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Drug release behaviors of a pH sensitive semi-interpenetrating polymer network hydrogel composed of poly(vinyl alcohol) and star poly[2-(dimethylamino)ethyl methacrylate]

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ABSTRACT

A series of pH sensitive semi-interpenetrating polymer network (semi-IPN) structural hydrogels composed of poly(vinyl alcohol) (PVA) and 21-arm star poly[2-(dimethylamino)ethyl methacrylate] (star PDMAEMA) with different molecular weight were prepared. Riboflavin was used as a model drug to evaluate the drug loading capacities and drug release behaviors of the semi-IPN structural hydrogels. The molecular weight of the star PDMAEMA polymers was calculated by GPC, and the formation of semi-IPN structure was confirmed by FTIR and SEM. It was found that the molecular weight of star PDMAEMA has significant effect on the structure, swelling ratio and drug release behaviors of the semi-IPN hydrogel at different pH conditions. The results suggested that the PVA/star PDMAEMA-50,000 hydrogel exhibited highest swelling ratio and drug loading capacity. The pH-sensitive semi-IPN hydrogel based on star PDMAEMA could be a promising drug delivery system due to the controllable porous structure.

1. Introduction

Hydrogels are chemically stable, hydrophilic three-dimensional networks composed of interlocked polymer backbones, which can absorb and retain a great quantity of water without being dissolved (Hennink and van Nostrum, 2002; Hoffman, 2002). Intelligent hydrogels have attracted particular attentions because they can undergo abrupt changes between their collapsed and swollen states in response to various environmental stimuli changes, such as pH, temperature, light, press (Qiu and Park, 2001; Verestiuc et al., 2004; Wang et al., 2008; Milasinovic et al., 2010; Tsao et al., 2010). Therefore, they are often applied to protect drugs from hostile conditions, e.g., the presence of abundant enzymes and low pH in the stomach (Qiu and Park, 2001). Among them, an interesting structure defined as interpenetrating polymer network (IPN) is developed to overcome the main disadvantage of the relatively low mechanical strength and to enhance the sensitivity of intelligent hydrogels (Miyata et al., 1999; Wu et al., 2004).

IPN structure is a mixture of two or more networks, which are at least partially interlaced with each other at the molecular level without covalent bond. And they cannot be separated unless chemical structures are broken (Zhang et al., 2004a,b; Liu et al., 2006; Saimani et al., 2010; Yao et al., 2010). It can significantly force the components keep interlaced and resist phase separation (Kim et al., 1999a). For instance, the IPN hydrogels could be composed of poly(vinyl alcohol) (PVA) and chitosan (Kim et al., 2003a), PVA and poly(acrylic acid) (PAA) (Peppas and Wright, 1998), polyethylene glycol (PEG) and eudragit (Buonaguidi et al., 1997), PEG grafted *N*-phthaloyl chitosan (PEG-g-NPHC) and sodium alginate, etc. (El-Sherbiny and Smyth, 2010), PVA and poly(*N*-isopropylacrylamide) (PNIPAAm) (Zhang et al., 2009). Such IPN structural hydrogel are mainly composed of both linear polymers. Recently, it has been reported that the introduction of poly(amidoamine) (PAMAM) dendrimers into semi-IPN hydrogels could significantly enhance the temperature response rates and swelling ratios of the resulting structure (Wu et al., 2004; Zhang et al., 2004a,b).

Based on the previous researches, it is found that star polymers have unique conformations, low viscosities at relatively high molecular weight and nanostructural functionalities compared with linear polymers (Connal et al., 2008). Compared with hyperbranched dendrimers, which would become a compact ball with rigid branches at high generations, the star polymers have more spatial freedom. Thus, the environmental sensitive star polymers could be easier to modify their conformations than linear counterparts to have stimuli-responsive functionalities, e.g., as a switch to control drug loading and release.

Poly[2-(dimethylamino)ethyl methacrylate] (PDMAEMA) is a kind of polymer sensitive to both pH and temperature. It has been

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widely applied in drug delivery systems because its critical phase transition pK_a is 7.6 in pure water and its lower critical solution temperature (LCST) in aqueous media fall in the wide range of 38–50 °C, which are both close to the physiological value (Emileh et al., 2007). It assumes that the introduction of star PDMAEMAs to hydrogels may not only provide their environmental sensitivity, but also significantly increase their mechanical properties as a result of the formation of semi-IPN structure.

