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A pH-Sensitive Hydrogel with Hydrophobic Association for Controlled Release of Poorly Water-Soluble Drugs

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A novel pH-sensitive hydrogel has been developed by UV induced radical polymerization of acrylic acid (AA) and amphiphilic macromonomer polyethylene glycol monolaurylether monoacrylate (PEGLA) with crosslinker ethylene glycol dimethacrylate for controlled release of acyclovir, a poor water-soluble model drug. The swelling behavior was investigated in the buffer of different pH at $I = 0.1$ M, as well as in the ethanol/water mixture. The hydrophobic association formed by the hydrocarbon chains in PEGLA was found to dominate the swelling properties of the hydrogels with subordinate pH sensitivity due to the ionization of the AA segments. Therefore, the drug loading of acyclovir has been improved and the release rate of acyclovir was slowed down with increasing the PEGLA content in the hydrogels. By fitting the release data with Weibull equation, the acyclovir release kinetics was changed from the Fickian diffusion to an anomalous diffusion when the PEGLA content in the hydrogels was beyond 20 mol%.

Keywords: pH-sensitive hydrogel, acrylic acid, amphiphilic macromonomer, acyclovir, controlled release

1 Introduction

Hydrogels have been popularly investigated in pharmaceutical and biomaterial applications due to their good biocompatibility and high hydrophilicity (1, 3). Hydrogels, exhibiting responsive behavior to the external stimuli, such as pH, temperature, ionic strength, electrical and light fields, are known as 'smart' or 'intelligent' hydrogels (4). These unique properties of the smart or intelligent hydrogels make them become one of the most promising carriers in the drug delivery system for controlled release (4, 5). Acrylic-based hydrogels are of particular interest in the drug delivery system because they can overcome the enzymatic degradation of drugs in the harsh environment of the stomach and the wash out effect in the gastrointestinal (GI) tract (6,7). Because these hydrogels collapse in acidic medium and swell to a high extent in neutral and basic solutions, protecting the encapsulated drug from the acidic stomach and releasing the drug in the basic intestinal environment. In past decades, the acrylic-based hydrogels attracted much attention as a specific carrier for the drug delivery (8, 10).

In the drug delivery system, a big challenge is the low bioavailability for the poorly water-soluble drugs. The low solubility in aqueous medium limits the absorption of the drug through oral administration. Many contributions have been devoted to enhance solubility of the drugs, including formation of the hydrophobic domain by using surfactant (11), emulsion (12), cosolvent (12), cyclodextrin (13), and so on. Acyclovir, for an example, was clinically used in treatment of infections induced by herpes simplex virus (HSV-1 and HSV-2) and varicella zoster virus (VZV) (14). Since acyclovir has low water solubility (about 1.5 mg/mL) (14) with short half-life (2–3 h) and incomplete absorption (bioavailability about 15–30%), its oral dosage must be taken five times daily, which is very inconvenient for patients (15).

In the present research, we designed a novel pH-sensitive hydrogel to improve the solubility of the hydrophobic drugs in the gel. The hydrogel was a copolymer of acrylic acid (AA) and amphiphilic macromonomer polyethylene glycol monolaurylether monoacrylate (PEGLA), designated as P(AA-*co*-PEGLA). This hydrogel was used for controlled release of acyclovir as a model hydrophobic drug with low water solubility. The amphiphilic macromonomer PEGLA with hydrocarbon tail (Scheme 1) was induced into the hydrogel to form hydrophobic associations, which were expected to enhance the loading amount of hydrophobic acyclovir and to control its release. The effect of amphiphilic PEGLA on the swelling, drug loading, and release mechanism was investigated.

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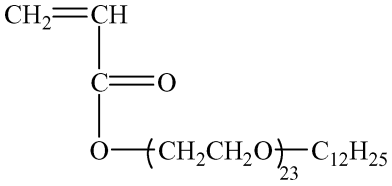

Sch. 1. Chemical structure of amphiphilic macromonomer PEGLA.

2 Experimental

2.1 Materials

Acrylic acid (AA, Tianjin Yuanli Chemical Co.) was distilled under reduced pressure prior to use. Polyoxyethylene(23) lauryl ether (Brij 35, Acros), crosslinking reagent ethylene glycol dimethacrylate (EGDMA, Acros), photo-initiator 2-oxoglutaric acid (Acros), and model drug acyclovir (Zhejiang Zhebei Pharmaceutical Co.) were used as received. All other reagents were analytical grade and purified with standard methods. Water used in all experiments was purified by deionization and filtration with a Millipore purification apparatus.

