model drug, ephedrine. Drug absorption and release capacities of hydrogel systems and influence of pH of the medium, porosity and the crosslinker content on the release properties were also examined.

MATERIAL AND METHODS

Materials

Ammonium persulfate (Fluka, Buchs, Switzerland) was used without further purification. Acrylic acid (AA) and styrene (ST) (Merck, Darmstadt, Germany) was used after vacuum distillation. All other chemicals were also of analytical grade. Bidistilled water was used for the hydrogel preparation and swelling measurements. The drug, ephedrine, was obtained from Jaberebne Hayan Pharmaceutical Co. (Tehran, Iran). The chemical structure of ephedrine is shown in Fig. 1. The simulated gastric fluid (SGF, pH 1.2) composed of 21.25 mL HCl, 11.18 g KCl and 1000 mL distilled water and the simulated intestinal ûuid (SIF, phosphate buffer solutions, PBS, pH 7.4) composed of 3.6 g KH_2PO_4, 4.8 g Na_2HPO_4 and 1000 mL distilled water were prepared as described in *US Pharmacopoeia 30*.

Preparation of hydrogel

A general procedure for chemically crosslinking copolymerization of AA and ST was conducted as follows. PST and PAA were chosen as hydrophobic and hydrophilic networks, respectively. Firstly, 1.5 g of ST was added into 1.0 g of DMF. The polymerization was carried using

benzoyl peroxide for 10 min. The obtained PST gel was taken out from the bottle, and immersed in acetone to remove the unreacted monomer. The samples were kept in fresh acetone that was changed for every 5 h, and lasted 6 days. Late, it was dried under ambient conditions for 1 day and in a vacuum oven at 50°C for 2 days.

Then, the PST gel was swollen in AA solution of DMF. The polymerization was carried out using the thermally dissociating initiator, i.e. APS, in the presence of methylene bisacrylamide (MBA) as a crosslinker. The obtained PST/PAA gel was cut into thin disks of 10 mm in diameter, and immersed in distilled water to remove the unreacted AA. The samples were kept in fresh distilled water that was changed for every 5 h, and lasted 5 days. Late, they were dried under ambient conditions for 2 days and in a vacuum oven at 50 °C for 2 days. After grinding using mortar, the powdered superabsorbent was stored away from moisture, heat and light.

Swelling measurements

An accurately weighed sample of the powdered superabsorbent (0.2 ± 0.001 g) with average particle sizes between 40-60 mesh (250–350 μm) was immersed in distilled water (200 mL) and allowed to soak for 3 h at room temperature. The equilibrium swelling (ES) capacity was measured twice at room temperature according to a conventional tea bag method and using the following formula:

$$ES(g/g) = \frac{Weight\ of\ swollen\ gel - Weight\ of\ dried\ gel}{Weight\ of\ dried\ gel}$$

...(1)

Determination of drug loading

Hydrogel (0.10 g) was immersed in 10 mL of the phosphate buffer solution (pH 7.4) of ephedrine, 0.50 gram drug dissolved in 50 mL solution, in a 50 mL beaker for completely swelling at 37°C. The loaded swollen hydrogels were crushed in an agate mortar with a pestle and transferred into a conical flask, and then about 20 mL of the fresh phosphate buffer solution was added to the conical flask and the homogeneous mixture was sonicated for 20 min. The ephedrine solution was separated from the mixture after being centrifuged for 20 min at 5000 rpm. The amount of ephedrine entrapped was estimated by the

difference between the initial and the final amount of drug in gelling media. The drug loading (%) was calculated using the following equation:

$$Drug\ Loading\ (\%) = \frac{Weight\ of\ drug\ in\ hydrogel}{Weight\ of\ hydrogel} \times 100$$

...(2)

In vitro drug release

The dry samples (0.1±0.0001 g) were immersed into 50 mL of the release medium (simulated gastric and intestinal fluids, SGF and SIF) with different pH values (pH 1.2 or 7.4) at 37°C with agitation. At given time intervals, 1 mL of the release medium was removed using a syringe attached with a 0.45µm. Millipore filter and after suitable dilution the concentration of released drug was measured by UV spectrophotometer at 276 nm. The drug release percent was calculated twice using the following equation:

$$Re\ leased\ drug(\%) = \frac{R_t}{L} \times 100 \quad ...(3)$$

where L and R_t represent the initial amount of drug loaded and the final amount of drug released at time t.