In this work, a series of pH sensitive semi-IPN structural hydrogels composed of PVA and well-defined 21 arms star PDMAEMA polymers (Li et al., 2005; Guo et al., 2010a; Chen et al., 2011) are prepared and evaluated. The swelling ratios of the semi-IPN structural hydrogels and drug release behaviors of a model drug (riboflavin) from them are studied at different environmental conditions. The optimum combination of PVA and star PDMAEMA with suitable molecular weight could construct a feasible way to control the drugs delivery in response to environmental stimuli.

2. Materials and methods

2.1. Materials

Poly(vinyl alcohol)-124 (PVA-124) and riboflavin were procured from Chengdu Kelong Chemical Reagent Plant, China. Epichlorohydrin (EP) was obtained from Tianjin Kermel Reagent Co., Ltd., China. Dimethylaminoethyl methacrylate (DMAEMA) was purchased from Aladdin Reagent Ltd., China. *N*,*N*,*N*′,*N*′,*N*″-Pentamethyldiethylenetriamine (PMDETA) was provided by Beijing J&K Scientific Ltd., China. Before the syntheses of star PDMAEMA, an initiator (per-2,3,6-tri-*O*-chloroacetyl-β-cyclodextrin, 21Cl-β-CD) for atom transfer radical polymerization (ATRP) was prepared following the procedure in a previous work (Guo et al., 2010a). DMAEMA was distilled at reduced pressure before use, all the other reagents and solvents without special instructions were of AR grade and used without further purification. Distilled water was used throughout.

2.2. Syntheses and characterizations of star PDMAEMA

2.2.1. Syntheses of star PDMAEMA

Star PDMAEMA with different designed molecular weight, i.e., 25,000, 50,000 and 100,000 were synthesized by progressive ATRP method. The reaction conditions are presented in Table 1. For instance, a representative star PDMAEMA with designed molecular weight 25,000 (star PDMAEMA-25,000) was prepared as follows: 0.44 mL (2.1 mmol) PMDETA and 4.5 mL (0.534 mmol) DMAEMA were added into a three-necked flask with magnetic stirring. Then, 274 mg (0.1 mmol) 21Cl-β-CD was added to dissolve in the mixture before adding 2 mL methanol and 2 mL distilled water. After three times of freeze-pump-thaw cycles, 208 mg (2.1 mmol) CuCl was added under the protection of nitrogen. After repeating three times of freeze–pump–thaw cycles, the polymerization was carried out in a thermostatic oil bath at 60 °C for 12 h. The solution changed from light yellow to deep blue. The polymerization was ended by exposing to air, and solution was diluted with 200 mL tetrahydrofuran (THF). A light yellow solution was obtained after passing through a basic alumina column to remove the catalyst complex. After being concentrated in a rotary evaporator, the solution was dropped into cold *n*-hexane to yield a white solid. Finally, the collected star polymer was dried in a vacuum oven at 40 °C for 2 days.

2.2.2. Characterizations of star PDMAEMA

Gel permeation chromatography (GPC) analysis was carried out on a waters GPC system equipped with Waters Styragel columns, a Waters-2487 dual wavelength UV detector, and a Waters-2414 refractive index detector at 25 °C to determine the molecular of star PDMAEMA polymers. THF containing 2 vol% triethylamine was used as the eluent, and the flow rate was 1.0 mL/min. Monodispersed polystyrene was used as the GPC standard sample.

2.3. Preparations and characterizations of PVA/star PDMAEMA hydrogels

2.3.1. Preparations of PVA/star PDMAEMA hydrogels

The semi-IPN structural hydrogels are composed of PVA and star PDMAEMA with different designed molecular weight, i.e., 25,000, 50,000 and 100,000. For example, PVA/star PDMAEMA-25,000 was prepared as follows: 10 g PVA-124 was added to a 500 mL three-necked flask with 100 mL distilled water. After stirring at 98 °C for 6 h, it has become well-distributed transparent mucus. Then 10 mL PVA mucus was transferred to a conical flask with 0.5 mL DMSO. 0.5 g star-PDMAEMA-25,000 polymer was added into the flask. Then, 0.8 mL EP was slowly dropped in. After 0.5 h magnetic stirring, 2.5 mL (0.25 g/mL) KOH aqueous solution was added to the conical flask for another 0.5 h stirring. Finally, the mixture was poured into a petri dish and solidified at 28 °C for 12 h to obtain the PVA/star PDMAEMA-25,000 hydrogel. The preparation of other PVA/star PDMAEMA hydrogels were the same, except adding different star PDMAEMAs of the same weight.

