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# Synthesis and characterization of poly(methoxyl ethylene glycol-caprolactone-*co*-methacrylic acid-*co*-poly(ethylene glycol) methyl ether methacrylate) pH-sensitive hydrogel for delivery of dexamethasone

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ABSTRACT

In this work, a novel pH-sensitive hydrogels based on macromonomer of methoxyl poly(ethylene glycol)–poly(caprolactone)-acryloyl chloride (MPEG-PCL-AC, PCE-AC), poly(ethylene glycol) methyl ether methacrylate (MPEGMA), and methacrylic acid (MAA) were successfully synthesized by heat-initiated free radical polymerization method. The obtained macromonomers and hydrogels were characterized by $^1$H NMR and FT-IR, respectively. Morphology study, swelling behavior, *in vitro* drug release behavior, acute oral toxicity of hydrogels, and cytotoxicity of PCE-AC macromonomer were also investigated in this paper. Finally, the hydrogels demonstrated that the sharp change in different pH value, thus believing to be promising the suitability of the candidate for oral drug-delivery systems.



## 1. Introduction

Hydrogels are three-dimensional polymeric networks those swell quickly by imbibing a large amount of water or deswell in response to the changes of the external environment (Bajpai and Singh, 2006; Xu et al., 2006; Singh et al., 2007; Ju and Kim, 2001; Taşdelen et al., 2004). In the last decades, considerable attentions have been focused on the ability of hydrogels that are able to alter their volume and properties in response to environmental stimuli such as pH, temperature, ionic strength, and electric field (Liu et al., 2007; Huang et al., 2007; Zhang et al., 2005; Shin et al., 2003). Moreover, they might have great potential in targeted drug delivery system, protein–ligand recognition, on–off switches for modulated drug delivery or artificial organs, and immobilization of enzyme (Suzuki and Tanaka, 1990; Miyata et al., 1999; Li et al., 2006; Zhang et al., 2004). In more recent years, hydrogels have become popular carriers for drug delivery applications, especially for oral drug delivery, due to their biocompatibility and resemblance to biological tissues (Yin et al., 2009; Feng et al., 2009; He et al., 2009; Rekha and Sharma, 2009; Sweet et al., 2009). It is known that the oral route is the most convenient and comfortable way of administering drugs (Guo and Gao, 2006). By oral administering drugs directly to the site of action, hydrogel could be lower to the dose necessary for optimal treatment and a mount of side effects normally encountered when drugs are released and adsorbed in the upper gastro-intestinal tract (GIT).

Poly(ethylene glycol) methyl ether (MPEG) and poly($\varepsilon$-caprolactone) (PCL) are materials that are both biocompatible and have been used in several FDA approved products. PCL is a kind of biodegradable and non-toxic with great permeability (Albertsson and Varma, 2003; Zhu et al., 2007). In our previous work (Chen et al., 2008; Wang et al., 2009; Chao et al., 2008), a novel of pH-sensitive hydrogels had been synthesized with incorporation of PCL segment into P(MAA-MEG) hydrogel backbone. As advance smart drug delivery systems, pH-sensitive hydrogels act as a very important role (Iemma et al., 2006; Colinet et al., 2009; Qiu and Park, 2001). They had been investigated widely as site-specific drug delivery carriers to specific regions of the gastro-intestinal tract because of their adjustable swelling behavior in aqueous medium, which can control the drug release rates in a mild manner. At low pH value, the drug is sustained in the hydrogel, whereas in high pH, the drug can be released (George and Abraham, 2007; Gao et al., 2009; Lee et al., 2009; Dergunov and Mun, 2009).

For the treatment of inflammatory bowel disease (IBD), with anti-inflammatory agents, various approaches have the potential to address important unmet therapeutic needs including oral administration and have been used to target the drug molecules to the colon. A common goal in assessing oral drug delivery is correlation of *in vitro* and *in vivo* drug dissolution in the gastro-intestinal tract (GIT) (Friend, 2005). Dexamethasone is a synthetic steroidal anti-

