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# Preparation, properties, and drug release of thermo- and pH-sensitive poly((2-dimethylamino)ethyl methacrylate)/poly(*N*,*N*-diethylacrylamide) semi-IPN hydrogels

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**Abstract** In this paper, a series of semi-interpenetrating polymer network (semi-IPN) hydrogels based on poly((2-dimethylamino)ethyl methacrylate)/poly (*N*,*N*-diethylacrylamide) (PDMAEMA/PDEA) were synthesized by changing the initial PDMAEMA/DEA molar ratio at room temperature. The influence of this additive on the property of resulting PDEA hydrogels was investigated and characterized. The interior morphology by scanning electron microscopy (SEM) revealed that the semi-IPN hydrogels have interconnected porous network structures. The glass transition temperature ($T_g$) of the semi-IPN hydrogels was observed by differential scanning calorimetry (DSC). Equilibrium swelling ratio (ESR), swelling and deswelling dynamics of the hydrogels responding to temperature and pH were investigated in detail. Compared to PDEA, the semi-IPN hydrogels exhibited excellent mutative values in response to an alternation of the temperature and pH, and showed fast swelling and deswelling rates in response to temperature and pH change. The release behaviors of the model drug, aminophylline, were found dependent on hydrogel compositions and environmental temperature. These results suggest that the stimuli semi-IPN hydrogel have potential application as intelligent drug carriers.

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## Introduction

Hydrogels are three-dimensional polymeric networks that are able to absorb and retain large amounts of water. Environmental stimuli-sensitive hydrogels, with unique and desirable sensitivity to temperature, pH, magnetic field, and light, etc., have been extensively studied [1–3]. During last decade, thermo- and pH-sensitive hydrogels have attracted great interest and play an important role in controlled drug delivery systems because temperature and pH are important triggering signals for phase transitions in hydrogels and they are important environmental factors in biomedical and other systems [4–6]. In the case of thermo-sensitive hydrogels, the polymers of several N-substituted polyacrylamides exhibit thermo-sensitive behavior, and the poly(*N*,*N*-diethylacrylamide) (PDEA) hydrogel is a typical thermo-sensitive polymeric network, which exhibits a lower critical solution temperature (LCST) at about 31 °C [7, 8]. It absorbs water to a swollen state at a temperature below the LCST, and shrinks with an abrupt volume decrease when the temperature goes above the LCST because of the alteration in hydrophilicity and hydrophobicity. Poly((2-dimethylamino)ethyl methacrylate) (PDMAEMA) is a typical cationic component with

tertiary amine groups which are ionized in the lower pH region and positively charged, as a result, PDMAEMA, become more extended because of the increased osmotic pressure among hydrogels. On the other hand, it is difficult for PDMAEMA to produce enough ionized amino groups in the higher pH condition, so that the hydrogels take a contracted form. Due to its pH-sensitive, PDMAEMA can be used as controlled drug delivery system [9, 10].

In our previous studies, PDEA and P(DEA-*co*-DMAEMA) had no apparent cytotoxicity for HeLa cells, and have potential application as intelligent drug carriers [5]. However, the incorporation of hydrophilic components might decrease the thermo-sensitivity of the copolymerized hydrogel and a high content of co-monomer might lead to the complete suppression of thermo-sensitivity, and the slow swelling and deswelling rates of the PDEA hydrogel would also limit their application [11, 12]. So far, several strategies have been proposed in attempts to improve the response rate of PDEA hydrogel, such as employing high temperature techniques [13], use of mixed solvent [14], formation of macroporous structures [15]. Besides, introducing another polymer into PDEA hydrogel to form interpenetrating polymer network (IPN) is one of the promising and exciting choice to obtain the improvement on the properties. Semi-IPN technology is an important route to prepare thermo- and pH-sensitive hydrogels without decreasing their sensitive properties [16]. Three-dimensional crosslinked structures that contain entangled linear polymers form semi-IPN and have the potential advantage in offering a better control over the chemical composition and the final properties of the resulting material [17]. Moreover, the method has been reported to present some possible advantages. Such as, the process of preparation is simple and feasible, and the combination of temperature-response with other properties can retain its individual response behavior, and semi-IPN hydrogels have interconnected porous network structures, which lead hydrogels have much larger specific surface areas and a much more rapid swelling/deswelling rate than nonporous hydrogels [18].

In this paper, a series of thermo- and pH-sensitive PDMAEMA/PDEA semi-IPN hydrogels with different compositions were fabricated. The thermo- and pH-sensitive behaviors of these hydrogels were investigated. Moreover, the swelling and deswelling dynamics and oscillating swelling/deswelling behavior of the different composition ratios of PDMAEMA to DEA on the semi-IPN hydrogels were also investigated in detail. The outcomes are relatively dense hydrogel matrices featuring stiffer and tougher networks, with more widely controllable physical properties, and more efficient drug loading [19]. The model drug, aminophylline, was loaded into the hydrogels, and the in vitro release of the drug from these hydrogels was investigated at different temperatures.

## Experimental

### Materials

*N*,*N*-Diethylacrylamide (DEA) was synthesized according to the literature [7]. (2-Dimethylamino)ethylmethacrylate (DMAEMA, Acros, 99%) was distilled under vacuum. *N*,*N*-Azobisisobutyronitrile (AIBN) (C.P. grade) (Shanghai Fourth Reagents Plant, Shanghai, China) and *N*,*N*-methylenebisacrylamide (NNMBA) (C.P. grade) were recrystallized with 95% ethanol just before to use. Ammonium persulfate (APS) (Tianjin chemical company, China) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamide (TEMED) (Fluka Co. Ltd.) were analytical grade and used without further purification. Aminophylline was purchased from Ji'nan Orgachem Pharmaceutical Co. Ltd. (Ji'nan, China), and used without further purification. All other reagents were analytical grade and used without further purification. Double distilled water was used for preparing all the solutions of the experiment.

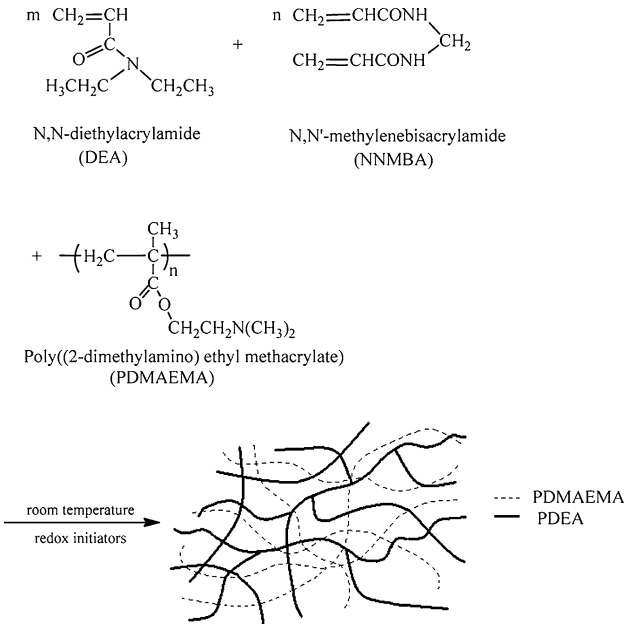
### Preparation of PDMAEMA

The linear PDMAEMA homopolymer was synthesized during the following experimental work. DMAEMA (4.665 g), AIBN (0.0493 g) were dissolved in tetrahydrofuran (THF) (2.5 mL). Dried nitrogen was bubbled into the solution for 30 min to remove oxygen. Polymerization was carried out at 70 °C for 6 h. After the reaction finished, the reactant was dissolved in acetone for 2 h, and then poured it into an excess of petroleum ether to precipitate for 3 h. Then the precipitation was collected by filtration and was purified by repeated precipitation in petroleum ether from acetone, and dried to constant weight under vacuum at room temperature.