FTIR analysis

Fourier transform infrared (**FTIR**) spectra of samples were taken in KBr pellets, using an ABB Bomem MB-100 FTIR spectrophotometer (Quebec, Canada), at room temperature.

Surface morphology

The surface morphology of the gel was examined using scanning electron microscopy (SEM). After Soxhlet extraction with methanol for 24 h and drying in an oven, superabsorbent powder was coated with a thin layer of gold and imaged in a SEM instrument (Leo, 1455 VP).

RESULT AND DISCUSSION

Morphology of hydrogel

A free radical polymerization was used to synthesize of an amphiphilic IPN sample under the above mentioned synthesis conditions. One of the most important properties that must be considered is hydrogel microstructure morphologies. Fig. 2. Shows the scanning electron microscope (SEM) photographs of the surface (Fig. 2A) and the cross-sectional area (Fig. 2B) of the hydrogel with interconnected pores. The hydrogel has a porous structure. It is supposed that these pores are the regions of water permeation and interaction sites of external stimuli with the hydrophilic groups of the graft copolymers. The cross-sectional view of hydrogels (Fig. 2B) also exhibited large, open, channel-like structure.

pH-Sensitivity and Pulsatile Behavior

Equilibrium swelling studies indicated that the ionic hydrogels were sensitive to environmental pH. Therefore, in this series of experiments, swelling ratio for the synthesized hydrogels was measured in different pH solutions ranged from 1.0 to 13.0 (Fig. 3). Since the swelling capacity of all "anionic" hydrogels is appreciably decreased by addition of counter ions (cations) to the swelling medium, no buffer solutions were used. Therefore, stock NaOH (pH 10.0) and HCl (1.0) solutions were diluted with distilled water to reach desired basic and acidic pHs, respectively. Maximum swelling (105 g/g) was obtained at pH 8. In acidic media, the most of carboxylate groups are protonated, so decreased repulsion of anionic groups leads to a decreased swelling ratio. With the increase in pH of medium after pKa of AA, carboxyl groups of AA convert to COONa groups with neutralization by NaOH in solution and then, they can ionize depending on pH of medium. The reason of the swelling-loss for the highly basic solutions is "charge screening effect" of excess Na^+ in the swelling media which shield the carboxylate anions and prevent effective anion-anion repulsion.

The PST/PAA hydrogels were also showed reproducible swelling-deswelling cycles at pH 2.0 and 8.0 as demonstrated in Figure 4. At pH 8.0, the hydrogel swells up to 67 g/g due to anion-anion repulsive electrostatic forces, while at pH 2.0, it shrinks within a few minutes due to protonation of carboxylate groups. This sharp swelling-deswelling behavior of the hydrogels makes them as suitable candidate for controlled drug delivery systems.
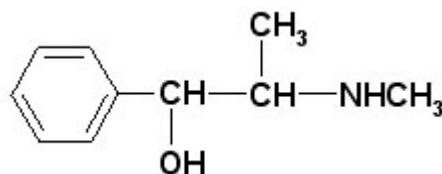
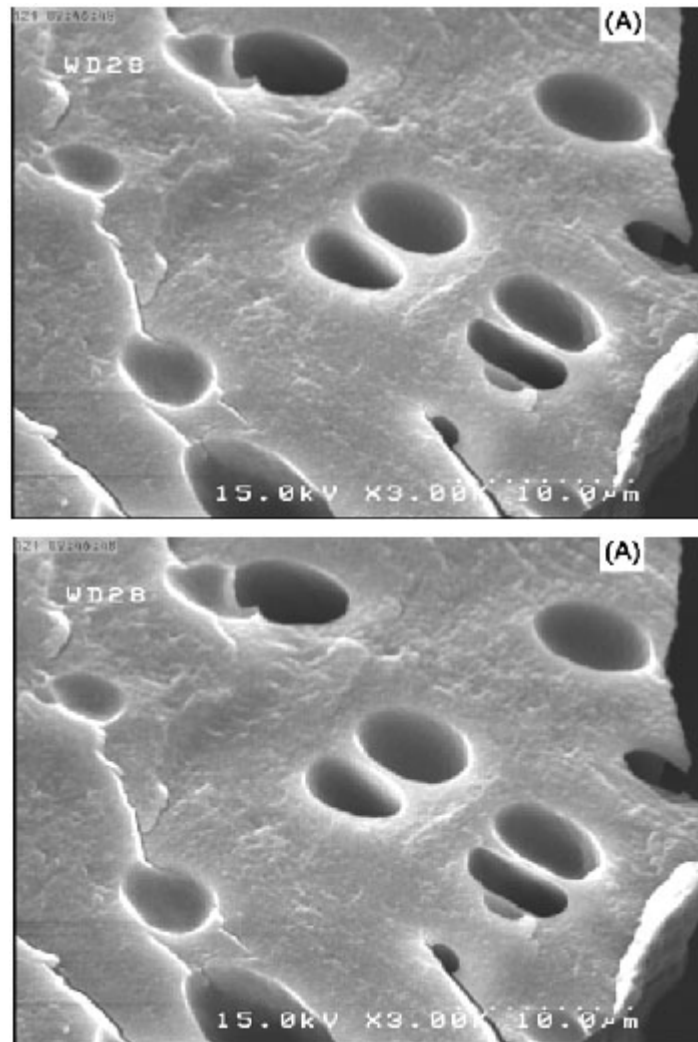