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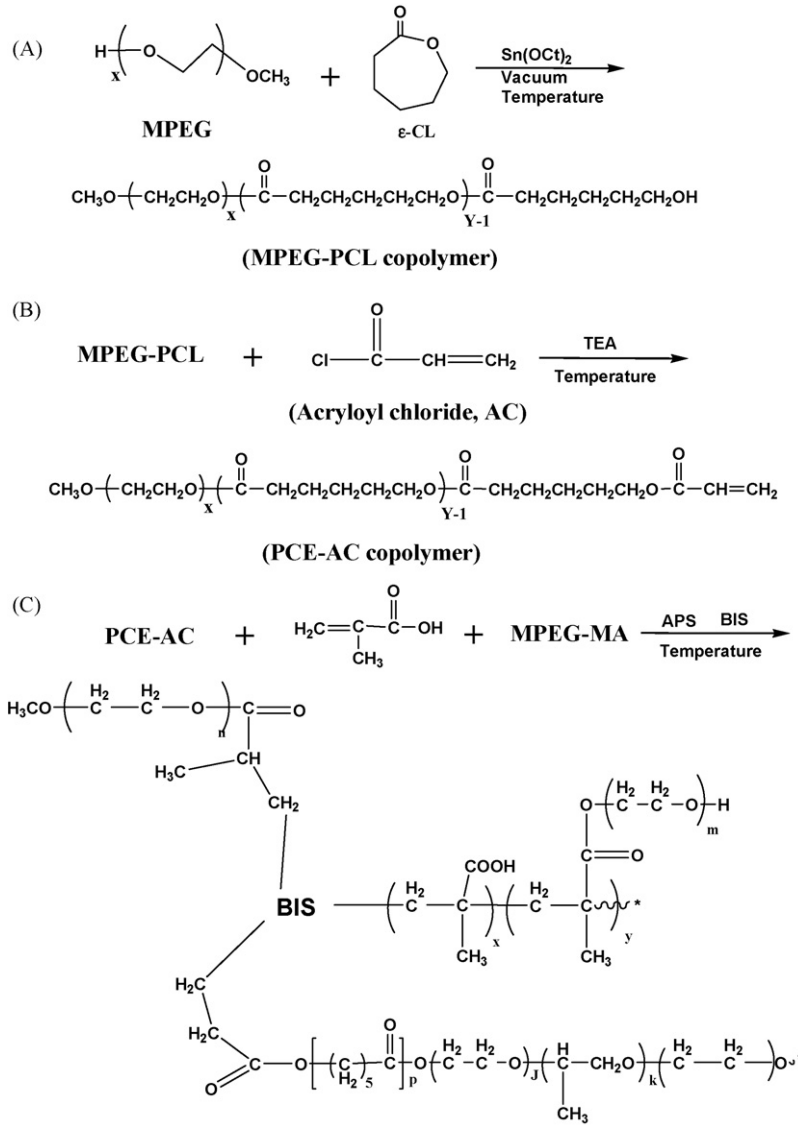



**Scheme 1.** Material synthesis: (A) synthesis of MPEG-PCL copolymer; (B) synthesis of PCE-AC copolymer; (C) synthesis of P(CE-MAA-MEG) hydrogel.

inflammatory drug (Kim and Chauhan, 2008). It has been incorporated into bioresorbable systems for several uses. Dexamethasone-containing pH-sensitive hydrogels, whose swelling depends on the environmental pH (e.g., in the GIT), were investigated for treatment of inflammatory bowel disease (IBD), and to control the inflammatory reaction at the site of GIT (Zilberman, 2005). This approach attempts to lower the absorption and release of the dexamethasone in the stomach and small intestine and thereby facilitate quantitative dexamethasone delivery to the colon.

In this study, a new kind of oral drug delivery system based on pH-sensitive P(CE-MAA-MEG) hydrogel through heating-initiated free radical polymerization method was successfully prepared. The swelling behavior is considerably investigated in detail. Cell viability assay of HEK293 cells were used to evaluate the cytotoxicity of PCE-AC copolymer (Shi et al., 2009; Gong et al., 2009b). And the safety of P(CE-MAA-MEG) hydrogel was evaluated *in vivo* by acute toxicity test in BALB/c mice because the safety evaluation of this hydrogel matrix is extremely important for its further application in biomedical fields (Chen et al., 2008; Gong et al., 2009b,c). *In vitro* dexamethasone release behavior from P(CE-MAA-MEG) hydrogel was studied in detail. Consequently, it is a suggesting candidate for being used as oral drug-delivery systems.

**Table 1**
The demonstrated hydrogels.

| Sample | CE:MPEG:MAA | PCL content (wt%)[a] | BIS content (wt%) | RI |
|---|---|---|---|---|
| S-1 | 40:30:30 | 14 | 6 | 34.7 |
| S-2 | 50:25:25 | 17.5 | 6 | 30.1 |
| S-3 | 30:35:35 | 10.5 | 6 | 48.1 |

[a] Calculated as following: PCL content = weight of PCL/weight of (CE + MAA + MPAA).

## 2. Materials and methods

### 2.1. Materials

Poly(ethylene glycol) methyl ether (MPEG, Mn = 2000), ε-caprolactone (ε-CL), *N,N′*-methylene-bis-acrylamide (BIS), methacrylic acid (MAA), poly(ethylene glycol) methyl ether methacrylate (MPEGMA, MEG, Mn = 475), tin (II) 2-etheylhexanoate, acryloyl chloride (97%), and ammonium persulfate (98%) (APS) were all analytical grade, and purchased from Aldrich Company, USA. All other reagents were also analytic grade and used as received.

BALB/c mice of both sexes weighing 20 ± 2 g were used in oral acute toxicity test and histopathological observations. The animals were purchased from Laboratory Animal Center of Sichuan University. Animals were sex-separately housed in an animal facility of IVC class (Certificate 011, by Sichuan provincial committee for experimental animal management), at controlled temperature of 20–22 °C, relative humidity of 50–60% and 12 h light–dark cycles. Free access to food and water was allowed. All the animals would be in quarantine for a week before treatment.

### 2.2. Synthesis and purification of P(CE-MAA-MEG) hydrogel

MPEG-PCL was synthesized by ring-opening polymerization (ROP) of ε-caprolactone initiated by MPEG2000 using tin (II) 2-etheylhexanoate as catalyst, which is similar to the method reported before (Wang et al., 2009). The obtained MPEG-PCL macromonomer was precipitated from cold petroleum ether and dried in vacuum at 25 °C. After polymerization, MPEG-PCL macromonomer was first dissolved in AR grade DCM, with a considerable amount of triethylamine, and reacted with acryloyl chloride at 40 °C, allowing reflux for 4 h according to Scheme 1. The products were purified by repeated dissolution into DCM and precipitated by cold petroleum ether and dried in vacuum at 25 °C. In the following text, MPEG-PCL-AC macromonomer was denoted as PCE-AC for simplification.