2.2 Synthesis of Amphiphilic Macromonomer (PEGLA)

The amphiphilic macromonomer polyethylene glycol monolaurylether monoacrylate (PEGLA) shown in Scheme 1 was synthesized according to the literature procedure (16). Brij 35 (120 g, 0.1 mol), AA (9 mL, 0.13 mol) and 100 mL of toluene were poured into a three-necked flask with *p*-toluenesulfonic acid (3.88 g, 3 wt% of Brij 35 and AA) and inhibitor hydroquinone (0.0094 g, 0.1 wt% of AA) and the esterification was allowed at 120°C for 6 h until stoichiometric water (1.8 mL) was removed. Then, the mixture was washed with aqueous solutions of sodium bicarbonate (5 wt%) and saturated sodium chloride in a separatory funnel to remove the residual catalyst, inhibitor and excessive AA. The organic phase was concentrated and purified by a column extraction of silica gel eluted with chloroform and isopropyl alcohol of volume ratio of 6:1. Finally, the white paste of the macromonomer PEGLA was obtained after evaporating solvent and drying under vacuum at room temperature for 48 h. ^{1}**H-NMR (δ_H, DMSO-D$_6$, 400Hz):** 6.34–5.95 (*m*, 3H, CH_2=CH–COOR); 4.20 (*t*, 2H, -αCH_2OOCCH=CH$_2$); 3.29–3.65 (*m*, 90H, -OCH_2CH_2O); 1.23–1.45 (*m*, 22H, –CH_2); 0.84(*t*, 3H, CH_3). **FT-IR (KBr)** as shown in Figure 1: 1635 cm^{-1} (–C=C), 1726 cm^{-1}(–C=O), 1062–1146 cm^{-1}(–CH$_2$–O–CH$_2$), 928 cm^{-1}(CH$_2$=CH–), 2884 cm^{-1} (–CH$_2$–).

2.3 Synthesis of P(AA-co-PEGLA) Hydrogel

The P(AA-*co*-PEGLA) hydrogel was prepared with AA, amphiphilic macromonomer PEGLA, and EGDMA using UV induced (by 2-oxoglutaric acid) free radical polymerization (17). The mole ratio of monomer AA to PEGLA was changed from 4:1 to 1:1.5 with EGDMA changed from 0.75 to 5 mol% of the total monomers. The photo-initiator was 1 wt% of the total monomers. The mixture was diluted with pure water to 50 wt% of the total monomers. Nitrogen was bubbled into the mixture for 20 min to eject dissolved oxygen. The mixture was placed into a quadrate mould of thickness of 2 mm and polymerized under UV light at intensity of 30 mW/cm^2. The prepared hydrogel was cut into discs of 10 mm diameter using a cork-borer. The discs were repeatedly washed with deionized water for 7 days to remove any unreacted monomer, initiator or other impurities, and dried in a vacuum oven at ambient temperature to constant weight.

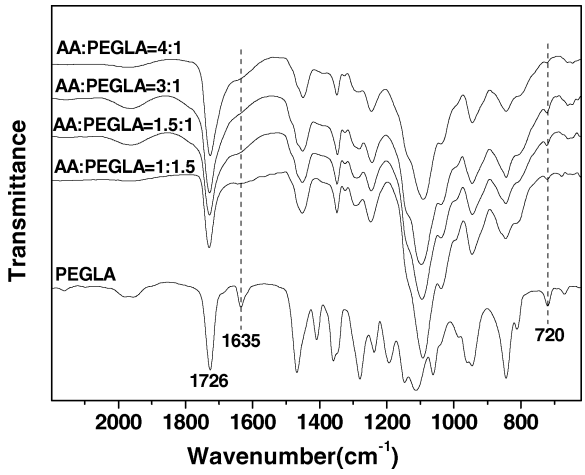

Fig. 1. ATR-FTIR spectra of P(AA-*co*-PEGLA) hydrogels with indicated monomer composition comparing with that of PEGLA.

Attenuated total reflectance-Fourier transform infrared (ATR-FTIR) spectrum of the dried hydrogel on a ZnSe crystal was observed with a FTIR spectrometer (Bruker Vector 33) over the wavenumber of 4000–600 cm^{-1} at a resolution of 4 cm^{-1}.