Fig. 1. Chemical structure of ephedrine

Fig. 2. SEM photograph of the hydrogel. (A) Surface of porous hydrogel;
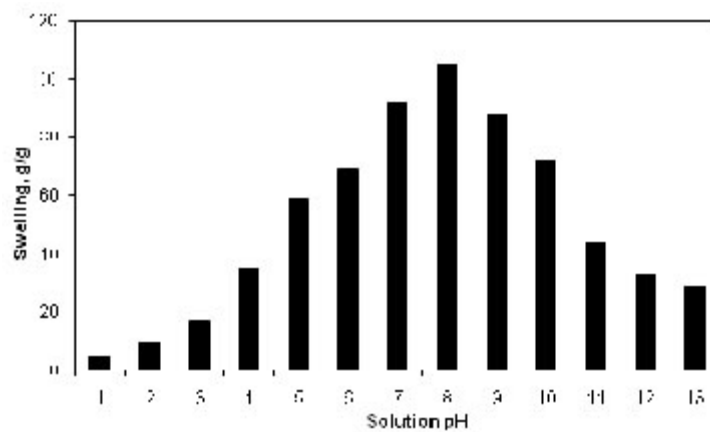(B) Cross-sectional area of porous hydrogel

Fig. 3. Effect of pH of solution on swelling of hydrogel

Drug loading efficiency

In this series of experiments, the drug loading of the hydrogels with different crosslinker content were shown in Fig. 5. As can be seen, the amount of drug loaded in the hydrogel beads decrease with increasing the content of crosslinker,

MBA. The increase in crosslink density decreases the swelling of hydrogel, and for that reason the amount of drug loaded into the hydrogel decreases.

Controlled ephedrine release

To determine the potential application of superabsorbent containing a pharmaceutically
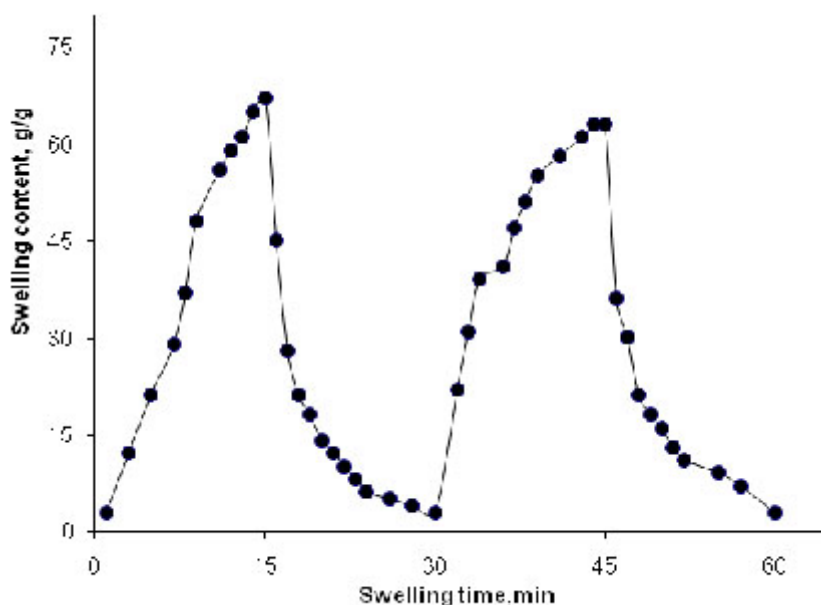