2.3.2. FTIR studies

The FTIR transmission spectrums of hydrogels were performed on a Nicolet Nexus 670 FTIR spectrometer (USA). Dried hydrogels were scanned from 650 to 4000 cm^{-1} at the reflex mode for their extremely thin and transparent characters.

2.3.3. Scanning electron microscopy (SEM) analyses

After dipping in a pH 5.0 solution at 37 °C for 3 h, hydrogels were freeze-dried at −50 °C for 12 h to fix their morphologies. An Inspect F SEM (20.0 kV) was used to observe the surface morphology of hydrogels.

2.4. Swelling ratios of hydrogels

The hydrogels composed of PVA and star PDMAEMAs with different molecular weight were dipped in 500 mL distilled water and the distilled water was refreshed three times every hour to remove residual EP and KOH. After dried in vacuum at 50 °C for 12 h, the swelling ratios of purified hydrogels were tested by soaking them at 37 °C in a pH 7.0 solution for a certain period of time. The swollen hydrogels were taken out to weight after solution on the hydrogels' surfaces being absolutely sucked up. Besides, the swelling ratios of the PVA/star PDMAEMA-50,000 hydrogel were further tested at 37 °C in different pH conditions, i.e., 5.0, 7.0 and 9.0, respectively. The swelling ratio (SR) was described as follows:

$$SR = \frac{W_s - W_d}{W_d}$$

where W_d is the weight of dried hydrogels and W_s is the weight of swollen hydrogels.

2.5. Drug loading and release studies

The dried PVA/star PDMAEMA hydrogels were added into beakers with 20 mL (0.1 g/mL) riboflavin saturated solution and mechanically vibrated at 37 °C for 12 h. After repeated washing with distilled water, the drug-loaded hydrogels were dried in the vacuum at 50 °C for 6 h. The drug-loaded hydrogels were added into 150 mL solution and vibrated at 37 °C in pH 5.0, 7.0 and 9.0, respectively. Then 5 mL solution was taken out to calculate their

Table 1
Conditions and results of syntheses of star PDMAEMAs via ATRP using 21Cl-β-CD as the initiator.

Sample	$[M]_0/[I]_0/[Cu]_0/[L]_0$[a]	Temp. (°C)	Time (h)	Conv. (%)[b]	M_n	M_w/M_n
Star PDMAEMA-25,000	267/1/1/1	60	12	63.41	25,800	1.21
Star PDMAEMA-50,000	530/1/1/1	60	12	62.27	51,500	1.26
Star PDMAEMA-100,000	1060/1/1/1	60	12	60.32	99,300	1.32

[a] The ratio of amount of $[M]_0$, $[I]_0$, $[Cu]_0$ and $[L]_0$ represented the content of DMAEMA, 21Cl-β-CD, CuCl and PMDETA, respectively.
[b] Conversion was calculated according to ^{1}H NMR data.

drug concentration and 5 mL original solution was added to supplement the release solution. Further, the drug-loaded hydrogel was alternately put into 150 mL solution of pH 5.0 and 9.0 every 30 min (37 °C) to measure the drug release profile.

