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Drug Release from pH-sensitive Interpenetrating Polymer Networks Hydrogel Based on Poly (ethylene glycol) Macromer and Poly (acrylic acid) Prepared by UV Cured Method

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Acrylate-terminated poly (ethylene glycol) (PEG) macromer was prepared by the reaction of PEG with acryloyl chloride. Photopolymerization of PEG macromer resulted in the formation of cross-linked PEG network. Interpenetrating polymer networks (IPNs) based on PEG and poly(acrylic acid) (PAA) was obtained via template polymerization of AA to the PEG network by UV curing. The swelling degree of the IPNs hydrogel increased with an increase of pH value due to the association-dissociation between carboxylic acid of PAA and ether of PEG through hydrogen bonding. The swelling-deswelling behavior proceeded reversibly for the IPNs upon changing pH. Release of indomethacin from the IPNs demonstrated "on-off" regulation with pH fluctuation.

Key words : PEG macromer, Interpenetrating polymer networks, Hydrogel, "On-off" regulation

INTRODUCTION

One of the novel approaches in delivering drug is stimuli-sensitive drug delivery system. This new controlled drug delivery system is being explored to overcome the tolerance problems that occur with a constant delivery rate, to mimic the physiological pattern of hormonal concentration and to supply drugs on demand (Langer, 1990). Stimuli-sensitive polymers, which are potentially useful for pulsed drug delivery, experience changes in either their structure or their chemical properties in response to changes in environmental conditions (Kost, 1990). Environmental stimuli include temperature (Hoffman *et al.*, 1986), pH (Siegel *et al.*, 1988a), light (Ishihara *et al.*, 1984, Suzuki *et al.*, 1990), electric field (Kwon *et al.*, 1990) or certain chemicals (Ishihara *et al.*, 1984). Intelligent materials are integral in this system because they not only sense the environmental conditions, but also regulate the release of drugs (Kost *et al.*, 1991).

Particularly, the pH-sensitive polymers can be used for enteric coating, site specific targeting, or tumor specific delivery. When they are used as an enteric coating material, acid labile drugs can be protected in the stomach. It was investigated the specific drug delivery to the colon where proteolysis is relatively low by using hydrogels that contain both acidic comonomers and enzymatically degradable azoaromatic crosslinks (Brondsted *et al.*, 1991). An insulin delivery system with feedback control was developed, using a pH-sensitive membrane in which glucose oxidase was immobilized. It was proposed that a new concept, wherein a pH-sensitive, swollen hydrogel acts as a force generator that is "turned on" when the pH inside the gel is lowered in response to an increased blood glucose level via the immobilized glucose oxidase (Siegel *et al.*, 1988b). Peppas *et al.* reported pH-sensitive hydrogels based on copolymers of hydroxyethyl methacrylate (HEMA) and methacrylic acid (MAAc) or maleic anhydride in order to investigate the mechanism of swelling-controlled, pH-sensitive drug release systems (Peppas *et al.*, 1989).

Most polymer pairs are more or less immiscible and hence incompatible. For improving the compatibility of given polymer pairs, we prepared an interpenetrating polymer networks (IPNs), in which two different polymers are forced to mix with each other through chemical cross-links within each component (Sperling, 1981). For IPNs, synergistic effects may result from two homopolymer components. To combine these advantageous features of the IPNs, we tailored poly (ethylene glycol) (PEG)/poly (acrylic acid) (PAA) IPNs via template polymerization so that reversible swelling-deswelling behavior would take

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place within the IPNs.

In this article, we want to report a modulated drug release based on IPNs hydrogel composed of PEG macromer and PAA for pH-sensitive drug delivery system. The IPNs hydrogel was prepared by UV curing method because there are no disposal of solvents into the atmosphere, low energy requirements, minimization of the thermal abuse of the polymer compositions during processing and a simple manufacturing procedure. It may be expected the drastic swelling change which show low swelling in low pH of the stomach and high swelling in the neutral pH of the small intestine. Also, we expect that this functional IPNs hydrogel can play an important role in the future design and development of modulated drug delivery systems.