Fig. 4. On-off switching behavior as reversible pulsatile swelling (pH 8.0) and deswelling (pH 2.0) of the hydrogel
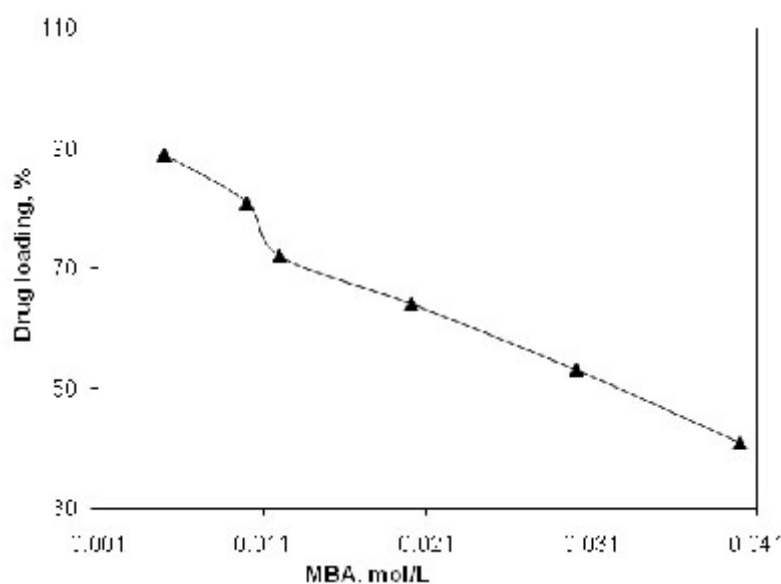

Fig. 5. Effect of crosslinker content on ephedrine release

active compound, we have investigated the drug release behavior form this system under physiological conditions. The percent of released drug from the polymeric carriers as a function of pH is shown in Fig. 6. The concentration of ephedrine released at selected time intervals was determined by UV spectrophotometer. The amount of ephedrine released in a specified time from the hydrogels decreased at pHs lower and higher than pH 8. At acidic pH values, electrostatic repulsion between the carboxylic acid groups of backbone is low, thus decreases gel swelling and minimizes release of ephedrine via diffusion. However, In alkaline media (pH>8), carboxylate groups of PAA can not ionize due to screening effect of counter ions (Na$^+$) in swelling medium, and for that reason the swelling of hydrogel decreases. As a consequence of decrease in the swelling of gel, drug release from the hydrogel decreases.

Fig. 7 shows the schematic of actuation at a distance and resultant squeezing effect for the pH-responsive system. Because of the high matrix
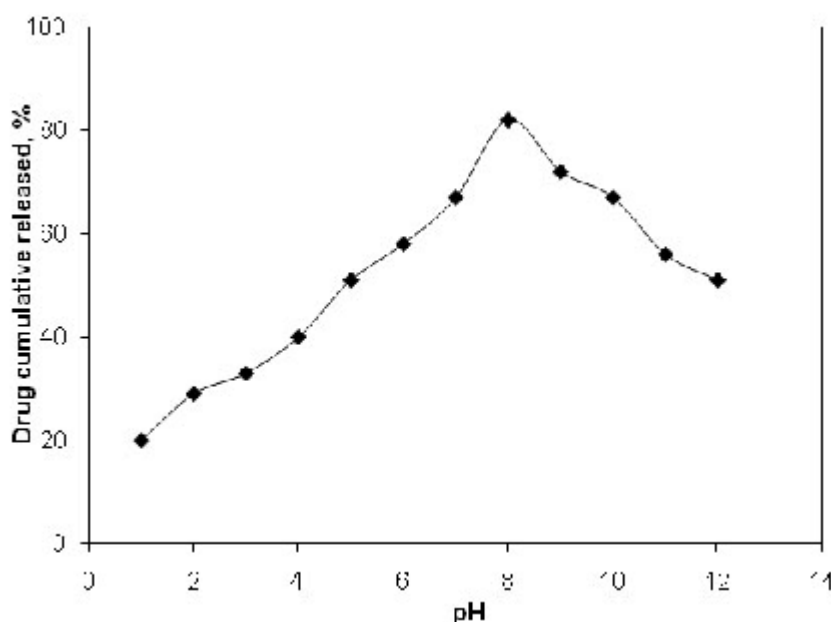

