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Radiation synthesis of poly[(dimethylaminoethyl methacrylate)-*co*-(diallyl dimethyl ammonium chloride)] hydrogels and its application as a carrier for notoginsenoside delivery

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Abstract

Novel pH/temperature sensitive hydrogel was synthesized by radiation induced copolymerization and cross-linking of dimethylaminoethyl methacrylate (DMAEMA) and diallyldimethyl ammonium chloride (DADMAC). Reactivity ratio of DADMAC (r_1) and DMAEMA (r_2) was determined as 1.02 and 0.98, which means that poly(DMAEMA-*co*-DADMAC) is an azeotropic copolymer. Content of DADMAC, i.e., charge density of the hydrogel was found to influence their properties significantly. Compared with polyDMAEMA hydrogel, poly(DMAEMA-*co*-DADMAC) showed enhanced equilibrium degree of swelling (EDS). Low critical solution temperature (LCST) of the hydrogel increased with the charged density. Content of DADMAC had no effect on the pH dependence of the final gel. Aiming at its application as a carrier for Chinese herb extract delivery system, the embedment and pH/temperature dependence of controlled release were investigated using notoginsenoside as a model drug. The maximum embedment amount of notoginsenoside was obtained in a gel containing 3 mol.% DADMAC. The temperature dependence and pH dependence of notoginsenoside release followed the same trend as that of EDS, for instance, higher ratio of notoginsenoside release occurred at 25 °C and pH 1.7, at which higher EDS was obtained. By these means, the release of notoginsenoside can be controlled by adjusting the pH, ionic strength, temperature of solution as well as the composition and structure of the gel.

Keywords: Poly(DMAEMA-*co*-DADMAC); Hydrogels; pH/Temperature stimuli-response; Controlled release; Notoginsenoside; Chinese herb extract

1. Introduction

Chinese herbs have been used as an important class of therapeutic agent in China for centuries

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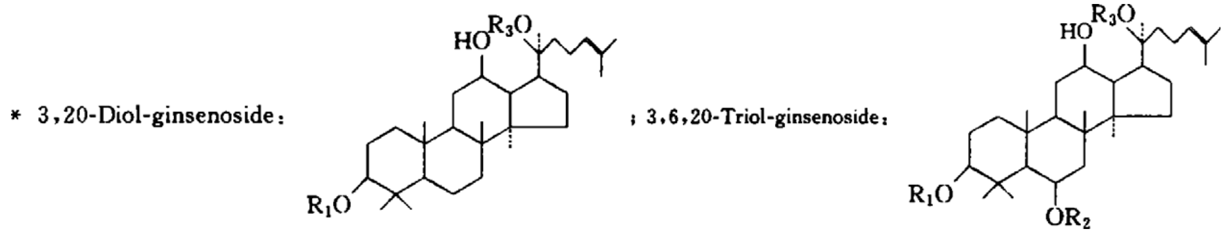

Scheme 1. Structure of ginsenoside.

due to their relative good curative and low side effect to patients. Traditional technology for processing Chinese herbs is time consuming so that Chinese herb extracts are widely used to produce oral medicine recently. However, little study has been done on drug delivery system of Chinese herb. Water-soluble constituents of *Panax notoginsen* (PANS), a famous Chinese herb, and its pharmacological activities have been intensively investigated. PANS compose of notoginsenoside (saponins), polysaccharide, amino acid, protein, peptide and inorganic compounds [1,2]. The main structure of ginsenoside is illustrated in Scheme 1, where R_1, R_2 and R_3 are –H, polypeptide, polysaccharide, amino acid, etc. The ratio of diol-ginsenoside and triol-ginsenoside in PANS extract is ca. 1:3. Notoginsenoside is found to be effective on stanching and curing the wound, accelerate the recovery of liver and a variety of disease; so that notoginsenoside-loaded hydrogel is expected to be an ideal control drug delivery system to prepare wound dressing or oral medicine.