P(CE-MAA-MEG) hydrogel was synthesized by heat-initiated free radical polymerization with APS as heat-initiator and BIS as cross-linker. The mixture of PCE-AC macromonomer (40 wt%), MAA (30 wt%), MPEG-MA (20 wt%), BIS (10 wt%), and APS (6%w/w of the total monomers) was dissolved in *N*,*N*′-dimethyl-sulfoxide (DMSO) (6 ml), then the mixture was poured into a weighing bottle and heated to 37 °C with nitrogen for about 1 h according to Scheme 1.

The just obtained P(CE-MAA-MEG) hydrogel hydrogel was immersed in distilled water for 7 days, and the water was refreshed everyday in order to remove excess DMSO. The purified hydrogels were first dried at room temperature for 1 day, and then dried at 40 °C under vacuum for 7 days. The dried hydrogels were kept in air-tight bags before use. The obtained samples in this work were shown in Table 1.

### 2.3. Fourier transforms infrared (FT-IR) analysis

FT-IR (KBr) spectra of the hydrogel sample and the macromonomers were recorded on NICOLET 200SXV spectrophotometer (Nicolet).

### 2.4. $^1H$ NMR

$^1H$ NMR spectrum (in $CDCl_3$) was recorded on Varian 400 spectrometer (Varian, USA) at 400 MHz using tetramethysilane as internal standard.

### 2.5. Scanning electron microscopy (SEM)

SEM was employed to investigate morphology of P(CE-MAA-MEG) hydrogel and drug-loaded hydrogel. The hydrogels were immersed in pH 1.2 and pH 6.8, respectively. And were frozen in liquid nitrogen and lyophilized for 72 h. Then, the hydrogels were sputtered with gold before observation. In this study, morphology of prepared particles was examined on JEOL SEM (JSM-5900LV, JEOL, and Japan).

### 2.6. Cytotoxicity assay of PCE-AC copolymer

Cytotoxicity of PCE-AC copolymer to human HEK 293 cells was evaluated by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) assay. All media were supplemented with 10% of fetal bovine serum (FBS) and 1% of PS, and were maintained in a 37 °C incubator with a humidified 5% $CO_2$ atmosphere. Both of cells were seeded in 96-well plates at a density of 2× 10,000 cells per well in 100 μl of medium and incubated overnight 24 h later, the cells were incubated in DMEM (HEK293) medium in the presence of a series of PCE-AC copolymer of different concentration for 24 and 48 h, respectively. After 48 h, the cell cultures were washed with PBS solution and MTT assay was conducted. Untreated cells were taken as control with 100% viability. The cell cytotoxicity of PCE-AC copolymer is defined as the relative viability, which is the ratio of the number of live cells to that of the control cells (100%).

### 2.7. Dynamic swelling/deswelling kinetics

The dynamic swelling/deswelling experiment was conducted by measuring the humid weight of the hydrogels immersed in aqueous medium with different pH value (pH 1.2 and 6.8) at 37 °C. The dried hydrogels about 0.1 g were first immersed in aqueous medium at pH 1.2 for 10, 20, 40, and 60 min, respectively. The surplus surface water was removed by filter paper, and then the humid weight was measured carefully. After the hydrogel was put in another aqueous medium at pH 6.8, and the swelling ratios at different time points were measured too. The pulsatile swelling/deswelling behavior was observed in aqueous medium with alternate pH value of 1.2 and 6.8 at 37 °C. The swelling ratios were calculated by following Eq. (1):

$$\text{Swelling ratio (SR)} = \frac{W_t}{W_0} \times 100\% \quad (1)$$

where $W_0$, being the initial dry weight and $W_t$ the wet weight of the small molar hydrogel at time $t$, respectively.

In the previous article (Chao et al., 2008), we define a responsive index (RI), which was used to personification pH sensitivity of the hydrogel. RI was calculated by following Eq. (2):

$$\text{RI} = \text{SR}_{(\text{pH 6.8}),\ t=120} - \text{SR}_{(\text{pH 1.2}),\ t=180} \quad (2)$$

where $\text{SR}_{(\text{pH 6.8}),\ t=120}$ and $\text{SR}_{(\text{pH 1.2}),\ t=180}$ is the swelling ratio at $t$ = 120 min (pH 6.8) and $t$ = 180 min (pH 1.2) respectively.

RI was defined as the difference between equilibrium swelling at pH 6.8 and pH 1.2. As RI increases, the difference between equilibrium swelling at pH 6.8 and pH 1.2 enhanced, which indicated that pH sensitivity of the hydrogel increased accordingly. The results were listed in Table 1.