The molecular weight of PDMAEMA was estimated by gel permeation chromatography (Waters GPC V2000 Empower Software) using THF as the mobile phase and polystyrene as the standard.

### Preparation of the PDMAEMA/PDEA semi-IPN hydrogels

Polymerization reactions were performed in glass tubes with the inner diameters of 1.2 cm, and lengths of 15 cm. In preparation of the PDMAEMA/PDEA semi-IPN hydrogels, the monomer, DEA, the crosslinker, NNMBA, and the various content of PDMAEMA were fully dissolved in water at room temperature. After nitrogen bubbling for 10 min through the solution, the accelerator, TEMED, and the initiator, APS, were added, respectively. Then, the free-radical polymerization was carried out at 15 °C for 24 h. The structures of PDMAEMA, DEA, and the synthesis




**Scheme 1** Synthesis route of PDMAEMA/PDEA semi-IPN hydrogel by radical copolymerization using NNMBA as the crosslinker

route of the PDMAEMA/PDEA semi-IPN hydrogel are shown in Scheme 1, respectively. At the end of the reaction, the glass tubes were broken carefully without destroying the cylindrical hydrogels. The resulting hydrogels were sliced into small cylinders with lengths of 2 mm and then immersed in distilled water for 6 days, and the water was refreshed four times every day in order to remove the residual unreacted monomer and the fraction of the product. The pure PDEA hydrogel was prepared with the same condition. Apart of samples for the resulting swollen hydrogels were dried at room temperature for 2 days, and were further dried under vacuum to constant weight at room temperature. Thus, the dried gels were obtained. The detailed feed compositions and samples codes of hydrogels are summarized in Table 1.

## FTIR measurements

Fourier transform infrared (FTIR) spectroscopy was carried out with Nicolet NEXUS 670 FTIR Spectrometer. The samples dried completely and ground to fine power, then push down to piece blending with KBr.

## SEM measurements

SEM (JSM-5600LV instrument, Japan) was used to observe the interior morphology of the hydrogels. To prepare samples for SEM, the hydrogels, after reaching their equilibrium swelling ratio in water at room temperature, were quickly frozen in liquid nitrogen and then freeze-dried under vacuum for 15 h with Labconco Freeze Dry system (LABCONCO 2.5 L, USA) to avoid the collapse of the porous structure, and then sputter-coated with gold.

**Table 1** The feed compositions and sample codes of the PDMAEMA/PDEA semi-IPN hydrogels

| Compositions | Sample codes | | | | |
|---|---|---|---|---|---|
| | PDEA | Semi-IPN1 | Semi-IPN2 | Semi-IPN3 | Semi-IPN4 |
| PDMAEMA (mg) | 0 | 25.4 | 50.1 | 90.9 | 152.4 |
| DEA (mL) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| NNMBA (mg) | 8.6 | 8.4 | 8.5 | 8.5 | 8.6 |
| $H_2O$ (mL) | 5.0 | 5.0 | 5.0 | 5.0 | 5.0 |
| TEMED (μL) | 15.0 | 15.0 | 15.0 | 15.0 | 15.0 |
| APS (mg) | 18.0 | 18.1 | 18.2 | 18.2 | 18.1 |

## DSC measurements

DSC measurements (Pyris Sapphire DSC, USA) were carried out in a nitrogen atmosphere to determine the $T_g$ values of the PDMAEMA/PDEA semi-IPN hydrogels. Typical procedure for $T_g$ was described as follows: first, the dried samples were heated to 200 °C at 10 °C $min^{-1}$ and then were cooled to 10 °C at 20 °C $min^{-1}$. This procedure ensured that the samples had the same thermal history; second, the samples were reheated to 200 °C at 10 °C $min^{-1}$. The onset of the abrupt decrease in the heat flow was taken as $T_g$.

## Swelling properties measurements

The classical gravimetric method was used to measure the ESR and the pH-sensitivity of the hydrogels. Swelling studies were performed in distilled water at different temperatures from 20 to 50 °C, which covered the expected range of the LCST of the hydrogel samples, and in buffer solutions of different pH (from 1.2 to 12) at fixed ionic strength. The buffer solution is prepared according to the literature [20]. The addition of NaCl is to maintain constant ionic strength ($I = 0.1$ mol $L^{-1}$) of buffer solutions. The hydrogels were immersed to reach a swollen equilibrium at each predetermined condition. Then the hydrogel samples were taken out, and excess water on the sample surface of the wet hydrogel was removed with wet filter papers and then weighed until a constant weight. Each sample was measured three times and the average value of three measurements was taken. The equilibrium swelling ratio (ESR) is defined as:

$$\mathrm{ESR} = (W_e - W_d)/W_d \quad (1)$$

where $W_e$ and $W_d$ are the weights of the equilibrated swollen hydrogel and the dried gel, respectively.

### Swelling dynamics of the hydrogels

The same method as above was utilized to record the swelling dynamics. The dried gels were immersed in water at 25 °C, and the samples were taken out from water at regular time intervals. After removing the water on the sample surface with wet filter paper, the sample weights were recorded as the average value of three measurements. The swelling ratio (SR) at time $t$ was defined as follows:

$$\mathrm{SR} = (W_t - W_d)/W_d \quad (2)$$

where $W_t$ is the weight of the wet hydrogel at time $t$ and other symbols are the same as defined above.

### Deswelling dynamics of the hydrogels

To study the deswelling dynamics, equilibrated swollen hydrogels in distilled water at 25 °C were transferred into distilled water at 60 °C. The weight changes of hydrogels were recorded during the course of deswelling after removing the excess water on the surface with moistened filter papers at regular time intervals. Each sample was weighed three times and the average value of three measurements was taken. Water retention (WR) is defined as:

$$\mathrm{WR}(\%) = [(W_t - W_d)/(W_e - W_d)] \times 100 \quad (3)$$

where $W_e$ is the weight of equilibrated swollen hydrogel at 25 °C, $W_t$ is the weight of hydrogel at regular time intervals, and $W_d$ is the weight of the dried gel.

### Oscillating dynamics of the hydrogels

The oscillating swelling/deswelling dynamics of the hydrogels was observed in distilled water maintained at alternate temperatures of 25 (below LCST) and 60 °C (above LCST), and in buffer solutions ($I = 0.1$ mol $L^{-1}$) with pH values between 1.2 and 3.0 at 25 °C. The hydrogel samples were first immersed in the solution (at 25 °C and pH 1.2, respectively) till it reached equilibrium, and then quickly transferred it to another solution (at 60 °C and pH 3.0, respectively). The weight of the hydrogels was measured every 5 min at the alternate temperatures and 1 h at the alternate pH values quoted, respectively. The weights of the samples were measured by gravimetrical method and the equilibrium swelling ratio at each pH value was calculated according to Eq. 2. Each sample was weighed three times and the average value of three measurements was taken.