Hydrogels prepared from poly(*N*,*N*-dimethylamino ethylmethacrylate) (polyDMAEMA) and its copolymers have attracted much interest for their thermal and pH-stimuli response. Pure polyDMAEMA hydrogel was reported to show low mechanical stability and ruptured upon swelling [3]. To find a solution, a series of hydrogels prepared from DMAEMA copolymer were synthesized for use as controlled drug delivery system, gene transfer agent etc. Van de Watering et al. synthesized a series of copolymers of DMAEMA with ethoxytriethylene glycol methacrylate (triEGMA), *N*-vinylpyrrodidone [4], methyl methacrylate (MMA) [5], or *N*-isopropyl acrylamide (NIPAAm) [6] to decrease cytoxicity and increase transfection efficiency in delivery of DNA. Kurisawa et al. synthesized the copolymer of DMAEMA, NIPAAm and butylmethacrylate to obtain a thermal controlled vector for DNA delivery [7]. Rungsardthong et al. and Deshpande et al. studied the effect of architecture of polyDMAEMA and poly(ethylene glycol) copolymer on complexes of oligonucleotides and improved the colloidal stability [8,9]. Yuk et al. and Traitel et al. applied the copolymers of DMAEMA with other monomers on improving the controlled release system of insulin [10,11]. Basan et al. investigated that diclofenac sodium releasing pH-sensitive monolithic devices prepared by cross-linking/copolymerization of 2-hydroxyethyl methacrylate with acrylic acid and DMAEMA [12]. In our previous study, polyDMAEMA based hydrogels have been synthesized by gamma or UV radiation, which has been used in adsorption of ReO_4^- [13–17].

In this work, diallyldimethylammonium chloride (DADMAC) is chosen to be the copolymer of DMAEMA. DADMAC is a water-soluble quaternary ammonium compound that can be cyclopolymerized to its corresponding polymer and is widely used in water treatment, paper manufacturing, mining, and biology [18]. It was found in our previous study that polyDADMAC hydrogel could absorb several hundred times of water [19–21]. Furthermore, quaternary ammonium compound is anti-bacterial which takes advantage to serve in medical application. Thus, poly(DMAEMA-*co*-DADMAC) hydrogel is to be synthesized and designed to be used as a carrier for notoginsenoside delivery.

2. Experimental

2.1. Materials

DADMAC (60% in water) was purchased from TCI, Tokyo Kasei Chemical Co. Ltd. (Japan) and used without further purification. DMAEMA was from Acros Chemical Industries (USA) and purified by distillation under reduced pressure. Notoginsenoside solution ($70\ \mathrm{mg} \cdot 2\ \mathrm{ml}^{-1}$) was obtained from Limin Pharmaceutical, Guangdong (China). Cross-linker (*N*,*N*′-methylene bisacrylamide) (Bis), and other reagents were obtained from Beijing Chemical Industry (China) and used as received.

2.2. Preparation and characterization of poly(DMAEMA-co-DADMAC) hydrogels

2.2.1. Reactivity ratio of DADMAC and DMAEMA

DADMAC–DMAEMA mixture solution (total concentration 2.00 mol L^{-1}) was put into glass tube with a diameter of 10 mm. After bubbling with N_2 for 20 min, the tube was sealed and irradiated by γ-ray at a dose rate of 55 Gy min^{-1}. Linear poly(DMAEMA-*co*-DADMAC) of different DADMAC feed were synthesized by radiation with low absorbed dose and purified by precipitating samples in acetone. The total conversion rate of DMAEMA and DADMAC was determined as the ratio of weight of precipitation and feeding. To avoid the formation of gel, the total conversion was controlled to be lower than 10%. ^{1}H NMR spectra of linear poly(DMAEMA-*co*-DADMAC) were measured with a Varian Mercury 200 MHz spectrometer (USA) using D_2O as solvent. The chemical shift of eight H atoms in $-CH_3$ and $-CH_2-$ groups connected to N of DMAEMA and DADMAC was found to locate in the range of 3.0–2.8 and 3.3–3.0 ppm, respectively. Mole fraction of DADMAC in the copolymer (m_1) was calculated from the integrate value of DMAEMA and DADMAC peak according to the method reported by Costas [22] and Kriz [23].

The initial reactivity ratio of DADMAC and DMAEMA was calculated using Fineman–Ross (FR) equation which showed in Eq. (1) [24] and then calculated by curve fitting method to gain the reactivity ratio of DADMAC and DMAEMA (r_1 and r_2), respectively.

$$\frac{M_{10}}{1-M_{10}}\left(2-\frac{1}{m_1}\right)=\frac{1-m_1}{m_1}\frac{M_{10}^2}{(1-M_{10})^2}r_{10}-r_{20} \tag{1}$$

where M_{10} and m_1 were the mole fraction of DADMAC in feed and copolymer; r_{10} and r_{20} represented the initial r_1 and r_2, respectively.