3. Results and discussion

The controlled polymerization of 2-(dimethylamino)ethyl methacrylate (DMAEMA) via ATRP in nonpolar solution was firstly reported by Zhang et al. (1998). After that, ATRP method is also used to obtain ultra high molecular weight or star-shaped DMAEMA polymers with well-defined structures in the mixture of methanol and water (Mao et al., 2006; Guo et al., 2010b; Xu and Yang, 2011). Table 1 shows the syntheses condition of star PDMAEMAs with different designed molecular weight based on β-cyclodextrin core. All the star PDMAEMAs have 21 arms radiated from the 21 initiation sites of the 21Cl-β-CD initiator. In the case of fixed reaction condition in solution (methanol/water: 1:1) at 60 °C for 12 h, star PDMAEMAs with different molecular weight are prepared by varying the relative ratio of DMAEMA monomer. Their reaction conversions calculated according to ^{1}H NMR dates are 63.41%, 62.27% and 60.32%, respectively (Table 1). Meanwhile, the low polydispersity index (PDI) indicates a well-defined star polymer structure under the control of ATRP.

The FTIR spectroscopy is used to confirm the semi-IPN structural formation of PVA and star PDMAEMA (Fig. 1). The strong characteristic absorption peak observed at 3400 cm^{-1} is attributed to the stretching vibration of O–H of PVA, which is both observed in the spectra of pure PVA hydrogel (a) and semi-IPN structural hydrogels (b–d). However, it is found that the new characteristic absorbing peaks appeared at 1724 and 1152 cm^{-1} could be attributed to the stretching vibration of C=O and C–O, which are the characteristic absorbing peaks of the ester of DMAEMA, indicating that star PDMAEMA polymers are successfully introduced into PVA hydrogels to form the semi-IPN structural hydrogels.

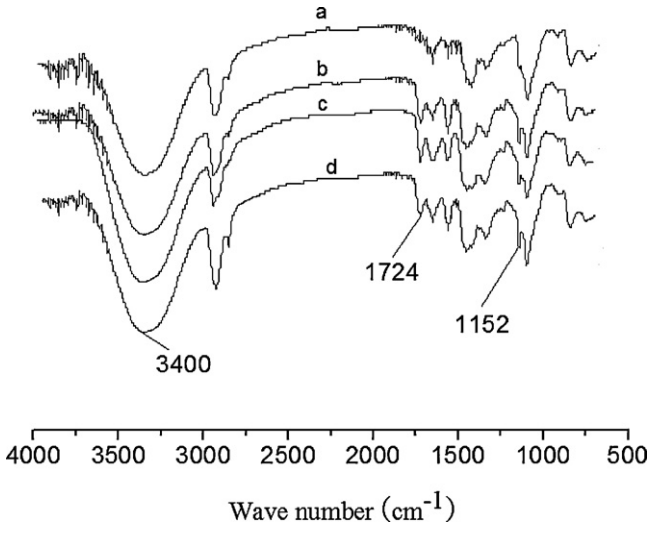

Fig. 1. FTIR spectra of pure PVA (a), PVA/star PDMAEMA-25,000 (b), PVA/star PDMAEMA-50,000 (c) and PVA/star PDMAEMA-100,000 (d) hydrogels.

As reported elsewhere, the average hydrodynamic diameters of star PDMAEMA could change along with pH altering (Kim et al., 2009; Guo et al., 2010b). Compared with linear PDMAEMA, the effective pK_a of star PDMAEMA polymer is slightly lower because of its unique ionic confinement effect. Usually, star polymer with more compact charged groups has a higher osmotic pressure (Kim et al., 2009). In our previous work, we found that star PDMAEMA presents more stretched conformation at relative low pH due to the electrostatic repulsion between their chains (Guo et al., 2010b). The apparently porous structures of the semi-IPN hydrogels can be easily observed at pH 5.0. Therefore, after fixing their morphologies by treating in pH 5.0 solution, the surface morphology change of chemical cross-linked hydrogels is characterized intuitively by SEM (Fig. 2). It is found that, after the acidic post-treatment, the surface of pure PVA hydrogel shows an intact and compact appearance (Fig. 2a) while the surfaces of hydrogels composed of PVA and star PDMAEMA polymers with a semi-IPN structure exhibit a high porous structure (Fig. 2b–d). Meanwhile, it is obvious that the extent of three dimensional networks porous structure of hydrogel is significantly affected by the molecular weight of star PDMAEMA. The PVA/star PDMAEMA-50,000 has the most porous structures with uniform pore diameters ranging from 10 to 20 μm. The porous structural properties may be inclined to offer a larger specific surface area, which can provide a better interaction between solution and hydrogels, allowing easier solution uptake. Furthermore, the porous structural hydrogels may have larger bulk for drugs loading and release. That could be important for controlling the drugs loading and release as a result of changing the conformation of star PDMAEMA at molecular levels.

