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Note

pH-responsive amphiphilic hydrogel networks with IPN structure: A strategy for controlled drug release

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Abstract

A pH-responsive amphiphilic hydrogel with interpenetrating polymer networks (IPN) structure for controlled drug release was proposed. The IPN was constructed with hydrophilic poly(acrylic acid) (PAA) and hydrophobic poly(butyl acrylate) (PBA). Using drug *N*-acetyl-5-methoxytryptamine (melatonin, MEL) as a model molecule, the controlled drug release behaviors of the IPN were investigated. It is found that not only the release of MEL from the IPN can respond to change in pH, but also the presence of hydrophobic network can overcome disadvantageous burst effect of hydrophilic network. This may be a result of hydrophobic aggregation encapsulating MEL molecules.

Keywords: Amphiphilic hydrogel; Interpenetrating polymer networks; pH-sensitivity; The controlled release

1. Introduction

The development of novel drug carriers for controlled release attracts great attentions from many polymer and biomaterial scientists. In recent years, amphiphilic polymers used as drug carriers have become a focus of the field. This is because the polymers combine hydrophilicity/hydrophobicity and can thus form hydrophobic aggregation which can encapsulate hydrophobic drug molecules in aqueous solution (Liggins and Burt, 2002; Lavasanifa et al., 2002; Kikuchi and Okano, 2002; Chung et al., 1999; Haigh et al., 2000; Rimmer et al., 2005; Triftaridou et al., 2002; Rösler et al., 2001). Based on this mechanism, many controlled drug delivery systems have been developed (Liggins and Burt, 2002; Lavasanifa et al., 2002; Kikuchi and Okano, 2002; Chung et al., 1999; Haigh et al., 2000; Rimmer et al., 2005). However, so far much more attentions were still paid on amphiphilic polymers with graft or block structures, which were prepared by graft or block copolymerization of a hydrophilic monomer with a hydrophobic monomer (Liggins and Burt, 2002; Lavasanifa et al., 2002; Kikuchi and Okano, 2002; Chung et al., 1999; Haigh et al., 2000; Rimmer et al., 2005). In fact, interpenetrating polymer networks (IPN) composed of hydrophilic and hydrophobic networks should possess amphiphilicity, and should be a family of amphiphilic polymers. This is because IPN is with physically interlocked structure of two polymer networks and there is no chemical bonding between two networks (Liu et al., 2003; Zhang and Peppas, 2000; Zhang et al., 2004; Lim et al., 1997). This leads to the fact that each polymer network can retain its individual properties like its homopolymer; but at the same time, owing to physically interlocked interaction of two networks, if one component swells or shrinks, the other component can be enforced to cooperate by attractive and repulsive interactions of whole network (Liu et al., 2003; Zhang and Peppas, 2000; Zhang et al., 2004; Lim et al., 1997). Therefore, when an amphiphilic IPN was swollen, hydrophobic network can form hydrophobic aggregation. The hydrophobic aggregation not only can limit swelling degree of hydrophilic network, but also may encapsulate hydrophobic drug molecules. If an amphiphilic IPN used as drug carrier, it is possible to overcome, to some extent, disadvantageous burst effect of hydrophilic network, and thus a novel controlled behavior may be obtained as expected. However, this concept has not yet been definitely proposed. Based on the consideration, in this paper, we suggest an amphiphilic polymer with IPN structure for controlled drug release, where hydrophilic network is for swelling IPN and hydrophobic network is for encapsulating drug molecules, and in vitro investigate the feasibility of use of the polymer as a possible carrier for controlled drug release.

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Owing to that the fact that smart hydrogels can conventionally change their volume in response to environmental stimuli including pH, temperature, ionic strength (Zhang and Peppas, 2000; Liu and Fan, 2002; Liu et al., 2003, 2004a,b; Philippova et al., 1997; Torres-Lugo and Peppas, 1999; Dong and Hoffman, 1991; Okano et al., 1990; Eeckman et al., 2004; Tasdelen et al., 2004), they were extensively investigated as intelligent carriers (Zhang and Peppas, 2000; Zhang et al., 2004; Lim et al., 1997; Liu and Fan, 2002; Liu et al., 2003, 2004a,b; Tasdelen et al., 2004). This leads to the fact that the diffusion and permeation of drug molecules (or solute) from the hydrogels can be controlled by external stimuli. Therefore, our aim is to construct an environment-responsive amphiphilic hydrogel with IPN structure for controlled drug release. For this purpose, poly(butyl acrylate) (PBA) was selected as hydrophobic network owing to its good flexibility of macromolecular chains, and poly(acrylic acid) (PAA) was used as hydrophilic network because of its pH-sensitivity and good biocompatibility (Chen and Hoffman, 1995).