2.2.2. Preparation of poly(DMAEMA-co-DADMAC) hydrogels

DADMAC–DMAEMA mixture with 0.5 mol.% Bis as cross-linking agent was dealt with the same procedure as the synthesis of linear poly(DMAEMA-*co*-DADMAC) copolymer, and then was irradiated by γ-ray until the hydrogels were formed. The hydrogels were carefully removed from the tube and cut into 4 mm slabs.

The poly(DMAEMA-*co*-DADMAC) hydrogels were immersed in deionized water in Soxhlet to extract sol part for 24 h, then were dried in vacuum oven at 40 °C to constant weight. Gel part of poly(DMAEMA-*co*-DADMAC) gels was kept to be used in the following experiments.

Gel fraction of the hydrogel was calculated from Eq. (2).

$$\text{Gel fraction } (\%) = W_g/W_0 \times 100 \tag{2}$$

where W_0, W_g were the weight of dried sample before and after extraction, respectively.

2.2.3. Swelling behavior

The dried gels were immersed in 40 ml deionized water at 25 °C for 48 h. The weight of the equilibrium swollen samples was measured after removing the water on their surface with laboratory tissue. The EDS was defined as:

$$\text{EDS } (\%) = W/W_a \times 100 \tag{3}$$

where W, W_a were the weight of swollen and dried sample, respectively.

Temperature and pH-sensitivity of EDS was investigated by measuring the EDS of the hydrogel at different temperature and pH. LCST of the hydrogels were estimated by measuring their EDS at different temperature in deionized water and determined by DSC. Ionic strength of buffer solutions for pH-sensitive investigation was adjusted to 0.02 mol L^{-1}. Dried gels were immersed in 40 ml buffer solution with different pH in the range of 1.7–10, and then the EDS of the gels in different media were measured.

2.2.4. FTIR analysis

In order to prepare a fine powder, dried gels were pulverized in liquid nitrogen and dried again after pulverization. The KBr pellet for FTIR analysis was make from 2.0 mg thus prepared dried gels and 18 mg KBr. FTIR spectra were recorded using a Bruker vector 22 FTIR spectrometer (Germany).

2.2.5. DSC measurement

The LCST of the hydrogels were determined by differential scanning calorimetry (DSC) using TA 2010 V4.3B DSC instrument. Equilibrium swollen hydrogels with weight of 10–15 mg was sealed in hermetic sample pans. The analysis was performed in the temperature range of 10–80 °C with heating rate of 2 °C $\min^{-1}$ and nitrogen flow rate of 20 ml $\min^{-1}$.

2.3. *Evaluation of poly(DMAEMA-co-DADMAC) hydrogel as a carrier for notoginsenoside delivery*

2.3.1. *Calibration curve for determination of notoginsenoside concentration*

Desired amount (less than 0.10 ml) of 2 mg mL^{-1} notoginsenoside solution was mixed with 0.50 ml of 8 wt.% vanillin methanol solution and 5.00 ml of 77% sulfuric acid solution. After kept at 60 °C for 10 min and then cooled at room temperature for 15 min, the mixture solution was measured at 550 nm by a UV–vis 756MC spectrometer (Shanghai, China). The calibration curve of notoginsenoside showed good linearly ($R = 0.9995$) in the range of 0–200 μg notoginsenoside, while the absorbency was 0.00517 μg^{-1} notoginsenoside.

2.3.2. *Embedment of notoginsenoside*

The dried gels were immersed in 25.0 ml notoginsenoside solution with different concentration. The equilibrium absorption of notoginsenoside into the gels leveled off when the concentration was higher than 6 mg mL^{-1}. Thus, 6 mg mL^{-1} notoginsenoside solution was used in further experiment. The amount of notoginsenoside embedment in the gels was calculated by the Eq. (4):

$$\text{Embedment amount} = \frac{C_0 \times 25.0 - C_t \times [25.0 - (m_e - m_0)/\rho]}{m_0}, \tag{4}$$

where C_0 and C_t were the concentration of notoginsenoside solution before and after gel absorption, respectively. m_e and m_0 were the weight of swollen gel and dried gel, respectively. ρ was the density of the drug solution, which was regard as that of water.