The swelling capability of hydrogel can be described in terms of the maximal amount of absorbed water and the swelling ratio at balance, which depends on the physiochemical properties of polymers and the surrounding environments (Kim et al., 2003b). The swelling ratios of four hydrogels without or with different star PDMAEMAs in distilled water are shown in Fig. 3. Each point represents the average data of triplicate measurements. As for the ultimate swelling ratio indicated by the last measured point, the ratio of pure PVA is only 3.2, while the ratio of the semi-IPN structural PVA/star PDMAEMA-25,000, 50,000 and 100,000 hydrogels are 12.3, 35.3 and 28.2, respectively. It comes to the conclusion that the ultimate swelling ratios of intelligent hydrogels with semi-IPN structure were much higher than that of the pure PVA hydrogel. Especially, the ultimate swelling ratio of semi-IPN structural PVA/star PDMAEMA-50,000 intelligent hydrogel is more than ten times higher than that of the pure PVA hydrogel. Besides, the pure PVA hydrogel reaches its saturation status much faster because of the limitation of storing bulk and adsorbing area. The results suggest that the swelling behavior of pH sensitive hydrogel is strongly governed by the semi-IPN structure. On the other hand, the swelling ratios of the semi-IPN structural hydrogels are obviously correlated with the molecular weight of star PDMAEMA. And the swelling ratio is in accordance with the morphologies and amounts of porous as shown in the SEM measurements (Fig. 2). That is, the more porous structure may be correlated with the higher degree of swelling. It is further proved that the introduction of star PDMAEMA into