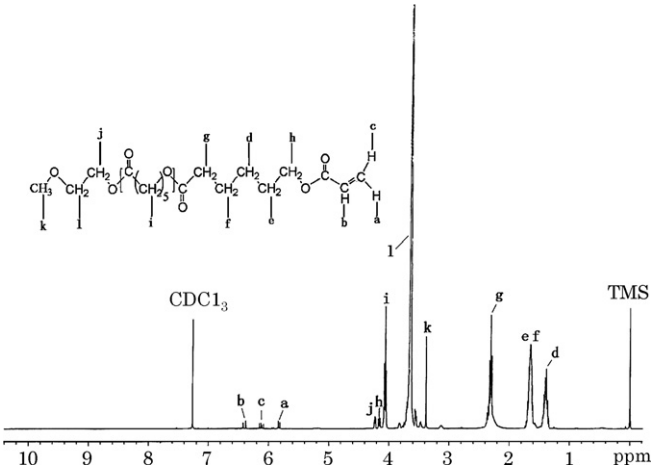



**Fig. 1.** $^1H$ NMR spectrum of PCE-AC macromonomer (in $CDCl_3$).

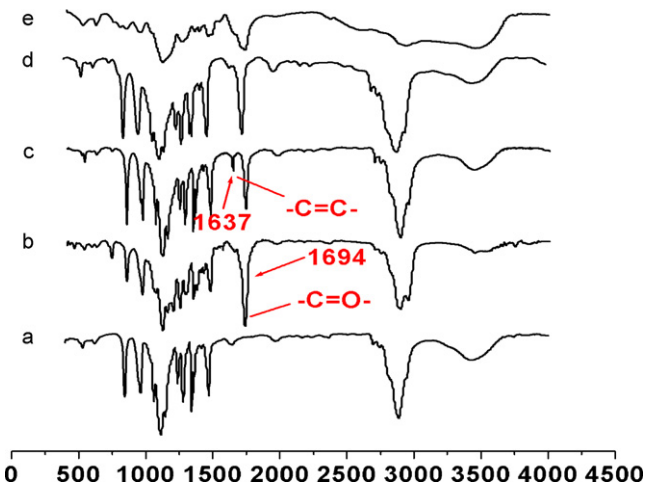



**Fig. 2.** FT-IR spectra of (a) MPEG; (b) MPEG-PCL; (c) PCE-AC; (d) P(CE-MAA-MEG) hydrogel; (e) dexamethasone loading hydrogel.

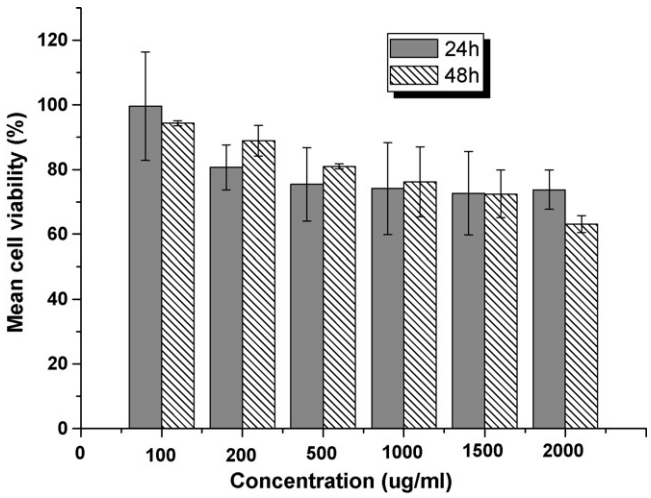



**Fig. 4.** The HEK293 cell viability assay. Cell containing 2× 10,000 cells in DMEM containing 10% FBS was incubated with PCE-AC copolymers in 96-well in a humidified atmosphere containing 5% $CO_2$ at 37 °C for 24 h and 48 h, respectively.

### 2.8. Acute oral toxicity test and histopathological study

The acute oral toxicity was generally defined as the adverse effects occurring within a short time after oral administration of a single dose of a substance or multiple doses in 24 h. Owing to great biodegradability and biocompatibility of P(CE-MAA-MEG) hydrogel and our preliminary experiment, no lethal dose or median lethal dose ($LD_{50}$) could be detected. We estimated the oral acute toxicity of P(CE-MAA-MEG) hydrogel using maximal tolerance dose (MTD) method.

Twenty mice of both sexes were equally divided into two groups ($n$ = 10, 5male and 5 female mice), and fasted over night, with water allowed to access freely. The mice were orally administrated with P(CE-MAA-MEG) hydrogel suspension twice (4 h intervals) in the volume of 0.2 ml/10 g b.w., at a dose of 10 g/kg b.w. So, the total dose given to each animal was up to 20 g/kg b.w.

All the animals were observed continuously for 14 days after administration, including mortality and the general conditions (the energy activity, hair, feces, behavior pattern, and other clinical signs).

### 2.9. Drug loaded into hydrogel

10 mg of dexamethasone was added into hydrogel during the heat-initiated free radical polymerization process. After polymerization, drug-loaded hydrogel was immersed in distilled water for 1 day. The purified drug-loaded hydrogel was first dried at room temperature for 1 day, and then dried at 40 °C under vacuum for 7 days. The dried hydrogels were kept in air-tight bags before use.