2.3.3. *Release of notoginsenoside*

The gels embedded notoginsenoside were immersed in 20.0 ml deionized water and shaken periodically, and then the concentration of notoginsenoside was measured. The amount of release was calculated as:

$$\text{Amount of release} = C_{rt} \times 20.0 \tag{5}$$

where C_{rt} was the concentration of notoginsenoside in the solution after released.

From Eqs. (4) and (5), the ratio of release was defined as:

$$\begin{aligned}&\text{Ratio of release}(\%)\\&\quad = \text{The amount of release/the amount of}\\&\qquad \text{embedment} \times 100.\end{aligned} \tag{6}$$

3. Results and discussion

3.1. *Copolymerization of DMAEMA and DADMAC*

In the process of radical copolymerization, the reactivity ratio of the monomers is an important parameter that reveals the structure of the copolymer. In this study, the reactivity ratio of DMAEMA and DADMAC was calculated by FR equation and curve fitting method [24]. To avoid the formation of gel, the total conversion was controlled to be lower than 10%. Table 1 shows the data of m_1 which was obtained from the result of ^{1}H NMR, as well as the mole fractions of DADMAC (M_{10}) in feed and corresponding conversion of copolymerization reaction.

Initial reactivity ratios of DADMAC (r_{10}) and DMAEMA (r_{20}) in FR equation were determined as 0.965 and 0.455, while the reactivity ratios of DADMAC (r_1) and DMAEMA (r_2) after curve fitting were 1.02 and 0.98, respectively. Both r_1 and r_2 were approximately equaled to 1, which means that the copolymerization of DADMAC and DMAEMA is an azeotropic one. m_0 was approximately equaled to M_{10} when the fraction of DADMAC was higher than 0.2 and was not affected by the conversion of copolymerization. It is well known that polyDADMAC is strong polyelectrolyte [18] so that the charge density of the copolymer can be regarded as the fraction of DADMAC in the gel. Hence, poly(DMAEMA-*co*-DADMAC) copolymer with desired charge density can be synthesized, while the charge was distributed uniformly along the polymer chains.

Table 1
Some parameters of poly(DMAEMA-*co*-DADMAC)

M_{10} (DADMAC)	0.112	0.218	0.528	0.627	0.816	0.911
Dose (kGy)[a]	0.55	0.83	1.65	1.65	3.30	3.30
Conversion (%)	4.7	8.3	4.0	6.5	6.6	10.0
m_1	0.201	0.237	0.509	0.670	0.866	0.899

[a] Samples was irradiated at dose rate of 55Gy $\min^{-1}$.

3.2. Syntheses and characterization of poly(DMAEMA-co-DADMAC) hydrogels

As mentioned in previous text, pure polyDMAEMA hydrogel showed low mechanical stability and ruptured upon swelling [13,14] so that the hydrogels prepared from copolymers of DMAEMA were demanded to achieve improved properties. In order to improve the swelling property of the gel, poly(DADMAC-*co*-DMAEMA) gels with different amount of DADMAC were synthesized and the effect of charge density on the properties of the gels was investigated as well.

The gels contained 1, 3, 5 and 10 mol.% DADMAC (charge density) were abbreviated as GD-1, GD-3, GD-5, GD-10, respectively. The gel fractions of GD-1, GD-3, and GD-10 at different dose were shown in Fig. 1. It revealed that gelation dose increased and gel fraction at certain dose decreased with increasing the amount of DADMAC feed. After 8 kGy, gel fraction leveled-off.

FTIR spectra of the gels with the range of 1500–1900 cm^{-1} were shown in Fig. 2. Generally methacrylate polymer such as PMMA, HEMA showed a sharp peak at around 1720 cm^{-1}, which is assigned to the ester carbonyl stretching vibration [25,26]. However, in the spectra of GD-1 gel, only one large peak appeared at 1640 cm^{-1}, which might be attributed to the ester carbonyl stretching vibration and the blue shift was caused by the influence of dimethylamino group. With the copolymerization of DADMAC with higher fraction, the peak was split into two components, while the new peak was appeared at 1720 cm^{-1}. Ali Said [27] reported that AAc/DMAEMA copolymer showed two peaks at around 1720 and 1640 cm^{-1}. They assigned 1720 cm^{-1} peak to carbonyl bond of PAAc and 1642 cm^{-1} peak to the intermolecular hydrogen bond between carboxylic groups. This explanation can not be used in our study, the appearing of new peak at 1720 cm^{-1} might be caused by the interaction between DADMAC and DMAEMA to make the carbonyl bond of DMAEMA exist in two statuses.