2.4 Swelling Equilibrium

To determine the equilibrium swelling degree of the P(AA-*co*-PEGLA) hydrogels, the discs were swollen in buffer solutions of pH 2.0, 4.0, 5.0, 6.0, and 8.0 at a constant ionic strength of $I = 0.1$ M. Each disc was weighed in dry state and submerged in a glass container filled with 25 mL of swelling medium. The equilibrium swelling ratio q was calculated from $q = W_s/W_d$, where W_s and W_d represented the disc weight at the equilibrium swollen and dry states, respectively. The data were taken as the average of triplicate observations. The equilibrium swelling observation was also conducted in water/ethanol mixed solvent.

2.5 Drug Loading and *in vitro* Release

For loading acyclovir, dried hydrogel discs were immersed in 20 mL of drug solution (1.8 mg/mL) of ethanol:water = 60:40 (vol) mixture for 48 h at 25°C. The UV absorbance at 252 nm of the solution was recorded before and after hydrogel immersion to estimate the amount of drug loading. The drug loaded discs were dried in a vacuum oven at 37°C and stored in a desiccator before use. The release of acyclovir was carried out at 37°C in a phosphate buffer solution of pH 7.4 (simulated intestinal condition) and the stirring rate was maintained at 100 rpm. The released quantity of the acyclovir was estimated by measuring UV absorbance of the buffer solution. All release experiments were repeated three times and the reported data were the average value.

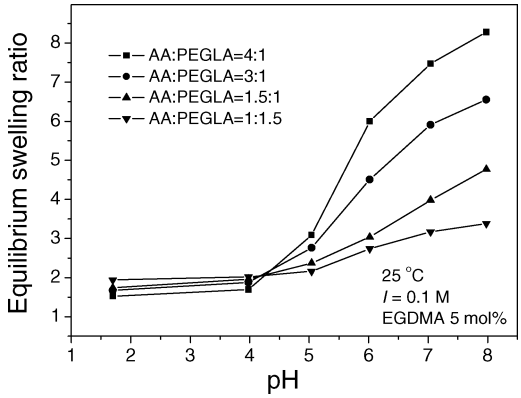

Fig. 2. Equilibrium swelling ratio of the P(AA-*co*-PEGLA) hydrogels with indicated AA:EG mole ratio as a function of pH.

3 Results and Discussion

3.1 P(AA-co-PEGLA) Hydrogel Characterization

The reaction mixture for synthesizing P(AA-*co*-PEGLA) hydrogel was a clear homogeneous solution to produce transparent P(AA-*co*-PEGLA) hydrogels with infinite molecular weight. This method avoids organic solvents and convenient to biomedical usages. The ATR-FTIR spectra of P(AA-co-PEGLA) hydrogels and PEGLA are shown in Figure 1. Because the transmittance is low for the IR light of high wave-number, the spectra at wave-number higher than 2200 cm^{-1} were omitted. The band at 1635 cm^{-1} for carbon double bonds disappears in the hydrogels, indicating no unreacted macromonomer in the hydrogels. The absorption appearing at 1726 cm^{-1} is for the C=O stretching, reflecting the presence of carbonyl groups in the hydrogels. The characteristic absorption bands around 1100 cm^{-1} for $-CH_2-O-CH_2$ stretching and at 720 cm^{-1} for $-CH_2$ rocking of the alkyl chain was observed from both the hydrogels and PEGLA. These IR spectra indicate that the hydrogels are the copolymer of AA and PEGLA.

3.2 Swelling Behavior

The equilibrium swelling ratio of the hydrogels is one of the most important properties because it determines the rate of water uptake and drug release (18, 19). The equilibrium swelling ratio of P(AA-*co*-PEGLA) hydrogels with different monomer compositions is shown in Figure 2 as a function of pH. First of all, the swelling ratio is less than 10, much lower than that of usual PAA gels, for which the swelling ratio is even higher than 1000 (20). This is due to the existence of hydrophobic association formed by hydrocarbon tail chains in PEGLA accompanied with hydrogen bond, which act as additional cross-linking in the P(AA-*co*-PEGLA) hydrogels. When pH is below than 5, the equilibrium swelling ratio is almost a constant lower than 2 and slightly decreases with increasing AA content in the hydrogels. The reason seems to be that the unionized AA groups in the hydrogels cause more hydrogen bonding between the polymer chains, decreasing the swelling capability (21). There is a drastic change in the equilibrium swelling ratio of the hydrogels above pH 5, which is approximately the pKa of PAA. At higher pH, the AA groups are ionized and the hydrogen bonding is dissociated, leading to high swelling degree due to high electrostatic osmotic pressure in the hydrogels. The hydrophobic association still exists in the hydrogels as the additional cross-linking and cannot be destroyed when swelled in the buffer solutions (22). As a result, the hydrogels containing more PEGLA segments exhibits lower swelling ratio. This swelling property also indicates the pH sensitivity of the P(AA-*co*-PEGLA) hydrogels. Thus, the hydrogel can protect the incorporated drug in the acidic environment of the stomach, while the entrapped drug can be released passing swollen gel in the basic and neutral environment of the intestine.