Our objective of this work is to synthesize a pH-responsive amphiphilic hydrogel networks with IPN structure. Using drug *N*-acetyl-5-methoxytryptamine (MEL), in vitro the release mechanism of MEL from the hydrogels was studied.

2. Experimental

2.1. Materials and methods

Tripropylene glycol diacrylate (TPGDA, crosslinker) and benzoin ethyl ester (BEE, photoinitiator) were of chemical grade. *N*-acetyl-5-methoxytryptamine (melatonin, MEL) was provided by Xi'an Modern Chemistry Institute. All other reagents including butyl acrylate (BA), acrylic acid (AA) and dimethyl formamide (DMF) were analyticalgrade and were made in China. They were used as received without further purification.

DSC (MDSC 2910, TA Instruments, USA) measurements were used to determine the glass transition temperature (T_g) of the polymers obtained. The scan rate was 10 K/min. First, the sample was heated from room temperature to 150 °C for the removal of thermal history. T_g is obtained by the second scanning and the value is from the midpoint of the special heat increment. UV–vis spectra were recorded on a spectrophotometer UV-2550 model (Shimadzu, Japan).

2.2. Synthesis of pH-responsive amphiphilic hydrogel

A sequential UV solution polymerization was to use to synthesize an amphiphilic IPN sample. PBA and PAA were chosen as hydrophobic and hydrophilic networks, respectively. Firstly, 1.2 g of BA was added into 0.8 g of DMF with 1 mol% of TPGDA and 1.5 wt.% of BEE (reference to monomer BA). The polymerization was carried out under an UV source (400 W, Middle-pressure mercury lamp, HOK4/120, Philips, Belgium) with a distance 20 cm from lamp to sample for 10 min. The obtained PBA gel was taken out from the bottle, and immersed in acetone to remove the unreacted monomer. The samples were kept in fresh acetone that was changed for every 6 h, and lasted 4 days. Late, it was dried under ambient conditions for 1 day and in a vacuum oven at 40 °C for 3 days.

Then, the PBA gel was swollen in AA solution of DMF (40 wt.%) with 0.8 mol% of TPGDA and 1 wt.% of BEE (reference to monomer AA). The polymerization was conducted under the same UV source for 10 min. The obtained PBA/PAA gel was cut into thin disks of 8 mm in diameter, and immersed in distilled water to remove the unreacted AA. The samples were kept in fresh distilled water that was changed for every 6 h, and lasted 5 days. Late, they were dried under ambient conditions for 2 days and in a vacuum oven at 40 °C for 5 days. The composition of two networks was calculated by weighting PBA and PBA/PAA gels and is found to be 40/60 (w/w). In addition, for comparison, PAA hydrogel with the same content of TPGDA was synthesized.

2.3. Swelling measurements

The swelling ratio (SR) of a hydrogel was measured after it was swollen to a desired state. It was carefully taken out from the solution, wiped with a filter paper for the removal of the free water on the surface, and then weighted. SR (g/g) of a sample was calculated using as follows:

$$\mathrm{SR} = \frac{(w_t - w_d)}{w_d}$$

where w_d and w_t are the weights of dry and wet samples at time t, respectively. When a hydrogel reaches its swelling equilibrium state under a fixed condition, its swelling ratio is called equilibrium swelling ratio (ESR). All measurements were triplicated for each sample.

2.4. Drug loading and in vitro release studies

Loading model drug into IPN hydrogel was performed in water/acetone mixture (50/50, w/w) with MEL of 0.8 wt.%, whereas the loaded PAA sample was prepared by immersing PAA in solution of MEL of 0.4 wt.%. After the hydrogels were swollen in the solution at room temperature for 24 h, they were carefully taken out and washed with the mixture for the removal of free MEL on the surface. Then, the loaded samples were dried under an ambient condition for 1 day, and in a vacuum oven at 50 °C for 3 days. It is found that MEL contents of the loaded IPN and PAA samples which is defined as MEL weight content in 100 mg of dried gel, 3.5 mg and 4.6 mg, respectively.