### Drug loading and in vitro release studies

The loading of the model drug in crosslinked polymer networks can be accomplished by two loading techniques: an equilibrium partitioning and copolymerization/crosslinking in the presence of the drug [21]. In this work, the dried PDEA and semi-IPN3 hydrogel disks were immersed in a 0.05 mol $L^{-1}$ aminophylline solution to allow the drug solution being sufficiently absorbed by the hydrogel networks for 4 days at 4 °C. The total drug loaded was determined by the mass change of hydrogels in the solution before and after loading. Each loading experiment was carried out in sextuples. After imbibition, the samples were removed from the drug solutions, and dried to constant weight under vacuum at room temperature. After that, drug release experiments were conducted by immersing the above dried drug loaded gel samples in a wide-mouthed conical flask filled with 50 mL phosphate buffer solution (PBS) (pH 7.4) at 25 or 37 °C. At a predetermined period of the in vitro release experiment, a 5 mL aliquot was withdrawn periodically from the conical flask and the concentration of the drug in that aliquot was monitored at 278 nm by using a UV–vis spectrophotometer (Lambda 35 UV–vis spectrometer, Perkin Elmer Crop., Norwalk, CT. USA). A 5 mL fresh PBS was added back to the conical flask to maintain the same total solution volume. The absorbance values were translated to concentration values by comparing to standard solutions. Standard solutions were prepared in the release environment volume ranging in concentration from 0.005 to 1 mg $mL^{-1}$. Drug release behaviors from three samples were tested and the average value was used. The results were presented in terms of cumulative release as a function of time:

$$\text{Cumulative amount released}(\%) = W_t/W_{\mathrm{drug}} \times 100 \quad (4)$$

where $W_t$ is the amount of drug released from the hydrogel at time $t$ and $W_{\mathrm{drug}}$ is the weight of the drug in the hydrogel.

## Results and discussion

### Synthesis of the PDMAEMA/PDEA semi-IPN hydrogels

The synthesis of the semi-IPN hydrogels involved two steps. First, the linear PDMAEMA homopolymer was synthesized by radical polymerization with monomers DMAEMA using AIBN as an initiator in THF solvent, and the weight-average and number-average molecular weights of the linear homopolymer are, respectively, determined to be 46553 and 31209 Da by GPC, and the polydispersity is 1.49. Second, the PDMAEMA/PDEA semi-IPN hydrogels are prepared from DEA in PDMAEMA aqueous solutions via radical polymerization in the presence of crosslinker, NNMBA. In this work, APS/TEMED as a pair of redox initiators is utilized to initiate the radical polymerization, and the DEA and NNMBA for one network are

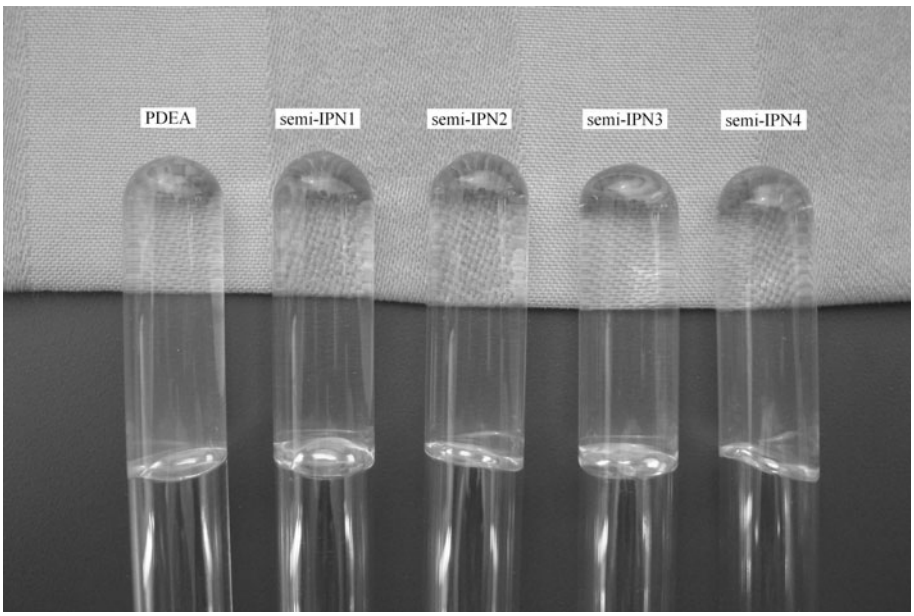



**Fig. 1** Digital Photo of reaction cuvettes for semi-IPN hydrogels

polymerized/crosslinked. It is well-known that APS and TEMED have been widely used for many advantages, such as high initiation efficiency and fast polymerization rate [5, 8, 12, 14, 18, 22]. The polymerization is carried out at 15 °C while the reaction vessel is neither heated nor cooled. The image of the PDEA and semi-IPN hydrogels is transparent in appearance (Fig. 1). This is because that the network structure is homogeneous on the length scales above visible wavelengths. In all the formulations, the gelation processes of all hydrogels took place within 10 min after addition of the redox initiators. However, the polymerization reactions were continued for 24 h to obtain complete crosslinked network.

## FTIR spectra of the hydrogels

The molecular structure of the semi-IPN gel is investigated in detail using FTIR. Figure 2 shows the FTIR spectra of PDEA and the semi-IPN3 xerogel. As expected, the absorption bands at 2973 and 2930 $cm^{-1}$ are resulting from the C–H stretching vibrations of $–CH_3$ and $–CH_2–$ groups. One can also observe two typical bands of C–H vibration with almost the same intensity at about 1458 and 1386 $cm^{-1}$ in each spectrum, which belong to the bands of $–CH_2–$ and $–CH_3$ groups. A sharp peak observed at 1726 $cm^{-1}$ corresponds to the ester carbonyl stretching vibration. In addition, because the presence and increasing of PDMAEMA content in hydrogels could be confirmed by the appearing of two absorption bands at 2819 and 2771 $cm^{-1}$ which are resulting from dimethyl amino groups which are adjacent to the nitrogen atom in the PDMAEMA structure [23].