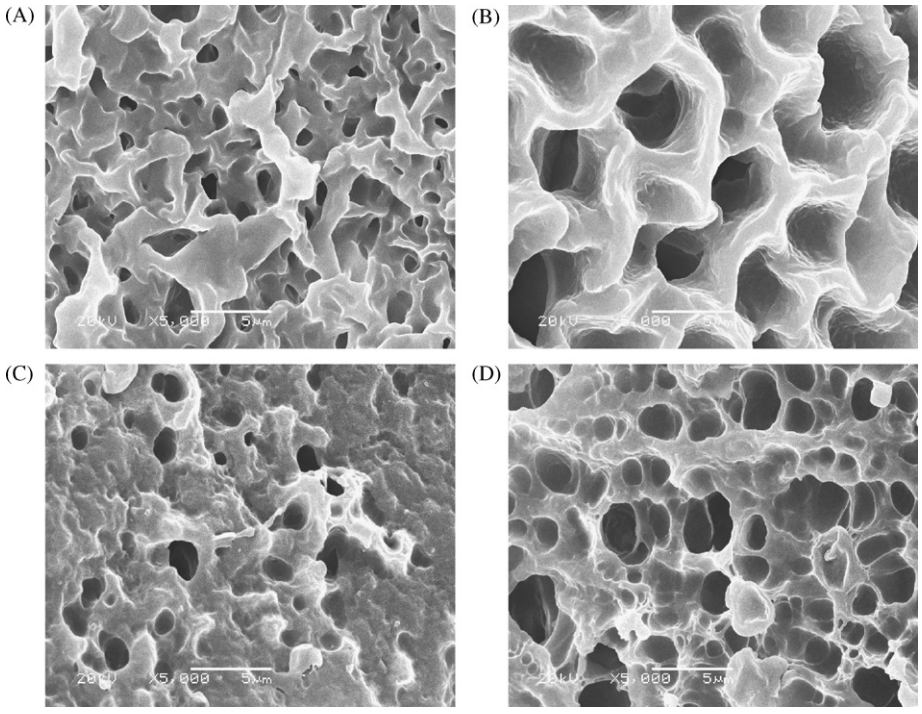



**Fig. 3.** SEM observation of (A) blank hydrogel in pH 1.2; (B) blank hydrogel in pH 6.8; (C) dexamethasone loaded hydrogel in pH 1.2; (D) dexamethasone loaded hydrogel in pH 6.8 (magnification: ×5000).

### 2.10. In vitro drug release behavior

The 0.1 g gels with different drug content were immersed in 4 ml of PBS (pH 6.8) or HCl/$H_2O$ solution (pH 1.2) respectively, and then were shaken at 100 rpm at 37 °C. At specific time intervals, all of release media were removed and replaced by fresh release media. After centrifuged at 13,000 rpm for 10 min, the supernatant of the removed release media were collected and stored at −20 °C before analysis. The collected supernatants were detected on HPLC to determine the concentration of dexamethasone. The cumulative release of dexamethasone was calculated according to the following Eq. (3) (Jia et al., 2007):

$$Q = C_n V_t + V_s \sum C_{n-1} \quad (3)$$

where $Q$ was cumulative release weight, and $C_n$ was the dexamethasone concentration at time $t$. $V_t$ was the volume of medium ($V_t$ = 4 ml), and $V_s$ was the volume of solution removed from supernatant ($V_s$ = 1 ml).

## 3. Results and discussion

### 3.1. Synthesis and characterization of macromonomer and hydrogel

The MPEG-PCL macromonomer was synthesized by ring-opening polymerization (ROP) of ε-caprolactone initiated by MPEG. And the hydrogel was synthesized by heat-initiated free radical polymerization. Table 1 summarized the influence factors of hydrogel, including PCL content, BIS content, MAA content, responsive index in different pH media and so on.

The structure of PCE-AC macromonomer was determined by $^1$H NMR in $CDCl_3$, and the spectrum is shown in Fig. 1. The peaks at 1.65 and 5.20 ppm belong to a methane (–CH) and methyl proton ($–CH_3$) of PCL segment, respectively, while the methane protons ($–CH_2–$) of PEG segment appear at 3.65 ppm. The 6.2 and 5.6 ppm correspond to protons of the carbon–carbon double bond. These results indicated that the terminal hydroxyl groups in the MPEG precursor were converted to acrylate groups completely. And the terminal hydroxyl groups in the MPEG-PCL macromonomer were linked by acryloyl chloride.

FT-IR spectra of PCE-AC macromonomer and the hydrogel after heat-initiated free radical polymerization were shown in Fig. 2. In general, the absorption bands at 1694 and 1143 $cm^{-1}$ presented in Fig. 2 were attributed to ester and ether stretching peaks, respectively. The peak at 1127 and 1454 $cm^{-1}$ belonged to the MPEG block. The peak at 1637 $cm^{-1}$ was attributed to C=C stretching of PCE-AC macromonomer. But it disappeared in S-1 sample, which indicated that in order to form the main chain, the end double bonds had been converted to carbon–carbon single bonds completely during the formation of hydrogel.

### 3.2. Morphological characterization

The typical scanning electron microphotographs of surfaces and cross-sections of hydrogels, including blank hydrogel and drug-loaded hydrogel in different aqueous media with pH 1.2 and 6.8 were presented in Fig. 3. According to this figure, the cross-sectional morphology of blank hydrogel and drug-loaded hydrogel in pH 1.2, are all very dense, and the mesh size are small. Conversely, the cross-sectional morphology became loose and the mesh size increased a lot after the hydrogels immersed in pH 6.8. Fig. 3C and D shows that the drug was well-adhered to the network crack. Nevertheless, the pH-responsibility of demonstrated hydrogels was still great enough to maintain after the drug was loaded into hydrogel. In all, these figures implied the pH-sensitive characterization of the prepared hydrogel, and indicated that the hydrogels have a good pH-responsibility.

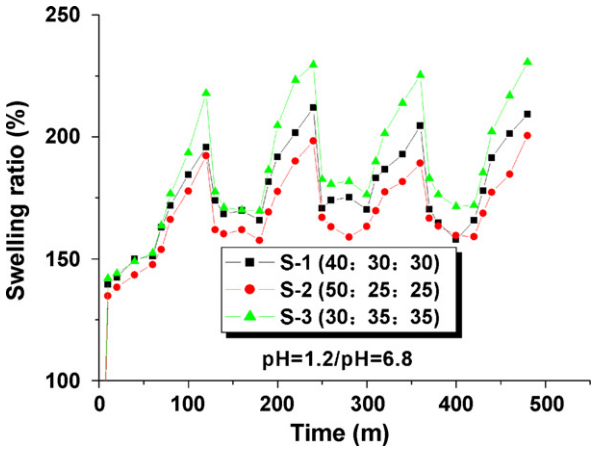



**Fig. 5.** Dynamic swelling/deswelling behavior of hydrogels in aqueous medium with pH 1.2 and pH 6.8 at an interval of 60 min respectively (37 °C).