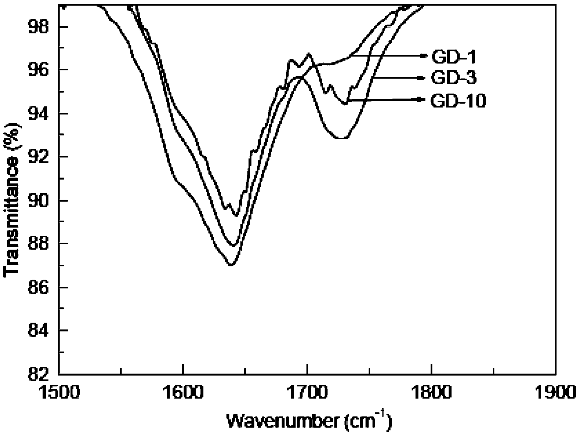

Fig. 2. FTIR spectra of poly(DMAEMA-*co*-DADMAC) copolymer with different amount of DADMAC.

The EDS of the gels with different charge density was illustrated in Fig. 3, showing a very specific effect of charge density on the swelling of poly(DADMAC-*co*-DMAEMA) hydrogels, for instance, the EDS of the hydrogels first increased sharply up to

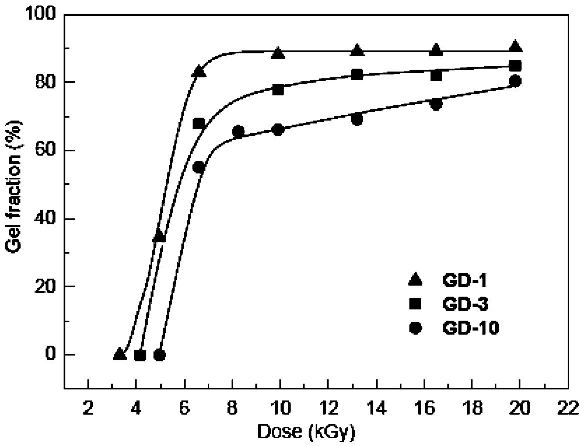

Fig. 1. Gel fraction as a function of absorbed dose for poly(DMAEMA-*co*-DADMAC) hydrogels with different amount of DADMAC.

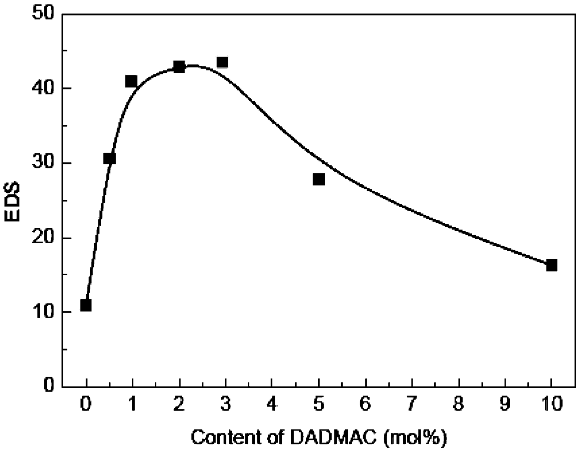

Fig. 3. Effect of DADMAC amount on the EDS of poly(DMAEMA-*co*-DADMAC) hydrogels.