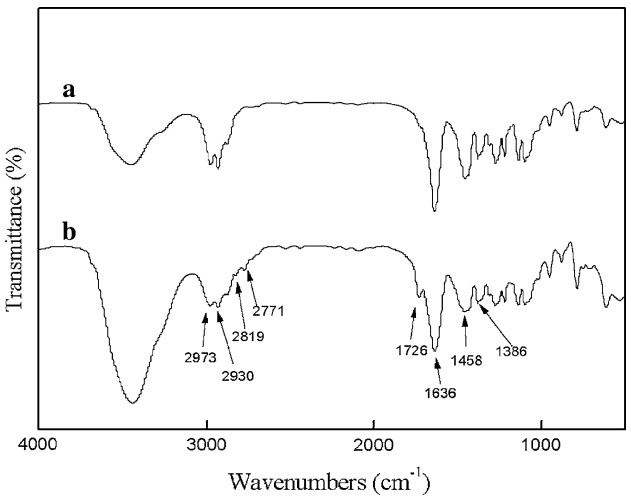



**Fig. 2** FTIR spectra of PDEA (**a**) and semi-IPN3 (**b**)

## Interior morphology of the hydrogels

SEM is a very useful technique to study the three-dimensional network structure and the matrix morphology of the resulting hydrogels. SEM micropictures of the freeze-dried, swollen hydrogel samples are shown in Fig. 3. The data clearly illustrate the dependence of interior morphology on the composition of the hydrogel. From Fig. 3, it can be found that the morphology of these hydrogel networks retain the porous structure that they have in the swollen state because of the employed freeze drying method, and the pore structures are different as the content of PDMAEMA changes. The PDEA hydrogel exhibits regular porous structures and the average pore size is about 18 μm, while semi-IPN hydrogels have an irregular porous structures. In the PDEA network, the thick wall is observed to be smooth

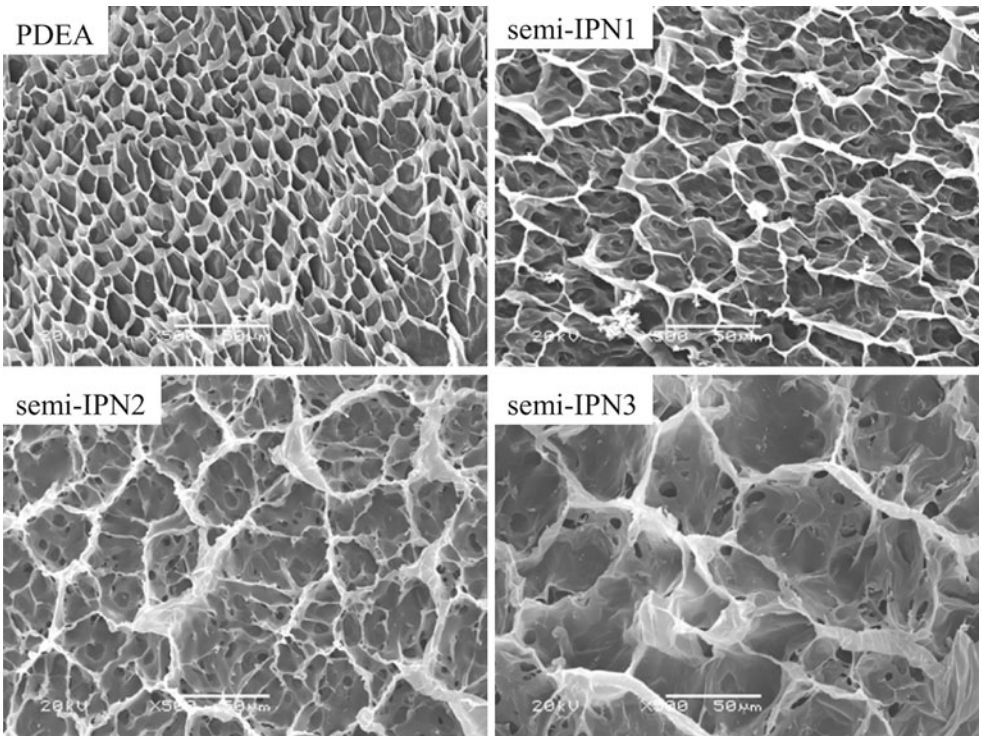



**Fig. 3** SEM images of the PDEA hydrogel and the semi-IPN hydrogels

and nonporous. However, in the semi-IPN network, due to the exist of the linear PDMAEMA polymer, the semi-IPN hydrogels have porous structure with more interconnected channel-like pores surrounded with thin walls and presented a sponge-like morphology [18]. In other words, the higher PDMAEMA content, the more channel-like pores can be observed.

Due to numerous interconnected pores in the hydrogel network, water molecules can easily diffuse. Therefore, incorporating PDMAEMA into the PDEA hydrogel network could enhance the rate of the swelling and deswelling processes [8, 18, 24].

## DSC analysis

Although the semi-IPN hydrogel is a crosslinked polymer, the higher swelling ratio of the hydrogel is defined in this work (the result is discussed in detail below) suggesting the flexibility and the favorable elasticity of the polymer segment. So the dried semi-IPN hydrogel should show obviously $T_g$. DSC thermograms were carried out to gain an insight into the characterization of $T_g$. Experiments showed that semi-IPN hydrogels have obviously $T_g$, meanwhile, the $T_g$ values of the hydrogels can be influenced by the formation of the hydrogel components. From Fig. 4, the $T_g$ values of PDEA hydrogel and the linear PDMAEMA polymer are 63.9 and 43.4 °C, respectively. The value of $T_g$ decreases with the increase of the amount of linear PDMAEMA polymer in semi-IPN hydrogel, and $T_g$ for semi-IPN1, semi-IPN3, semi-IPN4 hydrogels are 63.2, 60.9, 60.2 °C, respectively. When linear polymer is added into the hydrogels, the number of the interconnected pores increase, which could increase the activities of the chain segment, and thereby the $T_g$ of the hydrogels reduces. The SEM data (Fig. 3) described previously also support this

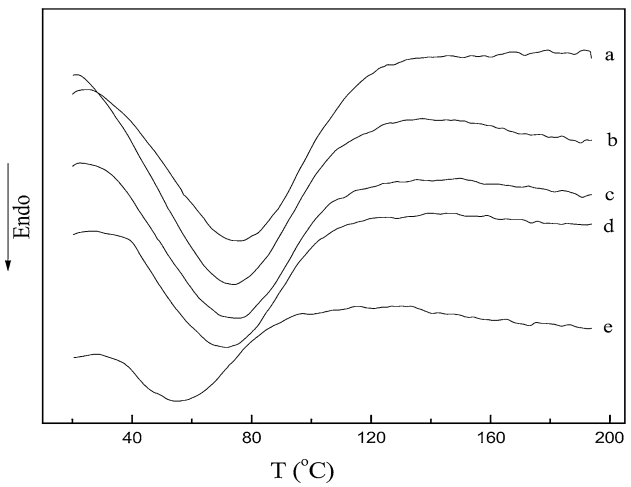



**Fig. 4** DSC thermograms of the PDEA hydrogel (**a**), semi-IPN1 hydrogel (**b**), semi-IPN3 hydrogel (**c**), semi-IPN4 hydrogel (**d**) and the linear PDMAEMA polymer (**e**)

relationship. Furthermore, each hydrogel only have one $T_g$, which shows that the semi-IPN structure hydrogel have good miscibility with their component.

## Effects of temperature and pH on the equilibrium swelling ratio

The equilibrium swelling ratio is one of the most important parameters for evaluating hydrogels because it illustrates their LCST behavior. The swelling behaviors of these hydrogels in water at different temperatures and in buffer solution with different pH values were studied and the results are shown in Figs. 5 and 6.