### 3.3. Cytotoxicity of PCE-AC copolymer

The cytotoxicity of the prepared PCE-AC copolymer was evaluated by cell viability through HEK293 cells for 24 and 48 h, respectively. As shown in Fig. 4, with increasing concentration of PCE-AC copolymer, cell viability of HEK293 decreased accordingly. But the HEK293 cell viability was yet higher than 60% even when the input PCE-AC copolymer concentration was from 100 to 2000 μg/ml, respectively. This study implied that the PCE-AC copolymer that being prepared in this article were biocompatible with low cell cytotoxicity. Therefore, hydrogel based on PCE-AC, hydrogel could be regarded as a safe drug delivery carrier, and it is very promising for oral drug delivery system.

### 3.4. Dynamic swelling/deswelling behavior (pH-sensitivity) of hydrogels

Environment pH value is a key factor to determine the swelling ratio in the P(CE-MAA-MEG) hydrogels. To evaluate the dynamic swelling/deswelling behavior (pH-sensitivity) of P(CE-MAA-MEG) hydrogels, equilibrium-reswelling behavior of the hydrogels was studied in this work, and the results were presented by the data in Fig. 5. Generally, these distinctive characteristics between two hydrogels can be attributed to the unique and rapid alternation of the hydrophilic and hydrophobic states. At the initial stage of hydrating, a gradual increase in swelling ratios from pH 1.2 to pH 6.8 at a determined interval of time is illustrated in Fig. 5. Then the swelling ratio decreased dramatically as the pH decreased from 6.8 to 1.2. The main reason for that is the free carboxylic acid groups of hydrogel tends to dissociate at a pH >4.5 (Bajpai and Singh, 2006; Huang et al., 2007). In low pH value (pH 1.2), most carboxylic acid groups are in the form of COOH, and large amounts of hydrogen bonds formed by MAA chain corresponding with PEG chain. As shown in Scheme 2, the hydrogen bond broke because the environmental pH value raise to 6.8, and carboxylic acid groups began to ionize. Meanwhile, the osmotic pressure inside the hydrogels increased, and electrostatic repulsion caused the network to expand (Serra et al., 2006). In all, these data showed that the P(CE-MAA-MEG) hydrogels have a good reswelling ability and maintain the high sensitivity to pH.