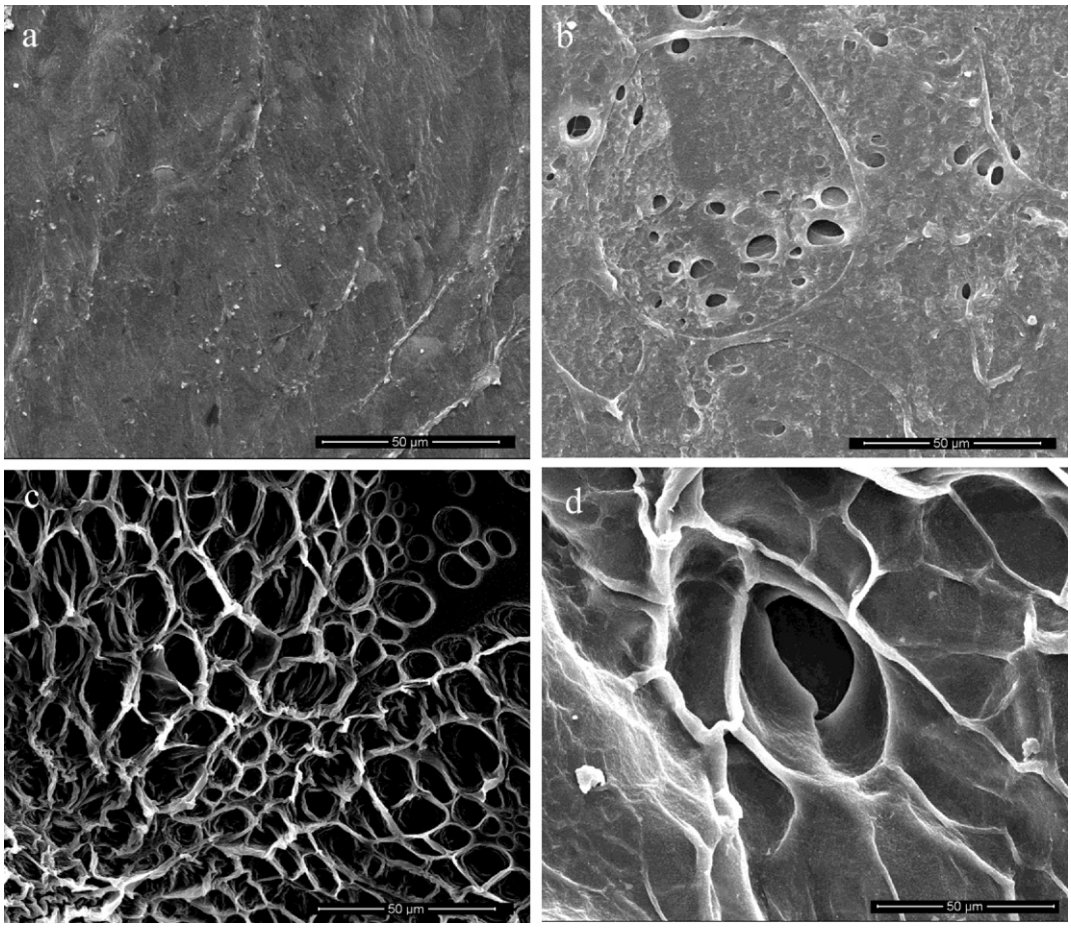

Fig. 2. Morphology of pure PVA (a), PVA/star PDMAEMA-25,000 (b), PVA/star PDMAEMA-50,000 (c) and PVA/star PDMAEMA-100,000 (d). SEM pictures of hydrogels' surfaces after being treated in pH 5.0 solution.

PVA would result in a semi-IPN structure, which may provide the superior capabilities with much more volume and porous surface morphology. The porous structures of semi-IPN hydrogels may provide an abundant of space for solution storing and enough surface areas for solution adsorbing. Comparing the changes of surface morphologies (Fig. 2) and swelling ratios (Fig. 3) of four samples, it is obviously that the PVA/star PDMAEMA-50,000 intelligent hydrogel has an ideal pH sensitive semi-IPN structure with a large number of porous structures due to the proper interlacing between PVA and star PDMAEMA.

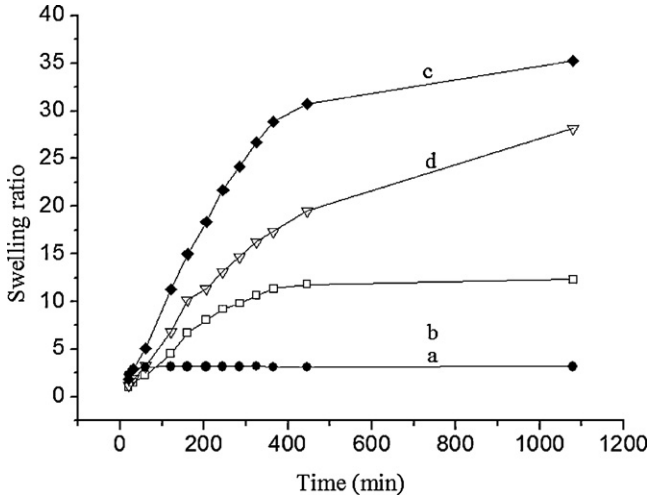

Fig. 3. Swelling ratio curves of pure PVA (●), PVA/star PDMAEMA-25,000 (□), PVA/star PDMAEMA-50,000 (♦) and PVA/star PDMAEMA-100,000 (▽) hydrogels at pH 7.0.

To further study the swelling behaviors of semi-IPN structural hydrogels, the PVA/star PDMAEMA-50,000 hydrogel, which has the largest amount of porous structures and highest swelling capacity, was chosen to study the swelling profiles at pH 5.0, 7.0 and 9.0 (Fig. 4). The ultimate swelling ratios of PVA/star PDMAEMA-50,000 intelligent hydrogel at pH 5.0, 7.0 and 9.0 are 47.5, 35.3 and 17.9, respectively. It is noted that semi-IPN structural PVA/star PDMAEMA-50,000 hydrogel is sensitive to the pH change. In the range of pH 5.0–9.0, the swelling ratio is higher at relative low pH condition due to the different protonation degree of star PDMAEMA polymer at different pH conditions. It means that the star PDMAEMA polymer presents a stretched conformation in the case of low pH but a much more constrained coiled conformation in the case of high pH value, which will lead to different morphologies and water absorbing capabilities.