MATERIALS AND METHODS

Materials

PEG with molecular weight 7.5 K was obtained from Wako Pure Chem. Inc.. Acryloyl chloride was purchased from Jassen of Reagent Chimica. Indomethacin was purchased from Sigma Chem. Co.. 2-Hydroxy isobutyl phenol was kindly supplied by Kansai Paint Co. Ltd.. Acrylic acid and methylene chloride were obtained from Junsei Chemical Co. Ltd.. 2, 2'-Dimethoxy-2-phenyl acetophenone (DPA) was purchased from Aldrich Chemical Company, Inc.. N, N'-methylene bisacrylamide(MBAAm) was purchased from Tokyo Kasei. PEG was purified by azeotropic distillation from benzene solution. Acrylic acid(AA) was purified by vacuum distillation. All other chemicals were of reagent grade and used without further purification.

Synthesis of PEG macromer

The method of the PEG macromer synthesis was previously reported (Kim *et al.*, 1995). A total of 12 g of purified PEG 7.5 K was added in 150 ml of benzene in a 500 ml round-bottomed flask and heated to 80°C in an oil-bath. A total of 0.46 ml of triethylamine and 0.61 ml of acryloyl chloride were added to the flask and the reaction mixture was stirred for 3h at 80°C. The reaction mixture was filtered to remove triethanolamine hydrochloride and the macromer was obtained by pouring the filtrate into n-hexane. Then, it was dried at 40°C under vacuum overnight.

Synthesis of PEG networks

Ten microliters of the initiator solution (2-hydroxy isobutyl phenol) was added to the methylene chloride solution of PEG macromer(concentration of PEG macromer 20wt-%: w/w). The solution was completely mingled by magnetic bar and irradiated using a low-density LWUV lamp (Toshiba Chemical Lamp FL 20LB : wave range 300~400 nm, maximum intensity 360 nm) for 3 min and the solution was then evaporated to dryness at 4°C. Then, the prepared network was repeatedly washed to remove unreacted PEG macromer with cold water 5 times with 30 min interval. The network was washed with acetone, and then dried at 40°C under vacuum overnight.

Preparation of PEG/PAA IPNs

The IPNs was prepared by sequential IPNs method. DPA (photoinitiator) and MBAAm (crosslinker) were added to the THF solution of AA monomer. The PEG network was immersed into AA solution for 24h at 4°C. Then the immersed network was irradiated for 5 min using a low-density LWUV lamp. The prepared IPNs were dried under vacuum overnight at 40°C.

Swelling measurement

The swelling ratio was measured by weighing the IPNs after wiping the excess water on the surface. Swelling ratio was calculated as Ws/Wd, where Ws and Wd are wet weight and dry weight of the IPNs, respectively. All the solutions prepared for swelling and release had the same ionic strength (I=0.1).

Indomethacin loading and *in vitro* release

The drug was loaded by soaking the IPNs in a saturated ethanolic solution of indomethacin in order to achieve a high drug loading in the IPNs. Then the indomethacin loaded disk was dried in vacuum at room temperature. The disk was introduced into an elenmeyer flask with 100 ml of one of the two buffer solutions (one was pH 1.4, the other pH 7.6), alternately. The mixture was allowed to stir in a shaker whose temperature was maintained at 37°C. At predetermined time intervals, the first buffer solution of the whole volume was withdrawn and 100 ml of the second buffer solution was put into the flask. The concentration of released indomethacin was monitored using a UV-spectrometer at 264 nm.

RESULTS AND DISCUSSION

The FT-IR spectrum of the PEG showed an absorption band at 3,447 cm^{-1} due to the terminal hydroxyl group (not shown in Fig.) (Deng *et al.*, 1990). This band became weak in the PEG macromer due to acrylation. A new absorption was seen at 1,726 cm^{-1} in the PEG macromer due to the carbonyl bond of acrylate group (Pavia *et al.*, 1979). The band at 2,872 cm^{-1} was attributed to the C-H stretch (Andini *et al.*,

1988) and was present in both polymers. Also, the NMR spectrum for PEG macromer showed small peaks for the three protons of acrylate group at 4.8, 5.0 and 5.2 ppm (not shown in Fig.). These results indicate that the terminal hydroxyl groups in the PEG precursor were converted to acrylate groups by the reaction with acryloyl chloride. Since PEG has two hydroxyl groups per molecule, the number of acrylic groups upon the PEG is expected to be 2.

The procedure for IPNs preparation is schematically shown in Fig. 1. The IPNs was prepared by sequential IPNs synthesis and hence two polymers in it are crosslinked within each component. For the IPNs, PEG and PAA chains which are present as independent chains between crosslinking points of each network can form ladder-like polymer complexes between carboxylic acid of PAA and ether of PEG through hydrogen bonding.