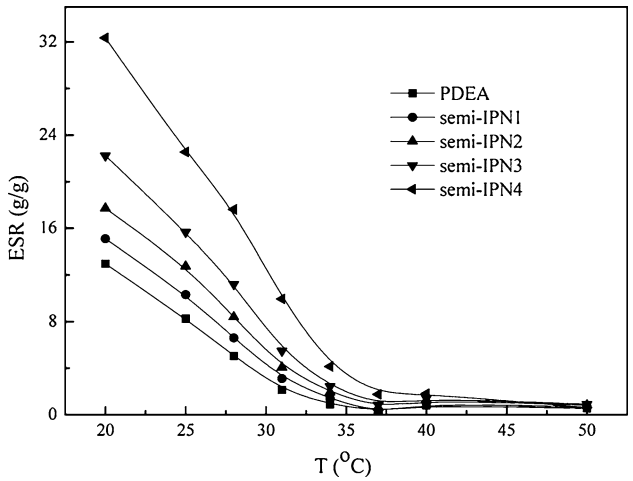



**Fig. 5** Temperature dependence of the ESRs of PDEA hydrogel and semi-IPN hydrogels in double distilled water over the temperature range from 20 to 50 °C

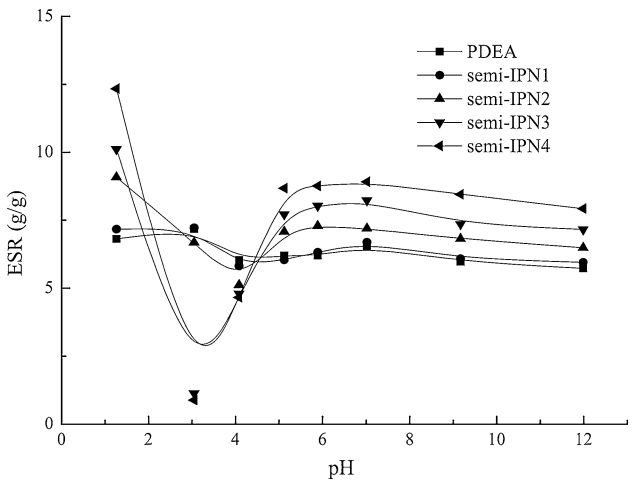



**Fig. 6** ESRs of the PDEA hydrogel and semi-IPN hydrogels in buffer solutions with different pH values at 25 °C

Figure 5 shows the temperature dependence of ESR of the hydrogels with different contents of the PDMAEMA. As clearly seen, at the same temperature (below the LCST), the ESR of the hydrogels increases with the increase of the PDMAEMA content in the corresponding hydrogel. For example, semi-IPN4 has the highest ESR (32.35 g $g^{-1}$) at 20 °C, while the ESRs of semi-IPN3, semi-IPN2, semi-IPN1, and PDEA are 22.23, 17.72, 15.11, and 12.96 g $g^{-1}$, respectively. It is known that there are hydrophilic groups ($–CONR_2$) and hydrophobic groups ($–CH_2CH_3$) in DEA, corresponding to hydrophilic and hydrophobic regions in the PDEA network [5, 7, 8]. At temperature below its LCST, the hydrophilic groups of the PDEA hydrogel bond to water molecules through hydrogen bonds, and these hydrogen bonds behave cooperatively to form a stable shell outside the hydrophobic groups. Therefore, the PDEA hydrogel exhibits a great water uptake [7, 25]. Moreover, the hydrogel compositions have also significant impacted on the swelling behavior, and plays an important role on the swelling ratios [8, 26]. When PDMAEMA is incorporated into the hydrogel network, the hydrophilicity of the resulting hydrogels would increase. Therefore, the higher PDMAEMA content, the more water is contained in the hydrogel below LCST.

From the Fig. 5, the ESR of the hydrogels decreases gradually as the temperature increases from 20 to 50 °C. Moreover, the hydrogels change their appearances from transparent to translucent, even opaque, and all hydrogels exhibited volume phase transition from swelling states to deswelling states. As the external temperature changes, the hydrophilic and hydrophobic balance is changed. The hydrophobic interactions among the hydrophobic groups overwhelm the hydrogen bonds, and phase separation occurs. The data in Fig. 5 also exhibit that the semi-IPN hydrogels have similar temperature dependence as the PDEA hydrogel, and the alike LCST of the PDEA and the semi-IPN hydrogels is in the region of 31 °C [8, 10, 25]. Regardless of the PDMAEMA content of the semi-IPN hydrogels, the linear PDMAEMA chains are uncrosslinked and hydrophilic in the hydrogel network, which are interpenetrated into the PDEA network. No chemical bonding exists between the two components, and each component may keep its own property [18, 26]. Therefore, the hydrophilic/hydrophobic balance in the PDEA chains determines the LCST of the semi-IPN hydrogels.

During the process of temperature increasing, the value of reduction in the ESR of the hydrogels is different. When the surroundings temperature is increased from 20 to 40 °C, semi-IPN4 has the largest alteration in the ESR ($\Delta ESR = ESR_{20°C} - ESR_{40°C}$) which is about 30.55, while the homologous changes in the ESR of semi-IPN3, semi-IPN2, semi-IPN1, and PDEA are about 20.81, 16.47, 14.1, and 12.14, respectively. It suggests that the capability

of the temperature of stimulating hydrogels is enhanced when the content of PDMAEMA in the hydrogels increases. The phenomena result from two factors. Firstly, the pores tend to larger with the increasing content of PDMAEMA. Secondly, the 2-dimethylamino groups in the linear polymer of PDMAEMA improve the hydrophilicity of the network. So the introduced PDMAEMA linear polymer within PDEA network would enhance the deswelling capability. The large change of the ESR is especially beneficial to improve the efficiencies of applications in drug delivery and separation process.

Figure 6 illustrates the ESR of the hydrogels using swelling tests in the pH range from 1.2 to 12 ($I = 0.1$ mol $L^{-1}$) at 25 °C. It is obvious that the ESRs of all the hydrogels change with different pH values. The ESR of the hydrogels in buffer solutions is much lower than that in water due to the high ionic strength in the buffer solutions.

As mentioned above, PDMAEMA can be protonized in acidic solution, which pH-sensitive point is reported to be at about pH 2.5 [5, 27, 28]. When pH is lower than 2, the amine group of the monomer becomes protonated, which increase the charge density on the networks. The internal osmotic pressure would increase when mobile counter ions came into the gels to balance the charge of the group. Thus, the hydrogels became swollen. As pH increases, the ionic PDMAEMA percentage decreases, and a lot of hydrogen bonds would exist among the free amino groups. The hydrogen bonded complex would limit the movement and relaxation of network chains. As a result, a compact hydrogel network is formed, and exhibited a lower ESR. However, as pH increase further, higher ESRs are obtained. This is because the groups (–$COOR_2$ and –$CONR_2$) of the hydrogels are hydrolyzed, and transform into carboxylic acid groups (–$COO^-$) which led to the break of hydrogen bonds and the generation of the electrostatic repulsion among polymer chains [5, 29].