A MEL-loaded disk was immersed in 10 mL of buffer solutions of pH 1.4 (or 7.4) with ionic strength of 0.1 mol L^{-1}. In a special interval, a 5 mL of the solution released was withdrawn and at the same time a 5 mL of fresh solution was added. The concentrations of the MEL released were analyzed by spectrophotometer at 222 nm. All release measurements were triplicated for each hydrogel and average values were plotted.

3. Results and discussion

A sequential UV solution polymerization was to use to synthesize an amphiphilic IPN sample under the above mentioned

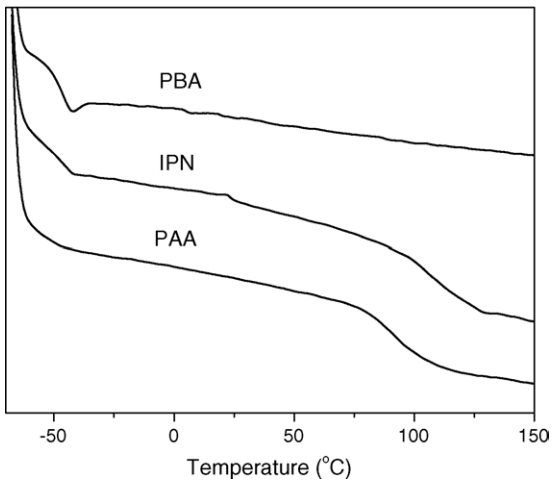

Fig. 1. DSC profiles of samples IPN, PAA and PBA.

synthesis conditions. The composition of two networks was calculated by weighting dried PBA and PBA/PAA IPN gels and is found to be 40/60 (w/w). Fig. 1 presents DSC profiles of PBA/PAA IPN, and its original materials PBA and PAA. As seen clearly from Fig. 1, there exist two glass transition temperatures (T_g) in DSC curve of the IPN sample, which correspond to −44.6 and 93.1 °C, respectively. The two values are close to the T_gs of pure PBA (−45.9 °C) and PAA (104.5 °C) gels (see Fig. 1). This means the PBA/PAA IPN is indeed formed because of PBA and PAA keeping their T_g values themselves in the IPN system. This result also indicates that PBA and PAA have poor miscibility, and they are in a state of microphase separation.

Fig. 2(a) indicates pH dependent swelling ratios of the IPN sample. The investigation of reswelling behaviors of the hydrogels was carried out in buffer solutions in a pH range from 1.4 to 8.6 with an ionic strength of 0.1 mol L^{-1} at 37 °C, respectively. As seen in Fig. 2(a), it is found that increasing pH leads to gel swelling, and an evident swelling transition of IPN hydrogel can be observed with pH increasing. This effect is related to the ionization of PAA network (Zhang and Peppas, 2000; Liu and Fan, 2002; Liu et al., 2004a,b; Philippova et al., 1997; Chen and Hoffman, 1995; Torres-Lugo and Peppas, 1999). With the increase in pH values, the ionized carboxylic acid groups' electrostatic repulsion forces hydrogel networks expanding, and cause its swelling degree reaching to a relatively larger value accordingly. Also, as seen clearly from Fig. 2(a), swelling transition of the IPN begins at pH 5 while that of hydrogel PAA is about pH 3, and the ESR value of the IPN show much less than that of pure PAA hydrogels at the same pH. These indicate that the presence of hydrophobic PBA network leads to the shift of pH-sensitivity of PAA to a higher pH region (Philippova et al., 1997), and can limit swelling degree of hydrophilic network. For example, at pH 1.4, the ESRs of IPN and PAA are 1.3 and 4.8, respectively; at pH 7.4, the ESR is 7.8 for the IPN, and 45.1 for PAA. These results are mainly due to amphiphilic structure of the IPN sample. When the IPN was immersed in an aqueous solution, a marked phase separation of hydrophobic PBA and hydrophilic PAA took place further. PAA network absorbed water and was swollen; while PBA network formed hydrophobic