Fig. 6. Release of ephedrine from hydrogel carrier as a function of pH at 37 ºC.
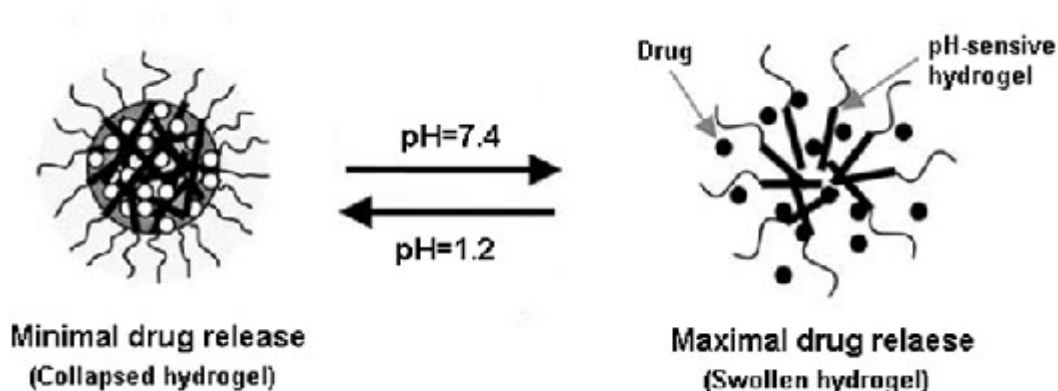

Fig. 7. Schematic showing the effect of ON–OFF cycles of pH on swelling behavior
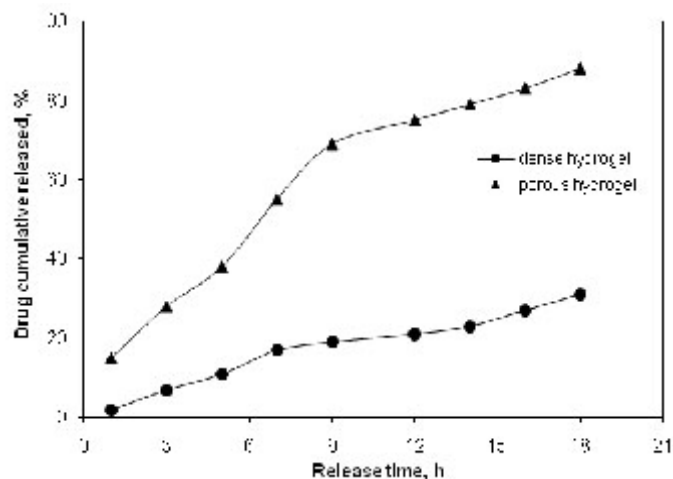
Fig. 8. Effects of porosity in the hydrogel on ephedrine release at pH 7.4 and 37 °C

porosity of the hydrogel, the capillary forces could reinforce the diffusion of solvent into the hydrogel; thereby the ephedrine release from the hydrogel matrix occurred mainly due to the diffusion of the drug though the pores of the swelled matrix in the intestinal pH.

Fig. 8 shows the effect of porosity of the hydrogel on ephedrine release. When compared to the dense hydrogel, the porous hydrogel provided a much faster ephedrine release. An initial burst release of 69 µg of ephedrine from the porous hydrogel was observed during the first 9 h of experiments, followed by a continuous release of 5-10 µg of ephedrine for up to 18 days. On the other hand, the hydrogel with dense structure showed a much lower initial burst ephedrine release, followed by a slower ephedrine release for up to 15 h. It should be pointed out that a dense structure would allow ephedrine release to occur primarily at the surface. In this regard, drug release is more dependent on the swelling kinetics of the hydrogel.

Although swelling degree of the hydrogels is a factor for ephedrine release, the presence of hydrophobic aggregation may be a dominant factor. In fact, the hydrophobic moieties may encapsulate ephedrine molecules.