Riboflavin was chosen as the model drug and loaded into hydrogels (Fig. 5). It is found that PVA/star PDMAEMA-50,000 (B) has the deepest yellow color, which indicates that a greater amount of riboflavin has been loaded due to its porous structure. The drug release behaviors of riboflavin loaded PVA/star PDMAEMA-50,000 intelligent hydrogel are investigated at pH 5.0, 7.0 and 9.0 as shown in Fig. 6. The amounts of drug released at infinite time in pH 5.0, 7.0 and 9.0 conditions are 299.3 μg, 241.2 μg and 148.6 μg, respectively. Compared with the swelling behaviors of hydrogels without drug in the distilled water at pH 7.0 (Fig. 4), the release behav-

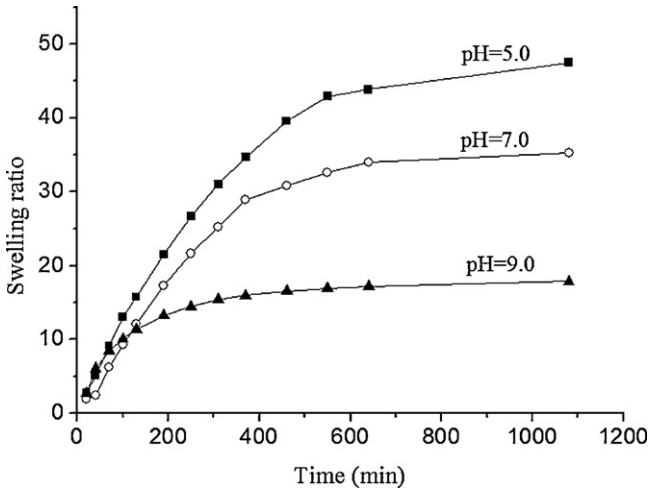

Fig. 4. Swelling ratios of PVA/star PDMAEMA-50,000 semi-IPN hydrogel at pH 5.0 (□), 7.0 (○) and 9.0 (▲).

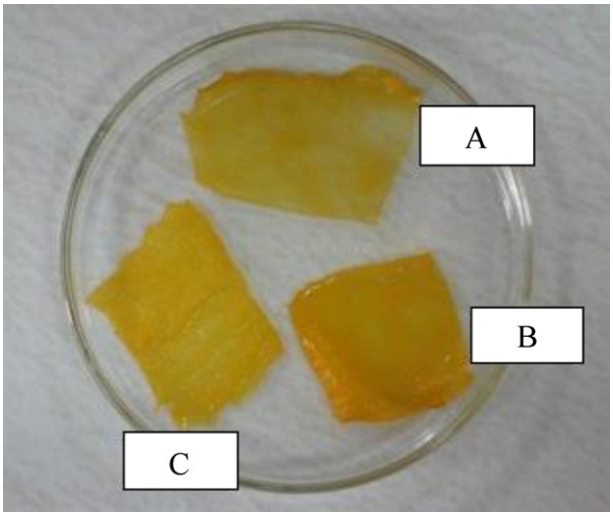

Fig. 5. The images of drug-loaded hydrogels: (A) PVA/star PDMAEMA-25,000, (B) PVA/star PDMAEMA-50,000 and (C) PVA/star PDMAEMA-100,000.

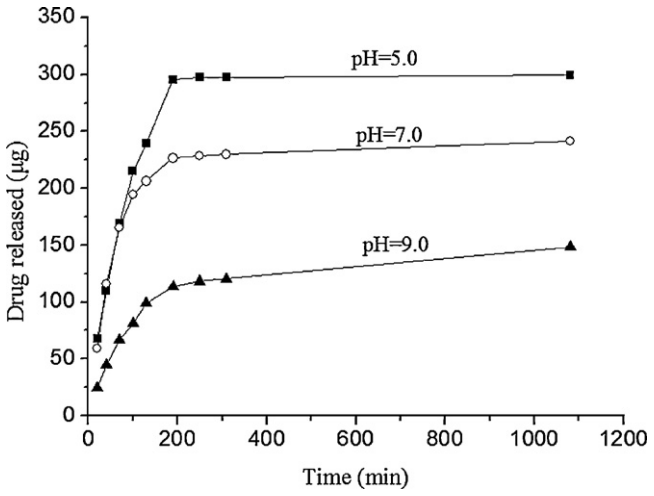

Fig. 6. Drug release curves of PVA/star PDMAEMA-50,000 at pH 5.0 (■), 7.0 (○) and 9.0 (▲).