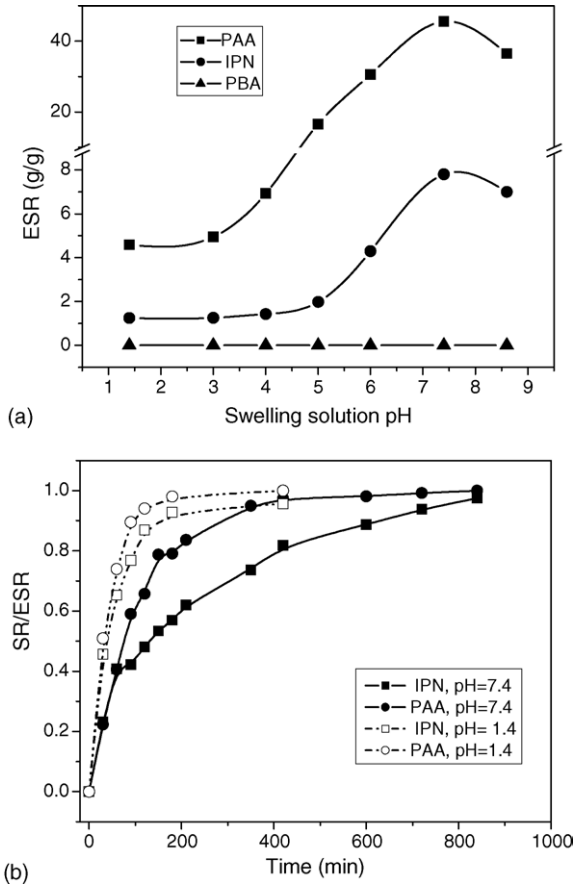

Fig. 2. Swelling behaviors of hydrogels IPN and PAA at 37 °C: (a) ESR as a function of pH; (b) swelling kinetic analysis.

aggregation. Thus, swelling PAA network must overcome resistance of hydrophobic aggregation of PBA. The final swelling degree of the IPN should be a balance of two adverse and competitive effects. Therefore, under fixed conditions, equilibrium swelling degree of the IPN depends on driving force from PAA network expanding, which is related to the ionization of PAA (Philippova et al., 1997). At low pH, PAA network remains collapsed, and as a result, the IPN has a low swelling degree. At

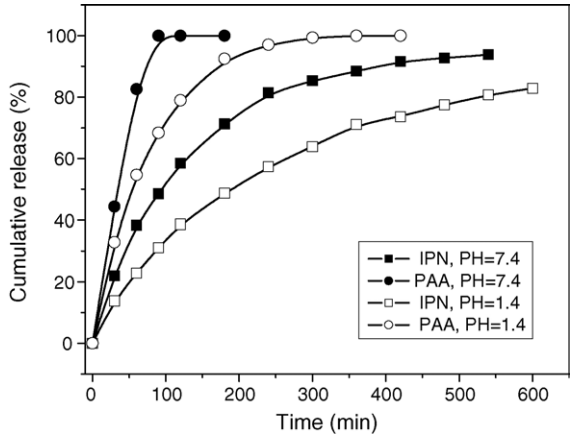

Fig. 3. Release profiles of MEL from hydrodels IPN and PAA under the conditions of pHs 1.4 and 7.4, and 37 °C.

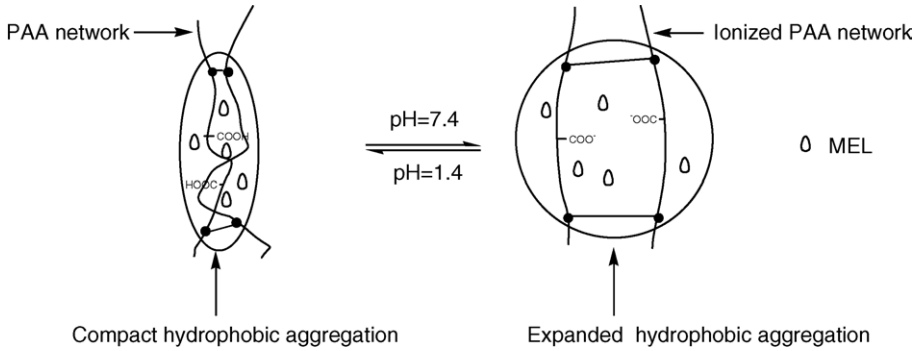

Fig. 4. Schematic illustrations for pH-dependent swelling and MEL release behaviors of the amphiphilic IPN.