## Swelling dynamics of the hydrogels

Figure 7 demonstrates the swelling behaviors of dried hydrogel samples in water at 25 °C. As the content of PDMAEMA in the semi-IPN hydrogel increases, the swelling rate of the semi-IPN hydrogels increases. In the case of PDEA, its hydrated process was slow and the corresponding swelling ratio reached 6.86 within 180 min, 10.48 within 600 min. While the SR of semi-IPN1, semi-IPN2, semi-IPN3, and semi-IPN4 is about 7.41, 8.03, 9.56, and 12.22 within 180 min, and about 12.11, 13.43, 16.78, and 24.24 within 600 min, respectively. For the semi-IPN hydrogels, due to the existence of PDMAEMA, which acts as water-pervading channels, water molecules may easily diffuse into the hydrogel network, and the expansion of the

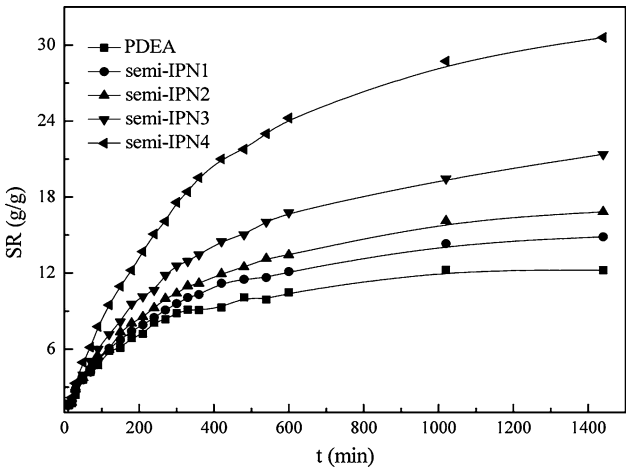



**Fig. 7** Swelling dynamics of the PDEA hydrogel and semi-IPN hydrogels in double distilled water at 25 °C

polymer chains may easily occur [8]. Moreover, during the swelling process, the interconnected pore structure of the semi-IPN hydrogel begins to recover gradually, which also plays an important role and leads to a faster swelling rate, because they could make the water molecules transfer easily between the hydrogel network and the external aqueous phase [15]. Therefore, the swelling rate is improved with the increase of PDMAEMA content due to excellent hydrophilicity and interconnected porous structure.

To obtain a more quantitative comprehension of the nature of the transport kinetic in the hydrogels, the swelling ratio is analyzed as a function of the time for $0 \leq (M_t/M_\infty) \leq 0.6$ [30]. The data were fitted to the following equation:

$$M_t/M_\infty = kt^n \quad (5)$$

where $M_t$ and $M_\infty$ are the weight of water absorbed by the hydrogel at time $t$ and at the equilibrium swollen state, respectively. $k$ is a characteristic constant related to the structure of the hydrogel network, and $n$ is a swelling exponent. The $n$ and $k$ would be calculated from the slope and intercept of the plot of log $(M_t/M_\infty)$ against log $t$, respectively. The value of $n$ should indicate the rate determining step of the swelling mechanism. There are three models, which describe the diverse range of responses of hydrophilic polymer networks to the presence of water. These models are based on the relative rates of penetrate diffusion and polymer chain relaxation [31]. As stated in the above literature, the value between 0.5 and 1 indicates that the water uptake or release is controlled by relaxation and diffusion, which is ascribed to Non-Fickian or anomalous diffusion. The corresponding values for $k$ and $n$ are listed in Table 2. It could be found the swelling exponent, $n$, for the hydrogels are between 0.539 and 0.719. They show that the swelling mechanism would be

**Table 2** Kinetic exponents, $n$, and characteristic constant, $k$, of the hydrogels

| | PDEA | Semi-IPN1 | Semi-IPN2 | Semi-IPN3 | Semi-IPN4 |
|---|---|---|---|---|---|
| $n$ | 0.539 | 0.559 | 0.595 | 0.669 | 0.719 |
| $K \times 10^2$ | 3.39 | 2.72 | 2.14 | 1.32 | 0.96 |
| $R^2$ | 0.967 | 0.993 | 0.989 | 0.986 | 0.994 |

transformed from Fickian diffusion transport to non-Fickian transport. So the PDMAEMA segment in the hydrogels affects the transport model. Besides, from Table 2, all the values of $R^2$ are close to 1, indicating that the re-swelling behavior of the hydrogels follows the Fickian model better.

## Deswelling dynamics of the hydrogels

Figure 8 shows the deswelling rates of hydrogels with different compositions after a temperature jump from 25 to 60 °C. The data illustrate that the semi-IPN hydrogels have a faster deswelling rate and lose more water to the surroundings temperature change than PDEA hydrogel within the same time. For example, PDEA hydrogel loses only 13.99% water within 20 min, while semi-IPN1, semi-IPN2, semi-IPN3 lose about 31.79, 65.24, 73.09% water, respectively. But semi-IPN4 hydrogel loses only 51.95% water.

The deswelling process is complicated because many factors influence and control the deswelling rate. When the PDEA hydrogel is immersed into hot water at 60 °C, the outmost region of the hydrogel would be affected firstly and the hydrophobic interactions among the hydrophobic groups become stronger, which leads a rapid shrinkage of the outmost surface and a dense skin layer. Consequently, the free water molecules in the hydrogel interior are prevented from diffusing out, which results in a slow response rate [8, 12, 32]. The introduction of the hydrophilic linear chains, PDMAEMA, could inhibit the formation of the dense skin layer, and the linear chains act as releasing channels for water molecules when the collapse occurred [8, 12]. The more PDMAEMA introduced into the hydrogel network, the more water-releasing channels formed. Moreover, the interconnected channels in the semi-IPN hydrogels are also favorable to the water release. Therefore, the deswelling rate increases with the increase of the PDMAEMA content from PDEA to semi-IPN3.

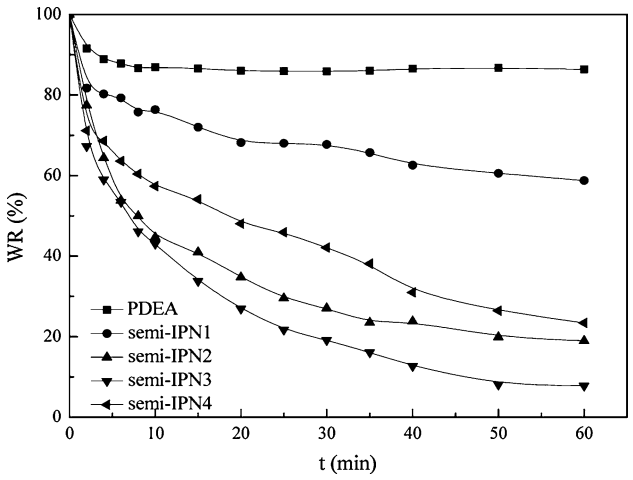



**Fig. 8** Deswelling dynamics of the PDEA hydrogel and semi-IPN hydrogels in double distilled water at 60 °C as measured from an equilibrium swelling state at 25 °C

However, for the semi-IPN4 hydrogel, the deswelling rate is not as fast as we expected. The reason is that much more hydrogen bonds are formed between water molecules and hydrophilic groups in the hydrogel network, which act cooperatively to form a more stable hydration structure around the hydrophobic groups on the PDEA chains. Therefore, the hydrogel needs more energy to destroy these hydrogen bonds, which results in a slow deswelling rate [8]. This characteristic could be advantageously used to adjust the desired responsive rate of the hydrogel.

## Oscillating dynamics of the hydrogels

Considering applications, especially in actuators for drug release regulation or artificial muscle, the oscillating stimuli-responsive swelling behavior of the hydrogels was also investigated.