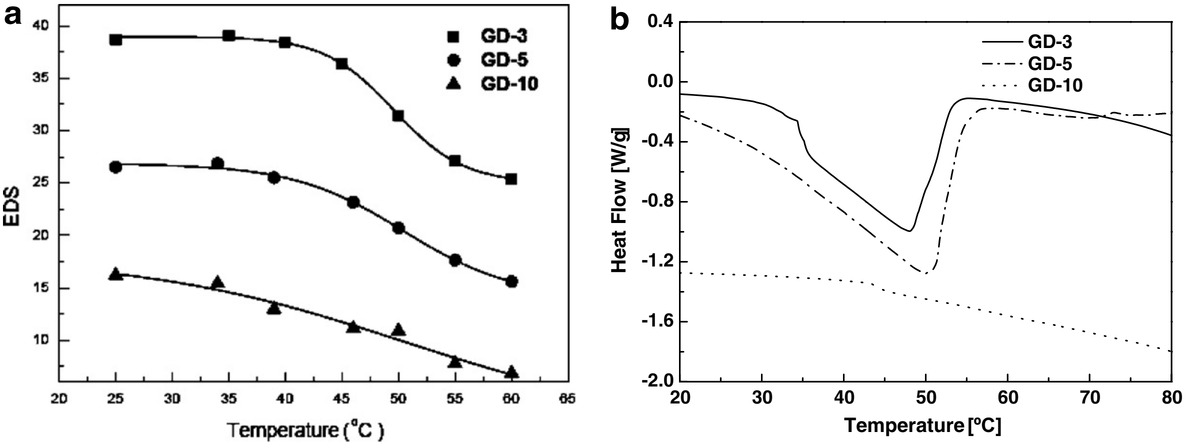

Fig. 4. Effect of DADMAC amount on the temperature sensitivity of poly(DMAEMA-*co*-DADMAC) hydrogels.

a charge density of 3% and then decreased remarkably with the increasing charge density. Generally the increasing number of ionic groups in the hydrogels led to an increment of their swelling capacity due to the additional osmotic pressure provided by counterions inside the gel. However, Oguz and Durmaz reported a similar charge density effects on elastic modulus and the swelling of another strong polyelectrolyte hydrogel based on acrylamide and 2-acrylamido-2-methylpropane sulfonic acid sodium salt (AMPS) [28]. The elastic modulus of the hydrogels was found to be first increased up to 5% charge density and then decreased continuously with increasing charge density due to the presence of a large fraction of excessive counterions in the gel which were ineffective in swelling process. Similar phenomenon was observed in a partially charged poly(4-vinyl pyridine) (P4VP) gel [29], i.e., when a charged group was introduced into a hydrophobic polymer matrix, an increase in polymer charge density does not always lead to increasing of EDS and gel collapse is possible to occur. The collapse was ascribed to the ion-pair formation between polymer charges and counterions, which lead to the formation of ionomer-type multiplet or ion cluster. The explanations of these two papers were essentially the same, and such gel collapse was called coil-globule transition which was more favorable for counterions which are strongly bound with the relevant polymer charged group. This statement can be supported by the fact that the critical charge density for gel collapse of strong polyelectrolyte such as AMPS and poly(DADMAC-*co*-DMAEMA) hydrogels (ca. 3–5%) were much lower than that of weak polyelectrolyte, i.e. partially charged P4VP gel (>30%).

As stated in previous text, polyDMAEMA hydrogel is one of the most important intelligent function materials with temperature and pH-stimuli response so that the influence of DADMAC to these properties is to be investigated. Fig. 4(a) illustrated the effect of charge density on the temperature-stimuli swelling of poly(DADMAC-*co*-DMAEMA) hydrogels in terms of EDS. Compared with polyDMAEMA [14], the volume transition with increasing temperature was only apparent for GD-3 and the temperature sensitivity became insignificant in hydrogels containing higher amount of DADMAC. To obtain more detail information on the temperature-stimuli response of the hydrogel, swollen sample of poly(DADMAC-*co*-DMAEMA) hydrogels were determined by DSC and showed in Fig. 4(b). The minimum temperatures of DSC endotherms were defined as the LCST of the hydrogel and the LCST of GD-3, GD-5 were determined to be 48.0 °C and 50.0 °C, respectively. The LCST for GD-3 and GD-5 were very close to that of PDMAEMA (50 °C in our unpublished work and literature data [30]) and the LCST for GD-10 was undetectable under the established experiment condition. These results were similar with that reported by Feil et al. and Gan et al. [31,32], i.e., increasing charge density leads to a large increase in LCST and no phase separation occurred if more than ca. 4 mol.% of the monomer was charged. The LCST for GD-3, 5 was proved to increase with increasing charge density and the less sensitive response of GD-10 was assumed to be caused by the presence of large

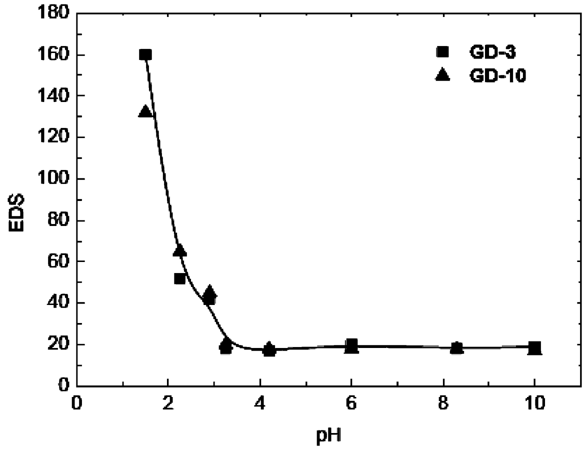

Fig. 5. pH as a function of EDS for poly(DMAEMA-*co*-DADMAC) hydrogels with different amount of DADMAC.