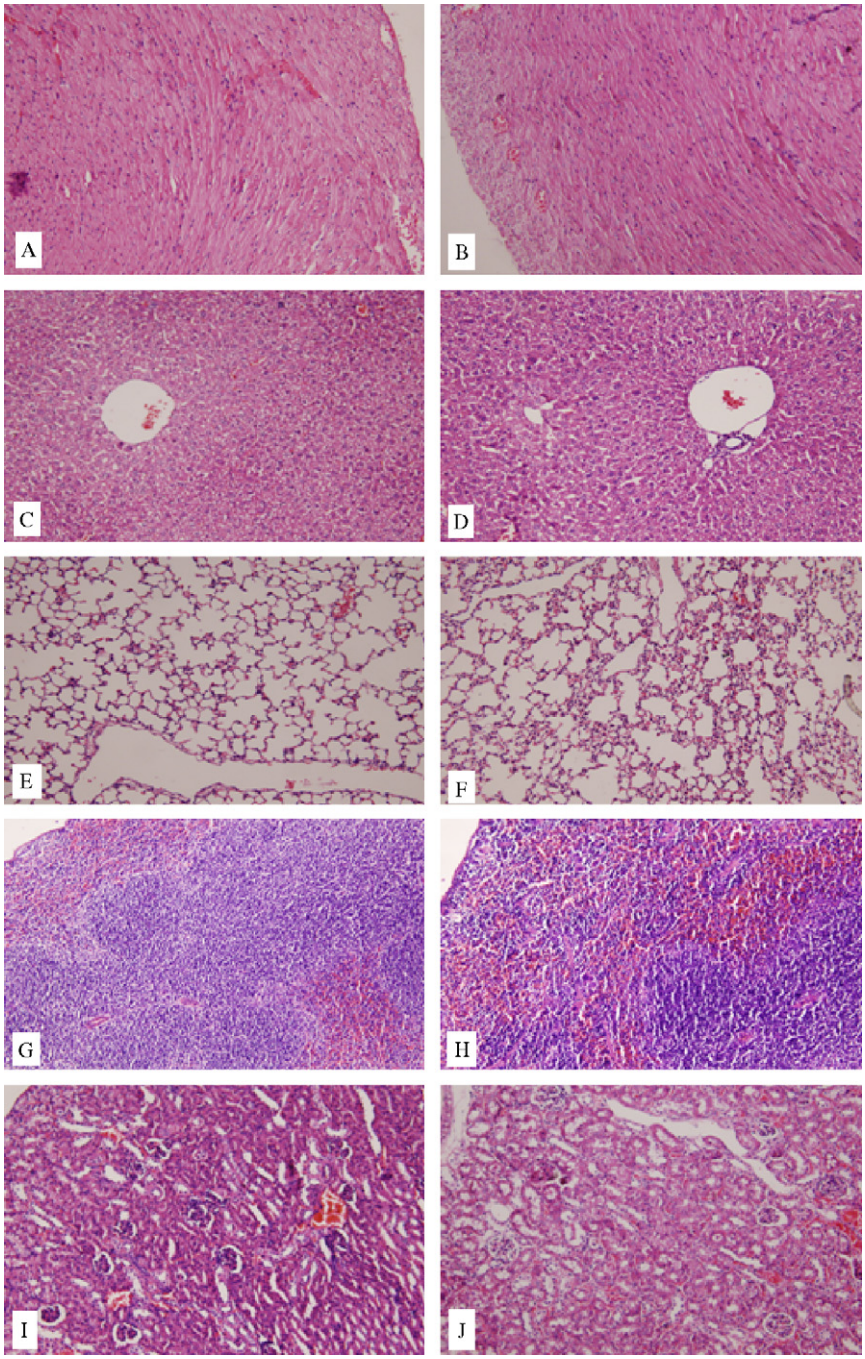



**Fig. 6.** Photograph of major organs after oral administration of P(CE-MAA-MEG) hydrogel (40×). Mice cardiac muscle, liver, spleen, lung, and kidneys photograph of control group (A, C, E, G, I) and P(CE-MAA-MEG) hydrogel-treated group (B, D, F, H, J), respectively.

### *3.5. Acute oral toxicity test*

#### *3.5.1. General conditions*

All animals had been observed continuously for 14 days after final administration, including mortality and the general conditions (the energy, hair, activity, feces, behavior pattern, and any other clinical signs). Each group of mice with P(CE-MAA-MEG) hydrogel and has no toxic effect. No death occurred and no toxic response was found in mice during the whole 14-day observation period. Mice were sensitive to sound light, and other stimulations, and they showed full of energy, normal behavior, free movement, and shining hair. There was no flare and ulcer in the skin. They had no vomit or salivation, no nose or mouth dryness or edema, no running nose or eye secretion. We found that animals' feces were in regular form and normal color without mucus or pus or blood.

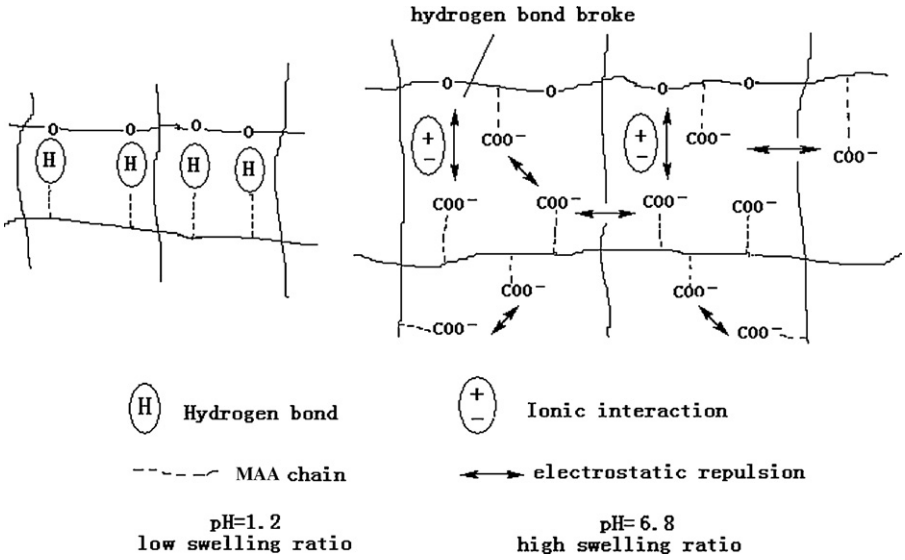
No macroscopic pathological alternations attributed to P(CE-MAA-MEG) hydrogels were found in all mice at necropsy.

#### *3.5.2. Maximal tolerance dose (MTD)*

Since the highest tested dose did not cause mortality, it can be concluded that the Maximal Tolerance Dose (MTD) of P(CE-MAA-MEG) hydrogels were greater than 20 g/kg b.w. in BALB/c mice.

#### *3.5.3. Histopathological study*

All samples were histopathologically observed by light microscope, and no significant histopathological changes were observed




**Scheme 2.** Schematic illustration of the swelling behavior of pH-sensitive and biodegradable P(CE-MAA-MEG) hydrogel at different pH.

as a result of the administration of the P(CE-MAA-MEG) in Fig. 6.

Fig. 6A and B exhibited the light micrograph of cardiac muscle treated with and without P(CL-MAA-EG) hydrogels, respectively. Cardiac myocytes were clear and arranging in good order, and there was no haemorrhage or necrosis or inflammatory exudates.

Fig. 6C and D showed that the light microscopic image of liver treated with P(CE-MAA-MEG) hydrogels and normal controls. The classic structure of liver lobule with central vein was clearly observed. No hepatocellular degeneration or necrosis, also no lymphocyte, neutrophil and macrophage infiltration was found.

In Fig. 6E and F, the tissue structure of spleen was normal. Spleen sinus did not show pathologic change.

In Fig. 6G and H, the morphology of the hydrogel-treated lung tissue did not show significant difference when compared with control group. No bronchioles and alveoli ectasia or collapse, no alveolar epithelial denaturation, and no inflammatory cell infiltration surrounding bronchus were observed.