Fig. 2 shows the swelling ratio of PEG/PAA IPNs against an incubation time with various pH values. These results show that swelling ratios are dependent on the solution pH and increase as the pH increases. It is thought that dissociation of polymer-polymer complex between PEG and PAA takes place with an increase of pH and results in the electrostatic repulsion of the carboxylate ions of PAA.

Fig. 3 demonstrates that size of IPNs was changed by repeatedly altering pH 1.4 and pH 7.6 solution as the medium in which the IPNs was suspended. In this figure, the original length l_0 refers to the scale of the disk at pH of 1.4 and Δl is the size changes in the IPNs length with a pH jump. The IPNs elongates and contracts as the pH of the medium is raised or lowered, respectively. The process was also reversible, although the rates of contraction and elongation became uneven upon repeated exchanges of the pH medium. It is also thought that association-dissociation of polymer-polymer complex occurs with changes of pH. The extent of elongation of the IPNs increases with pH increments.

Fig. 4 shows the dramatic swelling shifts of the IPNs by altering the medium pH. It may be considered that the reversible swelling ratio is the effect of the hydrogen bonding formation and destruction by switching pH by turns. Obviously, these results represent that the crosslinking density is a factor of swelling ratio. The IPNs with low crosslinking density shows higher swelling ratio than that with high crosslinking density.

Fig. 5 demonstrates the profile of indomethacin release by applying an on-off function of pH at 37°C. During the on step the pH was 7.6 and large amount of indomethacin was released. But small amount of indomethacin was released at pH 1.4 from the IPNs. In comparison with the above results of pH-dependent swelling ratio, it is possible to conclude that the release of loaded drug is controlled by the rate of

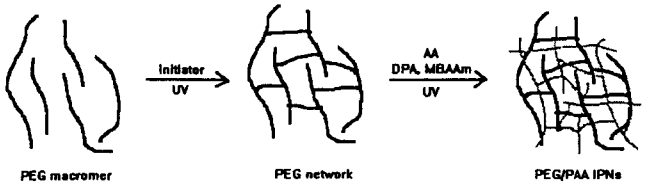

Fig. 1. Schematic diagram of the process of PEG/PAA IPNs preparation.

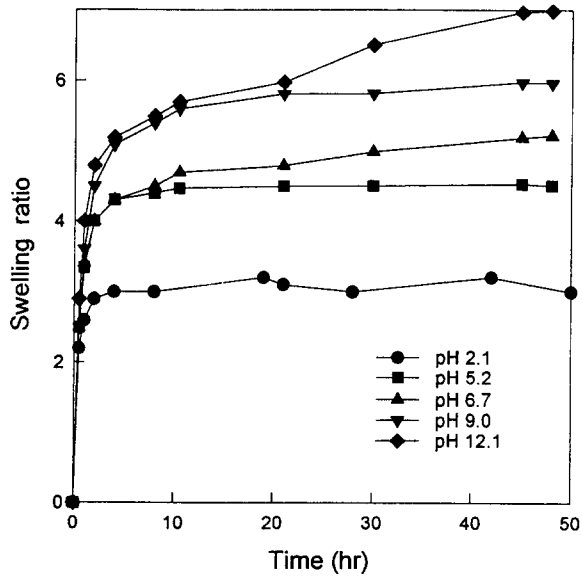

Fig. 2. Swelling ratio of PEG/PAA IPNs with various pH values. Each point represents the mean±SD of at least 3 experiments.

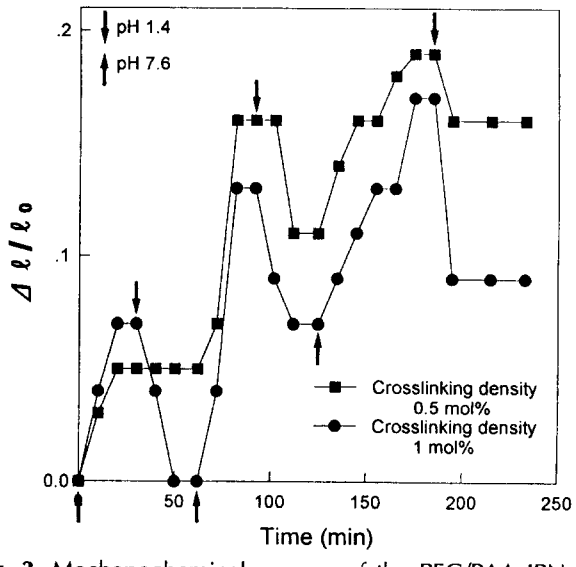

Fig. 3. Mechanochemical process of the PEG/PAA IPNs induced on alternating addition of pH 1.4 and pH 7.6 solution. Each point represents the mean±SD of at least 3 experiments.