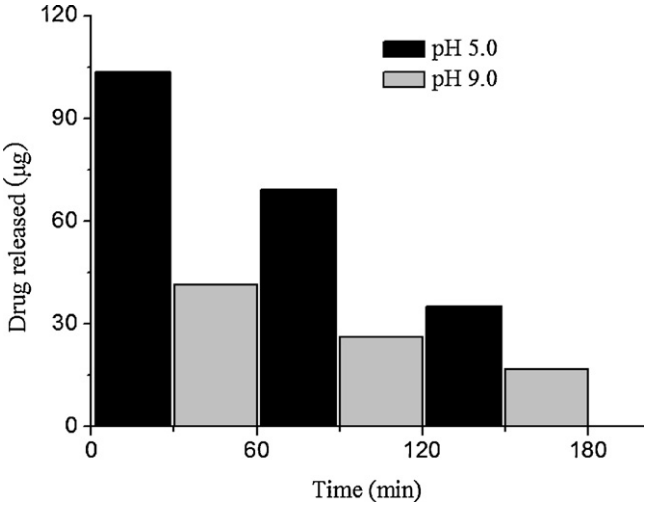

Fig. 7. Drug release behaviors of PVA/star PDMAEMA-50,000 hydrogel dipped at pH 5.0 and 9.0 alternately every 30 min.

iors of drug-loaded hydrogel shows a similar trend. However, the drug-loaded hydrogel exhibits a faster response at the same pH stimuli: it is about 200 min for the drug-loaded hydrogel to equilibrium state while it needs more than 600 min for the hydrogel without drug. The drug release behaviors of intelligent hydrogel depend on not only the PVA/star PDMAEMA semi-IPN structure, but also the drug-hydrogel interactions. The dried porous hydrogel could absorb abundant riboflavin during the swelling process in the riboflavin solution. In the case of drug-loaded hydrogel, riboflavin could be easily to spread from porous structures through the affinity effects between riboflavin and solution. It means that the drug-loaded hydrogel has a greater weight loss in a relatively short time. At the time of reaching the balanced release states in different pH conditions is almost the same, the amount of drug released is obviously higher at low pH, which is in consistent with former discussion.

In the case of the varying pH conditions, drug release behaviors of the hydrogels are further studied during pH pulse stimuli (Fig. 7). It shows an "ON–OFF" characteristic release controlled by the reversible volume changes of the pH-sensitive hydrogel. The rapid drug release is observed when the stimulus is at "ON" status, whereas they exhibit a relatively slow release during the "OFF" state, which is also reported about other systems (Kim et al., 1996; Kim and Lee, 1999b). This should be attributed to the association and disassociation between the semi-IPN structural hydrogel and drug. In the first 30 min, the profile shows the total released drug weight of PVA/star PDMAEMA-50,000 hydrogel at pH 5.0, while the next 30 min shows the total released drug weight at pH 9.0. Then, the characteristic "ON–OFF" profiles of the semi-IPN structural hydrogel varied with the pH pulse stimuli at 5.0 and 9.0 every 30 min in turn. In the case of same pH condition, the amount of released drug gradually reduces as the time went by. That is because the total drug-loaded weight of hydrogel is reducing during its releasing. As star PDMAEMA displays an extended conformation at pH 5.0, semi-IPN hydrogel shows the more porous structure, the more channels formed for quicker drug release. With its characteristic difference of sensitivities at different pH condition, the semi-IPN hydrogel may provide one probable way for controlled drug delivery systems.

4. Conclusions

A series of semi-IPN structural hydrogels with pH sensitivity were prepared with PVA and star PDMAEMAs of different molecular

weights. Among them, the PVA/star PDMAEMA-50,000 hydrogel exhibits the most obvious transition to porous morphology after acidic post-treatment, the highest swelling ratio and optimum drug release behaviors in response to pH stimuli. Drug release behaviors of hydrogel are enhanced because the porous structures provide not only more volumes and specific surface area for drug storing, but also more channels for drug release. Therefore, the pH-sensitive semi-IPN structural hydrogel could be a promising candidate to design a feasible drug controlled release system.

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