A stepwise swelling behavior was observed in distilled water at alternating temperatures (between 25 and 60 °C), as shown in Fig. 9a. The swelling ratio is measured every 5 min. It could be seen that all the hydrogels have excellent temperature reversibility. Compared to PDEA, the semi-IPN hydrogels exhibit much rapid, sharper and larger swelling/deswelling changes. The weight change of the oscillating swelling/deswelling increases with the increase of PDMAEMA content, and the more rapid and larger weight change of the oscillating swelling/deswelling is achieved with semi-IPN hydrogel. As mentioned above, due to the hydrophilicity of PDMAEMA polymer and the interconnected porous structures, the semi-IPN hydrogels demonstrate excellent swelling and deswelling rate. Therefore, the semi-IPN hydrogels possess thermo-sensitive reversibility. The data also show that all the hydrogels exhibit a consecutive reduction in the magnitude of SR due to their relatively slower swelling rate when compared with their shrinking rate.

As the same method, a stepwise swelling behavior was observed in buffer solutions ($I = 0.1$ mol $L^{-1}$) with alternating pH values (between 1.2 and 3.0) at 25 °C, as shown in Fig. 9b. The swelling ratio is measured every 1 h. It could be seen that all the hydrogels have excellent pH reversibility, and the larger magnitude of the change SR for

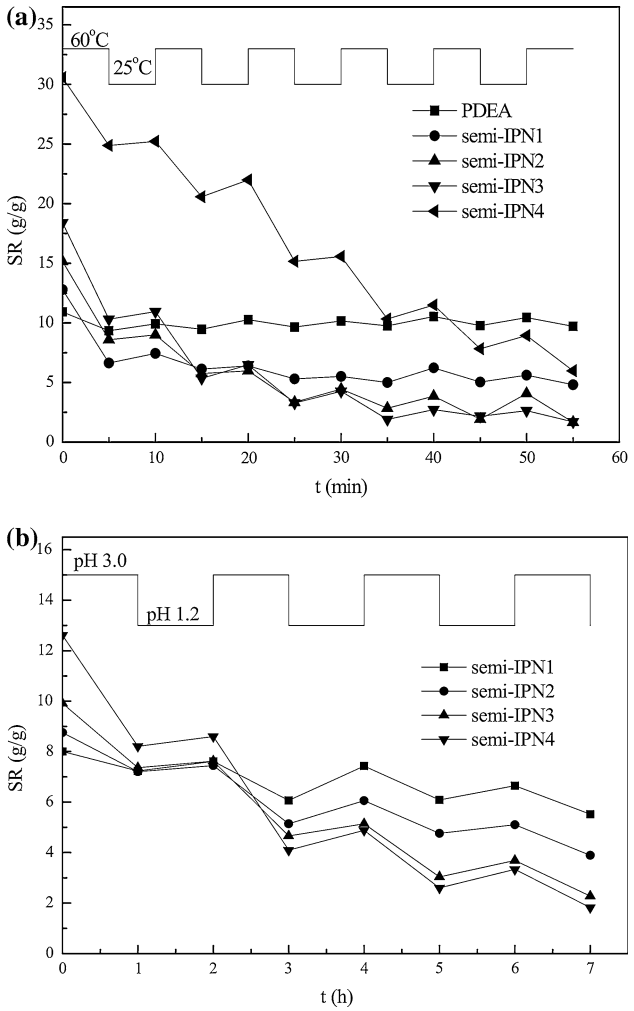



**Fig. 9** Oscillating dynamics of the PDEA hydrogel and semi-IPN hydrogels in distilled water at alternating temperatures (between 25 and 60 °C) (**a**) and in buffer solutions ($I = 0.1$ mol $L^{-1}$) with alternating pH values (between 1.2 and 3.0) at 25 °C (**b**)

the semi-IPN hydrogels in the swelling/deswelling cycle. It was shown that all hydrogels tended to shrink and lost water once the pH value of environment changes. The response rate of the hydrogels to pH changes was inherently slower than that to temperature changes, which was proved in our previous report [33]. This is because the $H^+$ transfers into the hydrogel network from the medium slower which is due to the concentration gradient compared with the heat transfer. So the hydrogel reached equilibrium state within several hours, and the deswelling equilibrium could not been found between successive pH jumps. Moreover, all the hydrogels exhibit a consecutive reduction in the magnitude of SR due to their relatively slower swelling rate when compared with their shrinking rate.

The magnitude of the change SR for the semi-IPN hydrogels in the temperature/pH cycle may be advantageous for practical applications in drug controlled system.

## Drug loading and in vitro drug release of the hydrogels

The interior morphology of PDEA and semi-IPN3 hydrogel before and 4 days after drug loading test (0.05 mol $L^{-1}$) was investigated by SEM. The hydrogels were frozen in liquid nitrogen and lyophilized for 15 h before the test. According to Fig. S1 (see Supporting information), the comparison of the SEM of before (a, c) and after drug loading (b, d) showed that both of the hydrogel samples had a porous three-dimension structure, and from Fig. S1b, d, the drug was distributed throughout the hydrogel networks, meaned the drug solution being sufficiently absorbed by the hydrogel networks for 4 days at 4 °C.

Drug release from a polymer matrix is closely related to many factors such as swelling behavior of polymer matrix, drug affinity to polymer chains, solubility of drug in water, drug change interval of release media [6, 21].

Percent of drug release as a function of time was determined in pH 7.4 and at different temperatures to investigate the influence of temperatures on drug release. Figure 10a shows the cumulative amounts of drug release from the hydrogels at 25 °C. Semi-IPN3 and PDEA hydrogels show an initial burst release of drug, which is also reported [5, 21, 34]. This may be due to that those drugs were located near the hydrogel surface. Since the concentration gradient is the driving force for drug diffusion, high drug concentration gradient between the hydrogel surface and the release medium during the elementary stages of contact leads to a higher initial burst and fast release rate. After the burst period, the hydrogel serves as diffusion barrier and the drug is mainly released by the diffusion mechanism. It can be found that the semi-IPN3 hydrogel exhibits a slower rate of release than the PDEA hydrogel. The mutual interactions between the drug and the hydrogel network would influence the drug release. As mentioned above, the groups $-NH_2$ of the aminophylline have a mutual interaction with the tertiary amine groups of PDMAEMA, which would entrap and prevent the remaining drug from releasing greatly. Therefore, the drug release rate of semi-IPN3 hydrogel is slow.

One of the most attractive characteristic of thermosensitive hydrogels as drug carriers is their intelligent property or adjustable function to external temperature changes [5, 20, 21]. It is important and practical to examine the aminophylline release data from semi-IPN3 hydrogel at the body temperature (37 °C). When the gel is immersed in PBS at 37 °C, the loaded drug inside the hydrogel is essential to maintain a constant concentration gradient. Although the hydrogel is collapsed, the drug release generally involves simultaneous absorption of water and desorption of drug. As shown in Fig. 10b, the release rate of drug at 37 °C is slower than that of at 25 °C. The reason is that the polymer chains are expanded and hence the mesh