higher pH, carboxylic acid groups' electrostatic repulsion forces IPN networks expanding, and this renders IPN having a higher swelling ratio. The hydrophobic effect was also observed in the copolymer hydrogels of AA with *n*-alkyl acrylates ($n = 8$, 12 and 18) by Philippova et al. (1997). Fig. 2(b) also shows swelling kinetic analysis of the IPN. Compared with pure PAA hydrogel, the needed time reaching equilibrium swelling state is much longer. This result indicates that the presence of hydrophobic PBA increase relaxation time of swelling the IPN (Torres-Lugo and Peppas, 1999). This result further confirms that swelling IPN is a process of PAA network expanding which overcomes resistance of hydrophobic aggregation of PBA.

Fig. 3 presents the release profiles of MEL from the IPN hydrogel and reference sample PAA at pHs 1.4 and 7.4, and 37 °C. As seen clearly from Fig. 3, the release rate of MEL from hydrogels IPN and PAA depends on hydrogel structures and pH conditions. Compared with hydrogels PAA, the release of MEL from the IPN shows lower release rate at regardless of pHs 1.4 or 7.4. At pH 7.4, the cumulative amounts of the MEL released from hydrogels IPN and PAA are 48.5% and about 100% for 90 min, respectively, and this means that the MEL release from PAA is a typically burst effect whereas the release from the IPN is a sustained release. At pH 1.4 for 90 min, the corresponding cumulative amounts of the MEL released are 31 and 68.4%, respectively. The results evidence that the presence of hydrophobic PBA retards the release of MEL and thus lead to a sustained release.

Although swelling degree of the hydrogels is a factor for MEL release, the presence of hydrophobic aggregation may be a dominant factor. This is because, although the ESR of the IPN at pH 7.4 is higher than that of PAA at pH 1.4 (see Fig. 2(a)), the release rate of MEL from PAA is higher at pH 1.4 (see Fig. 3). This result can be explained by hydrophobic aggregation of PBA network. As mentioned in swelling research of the IPN, PBA can forms hydrophobic moieties in hydrogel IPN as depicted in Fig. 4. The hydrophobic moieties may encapsulate MEL molecules. However, the density of hydrophobic aggregation depends on environment pH. At low pH, owing to PAA network possessing low swelling capacity, thus a compact hydrophobic aggregation can be formed in the IPN, leading to much more diffusion resistance of MEL loaded into the hydrophobic moieties and a low release rate of MEL. At pH 7.4, owing to higher swelling degree under expanding interaction of ionized PAA network due to interlocked structure, compact hydrophobic moieties may be weaken, or destroyed partly, leading to diffusion resistance of MEL loaded into the hydrophobic moieties reduced markedly and a higher release rate compared with that at pH 1.4. In our previous study, it is found that the release of MEL from poly(2-hydroxyethyl acrylate) (PHEA) hydrogel also shows higher rate and at 37 °C for 60 min, 72.1% of all loaded MEL can be release; however, the hydrophobic inclusion interaction of MEL with β-cyclodextrin can retard its release from PHEA (Liu and Fan, 2005). Therefore, here, we can conclude reasonably that the hydrophobic environment formed by PBA network indeed plays an important role in controlled MEL release. Actually, the new pH-modulated release was carried out by controlling density of hydrophobic aggregation related to environment pH, leading to controlled MEL release. The experiment indicates clearly that the amphiliphic IPN used as MEL carrier can indeed combine properties of pH-sensitivity of PAA and hydrophobicity of PBA. From the viewpoint of architecture forms of amphiphilic polymers, the IPN hydrogel is novel, since this is based on physically interlocked interaction of two networks without covalent bonding. This may be useful in designing and developing novel controlled delivery systems.

4. Conclusions

A pH-responsive amphiphilic hydrogel with IPN structure for controlled drug release was proposed. The IPN was constructed with hydrophilic PAA and hydrophobic PBA by a sequential UV solution polymerization. Here, the composition of PBA/PAA is found to be 40/60 (w/w). Using drug MEL as a model molecule, the controlled drug release behaviors of the IPN were investigated. It is found that not only the release of MEL from the IPN can respond to change in pH, but also the presence of hydrophobic network can overcome disadvantageous burst effect of hydrophilic network. This may be a result of hydrophobic aggregation encapsulating MEL molecules. The study will be very useful in designing and developing novel controlled delivery systems.

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