From light micrograph of mice kidney (Fig. 6I and J), we can find that various kidney tubes and renal glomerulus show normal shape, no degeneration and bleeding and necrosis.

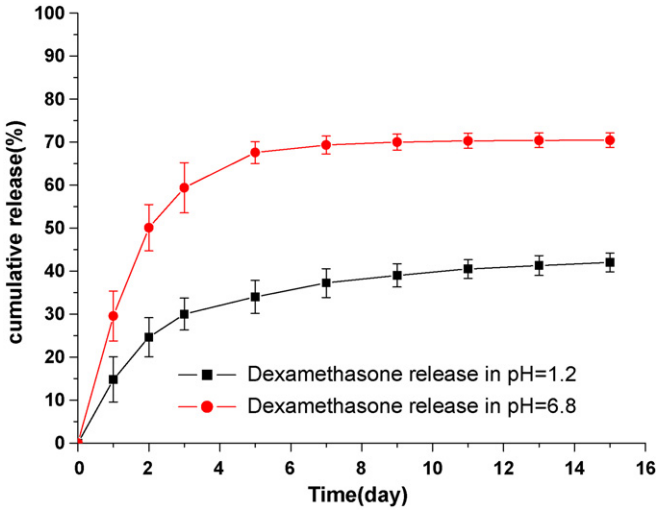
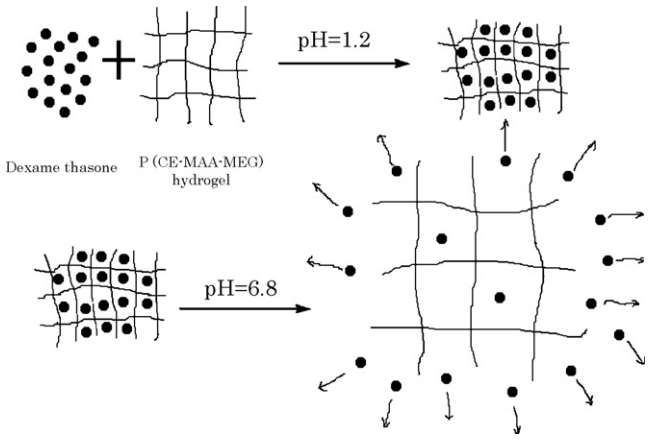



**Fig. 7.** *In vitro* release behavior of dexamethasone from dexamethasone/P(CE-MAA-MEG) hydrogel complexes in different pH value with 1.2 and 6.8, respectively.

### 3.6. In vitro drug release study

Dexamethasone, a multi-functional drug, has a great potential application in human disease therapy, especially in inflammatory therapy. In this study, dexamethasone was chosen as a hydrophobic model drug in this *in vitro* drug release study. The release of dexamethasone from P(CE-MAA-MEG) hydrogel in different pH (pH 1.2 and 6.8) was performed and its cumulative release profile is displayed in Fig. 7. From Fig. 7, we could find that pH value has a great effect on the release behavior of dexamethasone from this hydrogel. It is clear that the cumulative release rate of dexamethasone increased dramatically from 42.0% (pH 1.2) to 76.9% (pH 6.8) in a 15-day period. The burst release rates of dexamethasone were approximately 24.6% and 55.8% in the first 48 h, respectively. After that, dexamethasone could be released steadily from the hydrogel, which finally reached 42.0% and 76.9% of cumulative drug release rates in next 13 days. The performance of this drug release indicated that pH value had great effects on the hydrophobic dexamethasone release behavior. Generally, drug release behavior from hydrogel was driven by two forces: diffusion effect and degradation or erosion of the hydrogel (Bromberg et al., 1998). For hydrophobic drugs, low diffusion rate in water and strong intermolecular interaction with hydrogel dominated the drug release profile, which resulted




**Scheme 3.** Schematic drug diffusional illustration of dexamethasone loaded in P(CE-MAA-MEG) hydrogel with different of solution media at pH 1.2 and 6.8, respectively.

in the high residual drug in hydrogel and low release rate (Gong et al., 2009a). For pH-sensitive hydrogel, the permeability and release rate of drugs are influenced by the type of releasing agent and the water content in hydrogels (Varshosaz and Falamarzian, 2001). Despite the high water content of the pH-sensitive hydrogel, the system may also be used for the release of drugs that are poorly soluble in water. In our previous work (Wang et al., 2009), swelling behavior had been investigated, and we could find that larger water content was absorbed in a higher pH value. Therefore, it seems that the increasing the water content of this hydrogel at pH 6.8 increases the permeability of the solutes, which might accelerate the drug release rate. The dexamethasone release behavior from P(CE-MAA-MEG) hydrogel in different pH value is presented in Fig. 7 and Scheme 3, and these data is consistent with the explanation mentioned above.

## 4. Conclusions

A new kind of pH-sensitive P(CE-MAA-MEG) hydrogel was successfully synthesized by heat-initiated free radical polymerization method. The resultant macromonomer and hydrogel were characterized by $^1$H NMR and FT-IR, respectively. Dynamic swelling/deswelling behavior had been investigated in this study, and swelling ratio was depended on the different pH value. As a result, larger water content could be absorbed in a higher pH value, which might be useful for its application in many fields, such as oral drug delivery. Furthermore, *in vitro* drug release behavior, cytotoxicity of PCE-AC macromonomer and acute oral toxicity of hydrogel were also studied in this work. Because of the great pH-sensitivity of these hydrogels, an oral administration drug delivery system could be considered.

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