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Poly(MAA-co-AN) hydrogels with improved mechanical properties for theophylline controlled delivery

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Abstract

A hydrophobically improved copolymer hydrogel was constructed and developed based on methacrylic acid (MAA) and acrylonitrile (AN) monomers. The swelling investigations indicated that the hydrogels were highly sensitive to the pH and ionic strength of the surrounding environment. The swelling ratios of the gels in stimulated intestinal fluids (SIF, pH 7.4) were higher than those in stimulated gastric fluids (SGF, pH 1.4), and followed a non-Fickian and a Fickian diffusion mechanism, respectively. The results match well with scanning electron microscopy observations showing that mesh sizes in hydrogels in SGF are larger and more patulous than in SIF. It is believed that the phenomena are concerned with the electrostatic repulsion originating from the formation and dissociation of carboxyl groups, as well as a charge screening effect of the cations leading to the reduction of osmotic pressure. A dynamic mechanical analyzer revealed that the addition of hydrophobic AN units notably improved the compression mechanical properties of the control sample. With an increase in AN concentrations, the ability for the copolymers to resist compression deformation enhanced in distilled water and the compression strains have almost the same values in SIF environments. Differential scanning calorimetry was used to analyze the state of water and to determine the amounts of freezing and non-freezing water. The controlled release examination based on the theophylline model drug showed that the release rate in distilled water was faster than that in SIF or SGF. The introduction of the hydrophobic AN decreased the theophylline release rates in both SIF and SGF, and the release rate variation in SIF was notably larger than that in SGF. The drug release behavior of the AN-modified P(MAA-co-AN) copolymer hydrogel deviates from the Fickian diffusion control mechanism. This hydrogel is expected to be used as an excellent material in oral drug controlled release.

Keywords: Hydrogel networks; Controlled drug delivery; pH sensitivity; Mechanical property; Kinetic modeling

1. Introduction

In recent years, smart or intelligent materials have become one of the most promising carriers in controlled-release drug delivery systems (DDSs). They are the most capable materials for meeting a patient's physiological needs at an appropriate time or a right site [1]. The hydrogels used in drug delivery systems are always of great interest because hydrogels are able to alter their volume in response to environmental stimili expeditiously [1–4]. For some specific drugs, sustaining a long-time release feature is very important as it could provide a continuous delivery of drugs, thereby preventing any problems inherent in the cyclic variations in drug concentrations in the blood with time, and could offer a maximal pharmacological efficiency at a minimal drug dose [5].

In the design of oral drug delivery, drugs must be protected from such a harsh environment as gastric or intestinal media before they can be released and absorbed in some physiological medium. The pH values of physiological media should be precisely controlled because of their importance in all functions of the human body. One

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example is the change in pH values from the gastrointestinal tract to the small intestine; namely, from an acid pH to a neutral or slightly base pH environment. This physiological change plays an important role in selective absorption of drugs. Therefore, pH-sensitive hydrogels, as specific drug carriers, have attracted much attention and have presented a promising and immeasurable prospect recently [6–8]. Although mechanical properties are not essential from an oral delivery's point of view, the samples are mechanically too poor and brittle, and difficult to handle without breaking owing to the existence of a large quantity of water at a swollen state, which in turn has impact on the subsequent experimental operations, including swelling, drug loading and releasing [9]. On the other hand, as a possible candidate for tissue engineering materials, poor mechanical properties will limit the use of hydrogels for load-bearing applications such as the replacement of damaged or diseased tissues [10,11]. Therefore further improvement in mechanical properties is deemed necessary. This can be obtained by means of the preparation of interpenetrating polymer networks (IPN) [10], the incorporation of inorganic ordered systems [12], the increase in cross-linker concentration [13], a copolymerization with hydrophobic monomers or with rigid cyclic monomers [14].