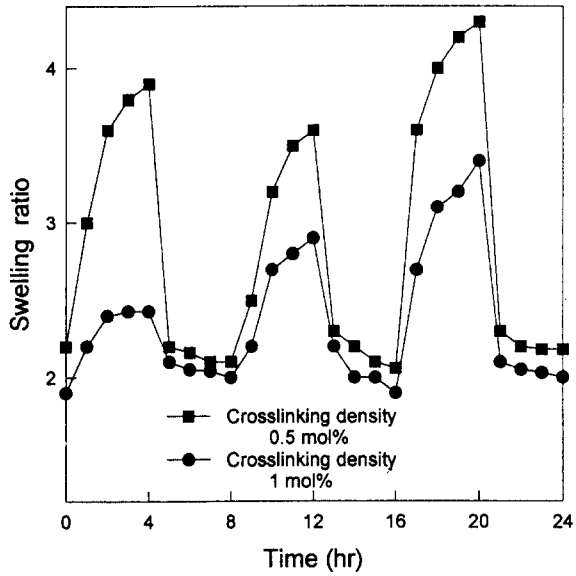

Fig. 4. Reversible swelling ratios of the IPNs induced upon pH change with different crosslinking density. Each point represents the mean±SD of at least 3 experiments.

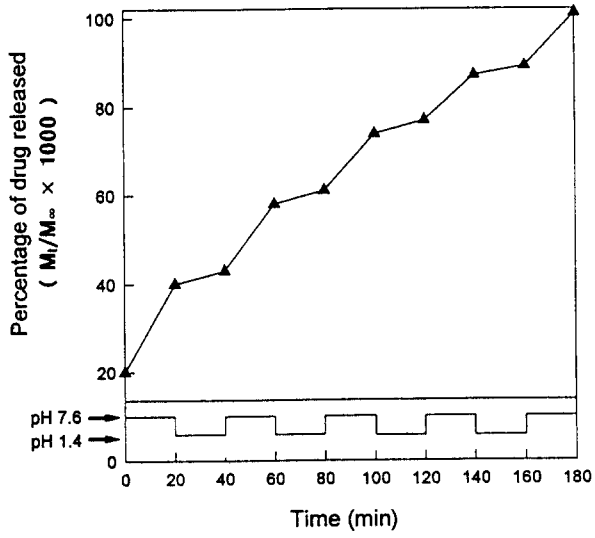

Fig. 5. Release of indomethacin from the PEG/PAA IPNs with the application of step-function pH. Each point represents the mean±SD of at least 3 experiments.

swelling.

Fig. 6 schematically illustrates the process of the hydrogen bonding formation and dissociation (Nishi *et al.*, 1989). This can be attributed to the association and dissociation through hydrogen bonding between carboxylic acid of PAA and ether of PEG. At the pH below the pKa value PAA is associated with PEG through hydrogen bonding and the chain relaxes into a more compact structure, whereas at the pH above the pKa value, PAA is dissociated from PEG and also releases protons from the carboxyl groups. As the number of carboxylate anions in the PAA network increases with pH, the swelling ratio also increases.

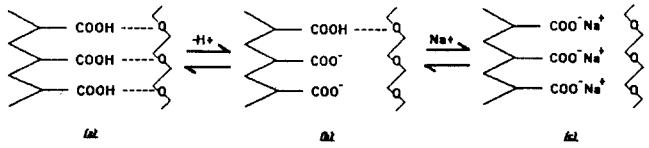

Fig. 6. A schematic illustration of the hydrogen bonding formation and dissociation according to pH values: below pKa value(a), around pKa value(b), and above pKa value of PAA (c).

These processes are reversible. Thus, at high pH, an increase in swelling degree is due to repulsion between the ionic charges within the IPNs. From these results, it may be applied to create a pulsed drug delivery system.

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