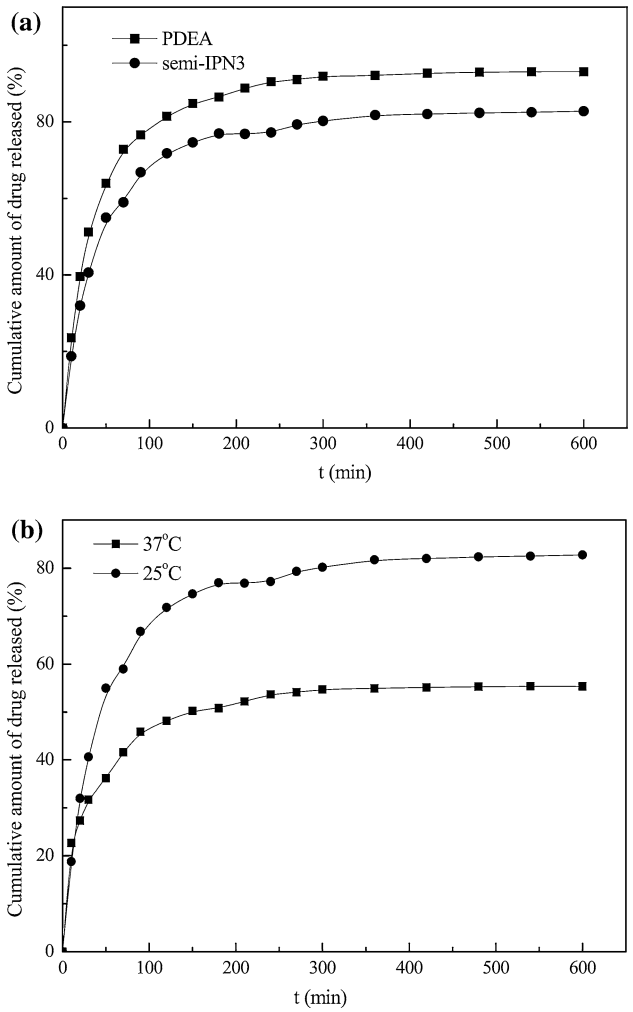



**Fig. 10** **a** Cumulative amounts of drug released from the PDEA hydrogel and semi-IPN3 hydrogel in pH = 7.4 buffer solutions at 25 °C. **b** Cumulative amounts of drug released from semi-IPN3 at different temperatures (25 and 37 °C)

size of pores is larger at 25 °C, while, at 37 °C, the polymers contract thereby decreasing the mesh size, so the rate of drug release is much slower. Therefore, the environment temperature and polymer composition have largely effect on the drug release.

## Conclusions

A series of thermo- and pH-sensitive semi-IPN hydrogels composed of PDMAEMA and PDEA were synthesized from DEA using APS/TEMED as an initiator/accelerator system in the presence of NNMBA as a crosslinker via free-radical polymerization in PDMAEMA aqueous solution. Owing to the introduction of PDMAEMA component, the interconnected porous structure is generated. The larger ESR of the PDMAEMA/PDEA semi-IPN hydrogels was attributed to the synergistic effect of the hydrophilicity of the PDMAEMA chains and the interconnected porous morphology at temperatures below LCST. Moreover, the synergistic effect would also influence the swelling and deswelling dynamics, that is, the different temperature-response rates of the semi-IPN hydrogels can be prepared by modifying the proportion of PDMAEMA to DEA. The oscillating swelling/deswelling behavior of the semi-IPN hydrogels upon temperature changes around LCST depends on the PDMAEMA content. In addition, due to the existence of tertiary amino groups in the chains of PDMAEMA, the semi-IPN hydrogels also possess pH-sensitivity. Compared to PDEA hydrogel, semi-IPN3 hydrogel shows a slower drug release rate, and the drug release rate reduces with increasing temperature, which is expected to obtain hydrogel with improved properties for potential applications in drug controlled system.

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## References

1. Gil ES, Hudson SM (2004) Prog Polym Sci 29:1173
2. Geever LM, Minguez CM, Devine DM, Nugent MJD, Kennedy JE, Hanley A, Higginbotham CL (2007) J Mater Sci 42:4136. doi:10.1007/s10853-006-0912-z
3. Irie M, Miyatake O, Uchida K (1992) J Am Chem Soc 114:8715
4. Sousa A, Maria DA, Sousa RG, Sousa EMB (2010) J Mater Sci 45:1478. doi:10.1007/s10853-009-4106-3
5. Chen J, Liu MZ, Chen W, Zhang NY, Zhu SY, Zhang SP, Xiong Y (2010) J Biomater Sci Polymer Edn. doi:10.1163/092050610X498196
6. Hoffman AS (2002) Adv Drug Deliv Rev 54:3
7. Shibanuma T, Aoki T, Sanui K, Ogata N, Kikuchi A, Sakurai V, Okano T (2000) Macromolecules 33:444
8. Chen J, Liu MZ, Chen SL (2009) Mater Chem Phys 115:339
9. Traitel T, Cohen Y, Kost J (2000) Biomaterials 21:1679
10. Basan H, Gümüsderelíoglu M, Orbey T (2002) Int J Pharm 245:191
11. Lee WF, Lin YH (2006) J Mater Sci 41:7333. doi:10.1007/s10853-006-0882-1
12. Zhang XZ, Yang YY, Chung TS (2002) Langmuir 18:2538
13. Wu XS, Hoffman AS, Yager P (1992) J Polym Sci A 30:2121
14. Li X, Zhang XZ, Chu YF, Xu XD, Cheng SX, Zhuo RX, Wang QR (2006) Eur Polym J 42:2458
15. Yin L, Fei L, Cui F, Tang C, Yin C (2007) Biomaterials 28:1258
16. Lipatov YS (2002) Prog Polym Sci 27:1721
17. Sperling LH, Mishra V (1996) Polymeric materials encyclopedia. CRC Press, Boca Raton
18. Zhao Q, Sun JZ, Ling QC, Zhou QY (2009) Langmuir 25:3249
19. Hoare TR, Kohane DS (2008) Polymer 49:1993
20. Chen SL, Liu MZ, Jin SP, Chen Y (2005) J Appl Polym Sci 98:1720
21. Brazel CS, Peppas NA (1999) Polymer 40:3383
22. Zhang JT, Bhat R, Jandt KD (2009) Acta Biomater 5:488
23. Jin L, Deng YH, Hu JH, Wang CC (2004) J Polym Sci A 42:6081

24. Zhao Q, Sun JZ, Ren H, Zhou QY, Lin QC (2008) J Polym Sci A 46:2222
25. Idziak I, Avoce D, Lessard D, Gravel D, Zhu XX (1999) Macromolecules 32:1260
26. Wander D, Wickramasinghe SR, Hussona SM (2010) J Memb Sci 357:6
27. Zhang Y, Xu L, Yi M, Zhai M, Wang J, Ha H (2006) Eur Polym J 42:2959
28. Mazied NA, Ismail SA, Taleb MFA (2009) Radiat Phys chem 78:899
29. González-Sáiz JM, Fernández-Torroba MA, Pizarro C (1997) Eur Polym J 33:475
30. Hariharan D, Peppas NA (1996) Polymer 37:149
31. Alfrey T, Gurnee EF, Lloyd WG (1966) J Polym Sci Polym Symp 12:249
32. Wang ZC, Xu XD, Chen CS, Wang GR, Wang B, Zhang XZ, Zhuo RX (2008) Colloid Surf B 67:245
33. Liu HL, Liu MZ, Ma LW, Chen J (2009) Eur Polym J 45:2060
34. Luo YL, Zhang KP, Wei QB, Liu ZQ, Chen YS (2009) Acta Biomater 5:316