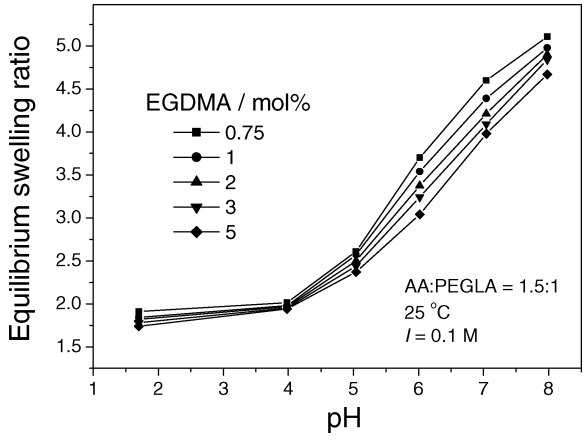

Fig. 3. Equilibrium swelling ratio of the P(AA-*co*-PEGLA) hydrogels of AA:EG = 1.5:1 in mole with indicated cross-linker EGDMA content as a function of pH.

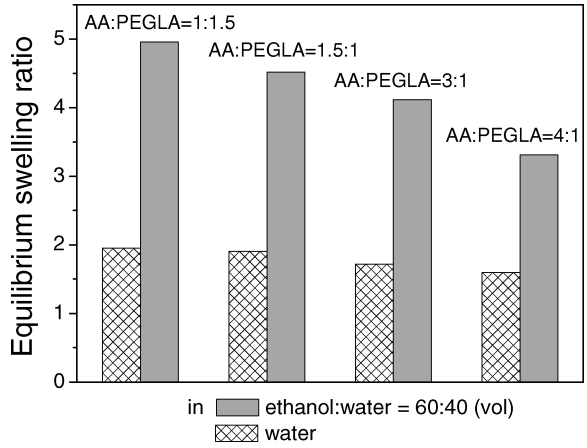

Fig. 4. Equilibrium swelling ratio in water and in ethanol:water = 60:40 (vol) mixture at 25°C for the hydrogels with different mole ratios of AA:PEGLA at constant EGDMA content of 5 mol%.

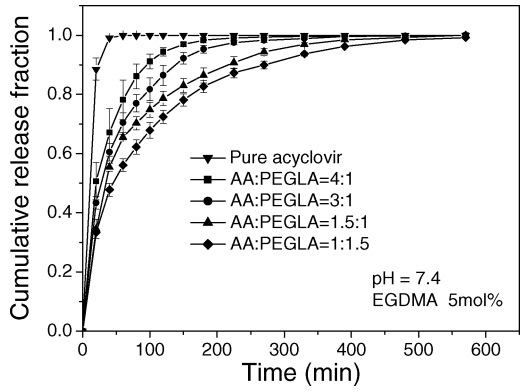

Fig. 5. Acyclovir release profiles in phosphate buffer of pH 7.4 from the P(AA-*co*-PEGLA) hydrogels with various AA:PEGLA mole ratios.

To investigate the effect of chemical cross-linker EGDMA on the swelling behavior, the swelling ratio of the P(AA-*co*-PEGLA) hydrogels containing different EGDMA contents is plotted against pH in Figure 3 for the samples of AA:EG = 1.5:1 (in mole). It is surprising that the swelling capacity only decreases slightly with increasing EGDMA when EDGMA ranges from 0.75 to 5 mol%. This appears to suggest that the hydrophobic association formed by the hydrocarbon chains of PEGLA in the hydrogels plays a crucial role to the swelling in water.