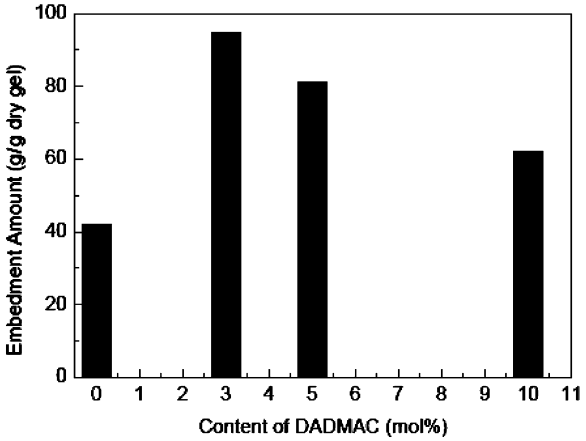

Fig. 6. Effect of DADMAC amount on the embedment of notoginsenoside into poly(DMAEMA-*co*-DADMAC) hydrogels.

amount of ion cluster inside the hydrogel which resulting in a compact status of the hydrogel.

pH-sensitive point of polyDMAEMA hydrogel was reported to be at around pH 2.5, which was ascribed to the protonation of the tertiary amino group [13]. Fig. 5 showed the EDS of poly(DMAEMA-*co*-DADMAC) hydrogel with charge density of 3% and 10% in buffer solutions with different pH. The EDS of the gel decreased significantly with increasing ionic strength of solution and then leveled off when the ionic strength was higher than 0.02 mol L^{-1} (data not show). For this reason, the ionic strength of buffer solutions was adjusted to 0.02 mol L^{-1} to avoid the influence of ionic-strength to the swelling of hydrogel. It is clear that the copolymerization of DADMAC had no effect on the pH-stimuli response of polyDMAEMA. The EDS of the gel was rather high in acidic buffer (pH 1.5–3) and deswelled dramatically with the increase of pH, the curve leveled off when pH is higher than 3.3. The EDS of the gel at pH 1.7 was ca. 9 folds to that at pH 7. This property should be very attractive in the application of pharmaceutical industry.

3.3. Embedment and release of notoginsenoside

The concentration of notoginsenoside for drug embedment was 6 mg mL^{-1} which was decided by a saturated absorption test. It was found that the saturated absorption of notoginsenoside increase with increasing the concentration of notoginsenoside up to 6 mg mL^{-1} and reach a constant value in solutions with higher notoginsenoside concentration. The effect of charge density on the embedment of notoginsenoside in poly(DADMAC-*co*-DMAEMA) hydrogels was illustrated in Fig. 6. It showed that the amount of embedment got a maximum value at GD-3 probably due to its excellent swelling capacity compared with other gels. Thus, GD-3 prepared under a condition of total monomer amount 2 mol L^{-1}, Bis 0.5%, dose rate 55 Gy min^{-1} and absorbed dose 19.8 kGy, following with drug embedment at 6 mg mL^{-1} notoginsenoside solution was chosen to be used in drug release investigation.

The effect of temperature on the release of notoginsenoside from notoginsenoside-loaded poly(DMAEMA-*co*-DADMAC) gels was illustrated in Fig. 7. The time course of notoginsenoside release at 25, 37 and 45 °C was investigated. The release curves were sharp in the first 5 h and reach equilibrium after 10 h at 45 °C while it took around

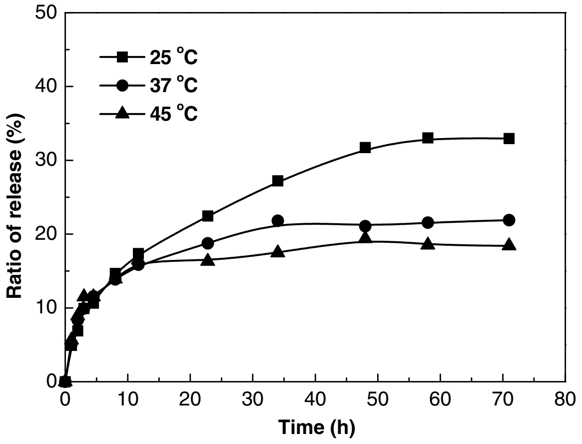

Fig. 7. Time course of notoginsenoside release from poly(DMAEMA-*co*-DADMAC) hydrogels at different temperature.