Polymethacrylic acid (PMAA) hydrogel, as a typical pH-responsive hydrogel, has received considerable recognition. In this work, our objective is to report a new kind of pH-responsive copolymer hydrogel containing acidic or other polar groups in polymer chains based on methacrylic acid (MAA) and acrylonitrile (AN) monomers, so as to improve mechanical and drug controlled release behavior of the control sample, the blank PMAA hydrogel. The resulting copolymer hydrogels are expected to have outstanding pH response and to be utilized in tissue engineering materials and drug control delivery fields as a potential biomaterial.

2 Materials and methods

2.1. Materials and reagents

The methacrylic acid (MAA), analytical grade (AG), supplied by the Tianjin Jinyu Fine Chemicals Ltd., Corp., was distilled in vacuum at 62 °C in a pressure of 0.09 MPa. The acrylonitrile (AN, AG), provided by the Xi'an Chemical Regent Factory, was distilled two times prior to use in order to remove inhibitors and trace water. The cross-linker, *N*,*N*-methylenebisacrylamide (BIS, AG), was purchased by the Tianjin Kermol Chemical Regent Developing Center. Ammonium persulfate (APS) and sodium bisulfite (SBS) as initiators were recrystallized before use. Phosphate buffers with various pH values of 1.4, 2.8, 5.5, 7.4, 8.8, and 11.7 as physiological mediums were prepared with Na_2HPO_4, NaH_2PO_4, and HCl, H_3PO_4 in order to examine the swelling behavior, and NaCl was used to adjust the ionic intensities. Theophylline, supplied by the No 2 Factory of Shanghai Chemical Regents, is an effective drug for the treatment of asthma and pulmonary disease [2] and was used as a model drug in release studies.

2.2. Synthesis of hydrogels

Hydrogels were synthesized based on two types of vinyl monomers. The quantities used in our study are shown in Table 1 (unless otherwise specified, symbols a, b, c and d represent one sample with varying compositions, respectively).

Two types of monomers with various compositional proportions were poured into a cannular reactor. Then double-distilled deionized water, APS, SBS and BIS (0.5 wt.% of the total weight of the two monomers, see also Table 1) were added into the monomer mixture in turn. The mixture solution was bubbled with nitrogen for 20 min to remove the dissolved oxygen that could inhibit the reaction. The polymerization reaction was carried out at 60 °C for 24 h. The crosslinked rod-like samples were cut into disks with a thickness of 3 mm. Subsequently, the disks were flushed with deionized water for one week to remove the residues of unreacted monomers and cross-linking agents. A NaOH solution of 1 M was employed to titrate the remaining aqueous solution after immersing until no acidic substance was detected. All disks were dried in a vacuum oven at 30 °C until constant weight. A Fourier transformation infrared spectroscopy was adopted to validate structures of the P(MAA-co-AN) copolymers prepared [15].

2.3. Swelling studies

The above-mentioned xerogel disks were allowed to hydrate in excess phosphate buffers of 1.4, 2.8, 5.5, 8.8, and 11.7 at 37 °C, respectively, in line with the literature [16]. After fully hydrating, the samples were taken out and the excess water on their surface was gently removed by filter paper. The weights of the hydrating samples were measured at timed intervals. The swelling ratio (R) and equilibrium swelling ratio (R_e) are calculated by the following equations [17,18]:

$$R = (W_s - W_d)/W_d \quad (1)$$

$$R_e = (W_e - W_d)/W_d \quad (2)$$

Where W_s is the weight of the swelled hydrogels at time t; W_d is the weight of the dried hydrogels and W_e denotes the weight of the gels at equilibrium swelling.

Table 1
Proportions of various ingredients used in the synthesis of hydrogels

Samples	a	b	c	d
Ratio of MAA to AN (w/w)	100: 0	94: 6	88: 12	84: 16

The amount of both APS and SBS (5 wt.%) was designated as approximately 1.4% of the total weight of MAA and AN monomers, and the content of BIS 1 wt.%.

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