If the hydrophobic association is true, addition of organic solvent will be a benefit to swelling of the P(AA-*co*-PEGLA) hydrogels with high PEGLA content. Figure 4 illustrates the equilibrium swelling ratio of the hydrogels in the mixed solvent of ethanol:water = 60:40, which was used for drug loading in our experiments, compared with that in water. The swelling ratio of the hydrogels is indeed higher in the mixed solvent than that in water, indicating the cross-linking effect of the hydrophobic association. Moreover, the P(AA-*co*-PEGLA) hydrogel with higher PEGLA contents swells to higher degree in the mixed solvent. The ethanol is believed to have stronger disassembly ability to the hydrophobic association among the PEGLA tails than water. Therefore, the drug loading of the hydrogels will be improved for poorly water-soluble drugs with high PEGLA content in ethanol/water mixed solvent (23). The drug loading of acyclovir is increased as 11.84, 15.78, 21.4, and 29.8 mg/g in the hydrogels of AA:PEGLA with 4:1, 3:1, 1.5:1, and 1:1.5 (in mole), respectively.

By careful observation, one may wonder that the P(AA-*co*-PEGLA) hydrogels swell higher in the pH = 7 buffer of $I = 0.1$ M (Figure 2) than that in pure water (Figure 4), e.g, the swelling ratio is 4 in the pH = 7 buffer but 1.9 in pure water for the sample of AA:PEGLA = 1.5:1. This seems to be the structure breaker effect of the salt in the buffer on the hydrophobic association, which enhances its disassembly, leading to higher swelling capacity (24). In other words, the hydrophobic interaction plays an important role in the P(AA-co-EG) hydrogels.

3.3 *In Vitro* Release

For the purpose of investigating the effect of the amphiphilic macromonomer PEGLA on the release of acyclovir from the P(AA-*co*-PEGLA) hydrogels, *in vitro* release was carried out in pH 7.4 (simulated intestinal condition). Figure 5 depicts the accumulative release profile of acyclovir from the hydrogels with various AA to PEGLA mole ratios. As expected, acyclovir release is slowed down when loaded in the hydrogels compared with that of the pure drug. 99% of pure acyclovir is released during the first 40 min, while only about 48% of acyclovir is released from the hydrogel of AA:PEGLA = 1:1.5 during the same time interval. The acyclovir release rate from the hydrogel with higher PEGLA content is significantly lower than that with lower PEGLA content. This result can be understood on the lower swelling capability in the basic environment of the hydrogel with higher PEGLA content (Figure 2), which in turn blocks the diffusion of acyclovir passing through the hydrogel. Consequently, the amphiphilic macromonomer PEGLA in the hydrogels plays an important role in controlling drug release.

In order to elucidate entire release profiles, the cumulative release data was fitted with the empirical Weibull equation (25, 26):

$$\frac{M_t}{M_\infty} = 1 - \exp(-at^b) \qquad (1)$$

Here, M_t/M_∞ is the fraction of drug released at time t, $a$is a constant and $b$is an exponent parameter, which represents the type of drug release kinetics through the polymer matrix. By fitting the curves in Figure 5 with Equation 1, the coefficients a and b were evaluated and listed in Table 1 with the correlation coefficient r. In the case of release

Table 1. Estimated values of a, b and correlation coefficient r of Equation 1

Hydrogels	a	b	r^2
AA:PEGLA = 4:1	0.085	0.719	0.989
AA:PEGLA = 3:1	0.054	0.793	0.994
AA:PEGLA = 1.5:1	0.037	0.779	0.986
AA:PEGLA = 1:1.5	0.044	0.763	0.993

from a fractal or Euclidian space,$b \leq 0.75$ indicates a Fickian diffusion, while anomalous mechanism (Fickian diffusion and Case II transport) is associated with $0.75 < b < 1$ (26). As known from Table 1, a satisfactory data fitting was established for the hydrogels. Acyclovir release follows the anomalous diffusion mechanism from the hydrogels of AA to PEGLA mole ratio as 3:1, 1.5:1, and 1:1.5. In contrast, acyclovir release from the hydrogel of AA: PEGLA = 4:1 follows the Fickian diffusion. Therefore, the PEGLA content in the hydrogels has an important effect on their swelling capability and the release mechanism.

4 Conclusions

We designed and synthesized homogeneous P(AA-*co*-PEGLA) hydrogels containing an amphiphilic macromonomer PEGLA for drug controlled release of poorly water-soluble acyclovir. The hydrophobic association formed by the hydrocarbon chains of PEGLA dominated the swelling properties of the hydrogels with subordinate pH sensitivity due to the ionization of the AA segments. Therefore, the drug loading of acyclovir was improved with increasing the PEGLA content in the hydrogels. The acyclovir release mechanism was changed from the Fickian diffusion to an anomalous diffusion when the PEGLA content in the hydrogels was beyond 20 mol%.

Acknowledgments

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