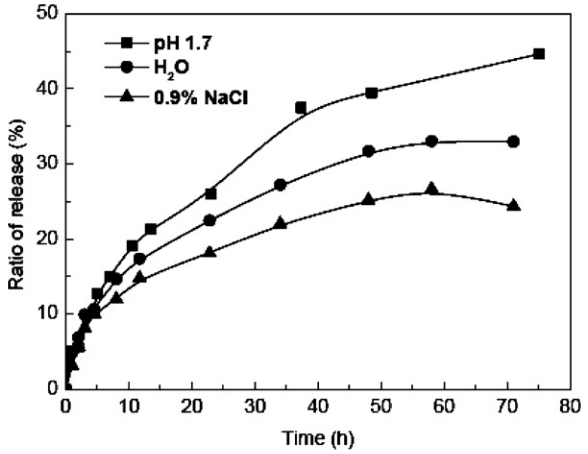

Fig. 8. Time course of notoginsenoside release from poly(DMAEMA-*co*-DADMAC) hydrogels in different media. The ionic strength of pH 1.7 solution was adjusted to the same as 0.9% NaCl solution.

2 days at 25 °C. The ratio of notoginsenoside release was remarkably higher at 25 °C than at 45 °C after 7 h and the equilibrium release amount was higher at former one. The cease of notoginsenoside release after 10 h at 45 °C might be caused by the shrinking of the gel at higher temperature and it implied that the pore of the gel was closed at a temperature higher than LCST. The curve of 37 °C was very close to that of 45 °C and the equilibrium notoginsenoside release at 37 °C was 20%.

Ratio of notogensenoside release as a function of time was determined in acidic buffer (pH 1.7) and 0.9% NaCl to investigate the influence of pH and ionic strength to drug release, the result obtained in deionized water was plot together for comparison (Fig. 8). Among the three media, highest ratio of notoginsenoside release was occurred in acidic media. On the contrary, ratio of notoginsenoside release was lowest in 0.9% NaCl which means that the drug release ability of the gel decreased in the presence of salt. The sequence of drug release ratio followed the sequence of EDS. It again implied that the size of pores was lower in low EDS gel, leading to a result of lower ratio of drug release. The release of notoginsenoside can be controlled by adjusting the pH, ionic strength, temperature of solution as well as the composition and structure of the gel.

4. Conclusion

Temperature/pH-sensitive hydrogels were synthesized from DMAEMA and DADMAC by γ-radiation. Poly(DMAEMA-*co*-DADMAC) was an azeotropic copolymer so that the fraction of each composition was the same as that in feed. Effect of charge density on EDS, temperature and pH-stimuli response of EDS was investigated. The EDS of the gel was significantly improved with the copolymerization of DADMAC especially with the addition of ca. 3% DADMAC. Temperature sensitivity remained apparently up to the existence of 5% DADMAC with LCST of ca. 50 °C. pH sensitivity of the gel was not affected by charge density and the EDS changed dramatically at a narrow range, i.e., pH 1.5–3.

Some properties concerning the application as drug delivery system of the gel using notoginsenoside as model drug has been carried on. Maximum embedment amount of notoginsenoside occurred in a 3% DADMAC gel. The release of notoginsenoside was temperature/pH- and ionic strength dependent, which was in good accordance with the counterpart effect on the EDS. The release ratio of notoginsenoside at 25 °C was around two times of that at 45 °C. A higher release amount was obtained at acidic media, for instance, pH 1.7 than neutral status. The drug release was hindered in a salt solution. These results indicated that the drug delivery of the gel was influenced by the structure of the gel and the release of notoginsenoside can be controlled by adjusting the pH, ionic strength, temperature of solution as well as the composition and structure of the gel.

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