CONCLUSION

A pH-responsive amphiphilic hydrogel with IPN structure for controlled ephedrine release

was proposed. The IPN was constructed with hydrophilic PAA and hydrophobic PST. It is found that not only the release of ephedrine from the IPN can respond to change in pH, but also the presence of hydrophobic network can overcome disadvantageous burst effect of hydrophilic network. This may be a result of hydrophobic aggregation encapsulating ephedrine molecules.

The superabsorbent hydrogels exhibited high sensitivity to pH, so that, several swelling changes of the hydrogel were observed in pH variations of a wide range[1-13].

Our results indicated that the porous hydrogel could potentially be used as a carrier for local and controlled delivery of drugs.

REFERENCES

1. Raghavendra, V.; Kulkarni, V.; Setty, S.M.; Sa, B. *Macromolecules*, **47**: 520–527 (2010).
2. Zhou, H. Y.; Zhang, Y. P.; Zhang, W. F.; Guang, X. *Carbohyd. Polym.* **83**: 1643-1651 (2011).
3. Hua, S.; Yang, H.; Wang, W.; Wang, A. *Appl. Clay Sci.* **50**: 112 –117 (2010).
4. Hori, K.; Sotozono, C.; Hamuro, J.; Yamasaki, K.; Kimura, Y.; Ozeki, M.; Tabata, Y.; Kinoshita, S. *J. Control. Rel.* **118**: 169-176 (2007).
5. Buchholz, F. L.; Graham, A. T. *Modern Superabsorbent Polymer Technology*. Elsevier: Amsterdam, (1997).
6. Chu, L.Y.; Kim, J.W.; Shah, R.K.; Weitz, D.A. *Adv. Funct. Mater.* **17**: 3499-3505 (2007).
7. Kim, S.J.; Spinks, G.M.; Prosser, S.; Whitten, P.G.; Wallace, G.G.; Kim, S.I. *Nat. Mater.* **5**: 48-

56 (2006).

8. Tatsuma, T.; Takada, K.; Miyazaki, T. *Adv. Mater.* **19**: 1249-1257 (2007).

9. Wang, W.; Liu, L.; Ju, X.J.; Zerrouki, D.; Xie, R.; Yang, L. *Chem. Phys. Chem.* **10**: 2405-2052 (2009).

10. Zhang, S.B.; Chu, L.Y.; Xu, D.; Zhang, J.; Ju, X.J.; Xie, R. *Polym. Adv. Technol.* **19**: 937-943 (2008).

11. Soppimath, K.S.; Aminabhavi, T.M.; Dave, A.M.; Kumbar, S.G.; Rudzinski, W.E. *Drug Dev. Ind. Pharm.* **28**: 957-964 (2002).

12. Chu, L.Y.; Yamaguchi, T.; Nakao, S. *Adv. Mater.* **14**: 386-391 (2002).

13. Thornton, P.D.; Mart, R.J.; Ulijn, R.V. *Adv. Mater.* **19**: 1252-1258 (2007).

14. Hamidi, M.; Azadi, A.; Raûei, P. *Adv. Drug Deliv. Rev.* **60**: 1638-1644 (2008).

15. Cheng, H.; Zhu, J.L.; Sun, Y.X.; Cheng, S.X.; Zhang, X.Z.; Zhuo, R.X. *Bioconjug. Chem.* **19**: 1368-1372 (2008).

16. Yang, M.; Chu, L.Y.; Wang, H.D.; Xie, R.; Song, H.; Niu, C.H. *Adv. Funct. Mater.* **18**: 652-658 (2008).

17. Eddington, D.T.; Beebe, D.J. *Adv. Drug Deliv. Rev.* **56**: 199-204 (2004).

18. Liu, Y.Y.; Fan, X.D.; Zhao, Q. *J. Macrom. Sci. Pure Appl. Chem.* **A40**: 1095–1105 (2003).

19. Zhang, J.; Peppas, N.A. *Macromolecules.* **33**: 102–107 (2000).

20. Zhang, X.Z.; Wu, D.Q.; Chu, C.C. *Biomaterials.* **25**: 3793–3805 (2004).

21. Lim, Y.H.; Kim, D.; Lee, D.S. *J. Appl. Polym. Sci.* **64**: 2647–2655 (1997).