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Swelling behavior of temperature- and pH-sensitive block terpolymers for drug delivery

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Summary

Hydrogels prepared by block terpolymerization of N-isopropylacrylamide (NIPAAm), acrylic acid (AA) and 2-hydroxyethyl methacrylate (HEMA) exhibit significant temperature sensitivity due to the block structure of the NIPAAm moiety, even at concentrations as low as 10 mol%. pH-Sensitivity was also observed due to the ionizable AA component. The swelling ratio dependence on temperature is significantly more prominent for block terpolymers than for the corresponding random terpolymers.

Introduction

The objective of the design of controlled drug delivery systems is to release a pharmacologically active agent in a predetermined, predictable, and reproducible fashion. Until recently, much of the work in this field focused on obtaining constant release of this active agent (1). However, pulsatile controlled release has received increased attention recently (2). A pulsatile controlled release device ideally releases increased levels of drug in response to external stimuli. Thus, the polymer carrier is designed to react to physiological changes, thus releasing the drug and imitating natural biofeedback mechanisms.

Hydrogels capable of reversible swelling with changes in environmental temperature and pH have been considered as a means of delivering drugs (2). As the hydrogel is stimulated to swell by its external aqueous environment, the mesh size of the matrix increases by allowing water to diffuse inwards. As a result, drug previously loaded into the matrix can diffuse out. When the environment changes, the hydrogel responds appropriately by decreasing its mesh size thereby limiting drug release from the system. Due to the crosslinked nature of hydrogels, their swelling/deswelling can be used to control drug diffusion behavior and is usually reversible over several cycles. Polymers of AA or methacrylic acid (MAA) demonstrate a sharp sensitivity to external pH.

Polymers of NIPAAm display temperature sensitivity due to a thermodynamic phenomenon known as lower critical solubility temperature (LCST) behavior. This behavior is associated with polymer phases separation as the external temperature is raised to a critical temperature of 32 °C for PNIPAAm (3). Copolymers of NIPAAm and AA have also been investigated for applications in which independent responsiveness to temperature and pH is required (3). However, in order for NIPAAm-containing random copolymers to show this temperature dependence, the NIPAAm content must be significant. For these reasons, various copolymers containing continuous segments of NIPAAm have been recently developed. For example, Chen and Hoffman (4) studied graft

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copolymers consisting of PNIPAAm side chains grafted onto a pH-sensitive backbone consisting predominantly of PAA. Yoshida et al. (5) prepared comb-type grafted hydrogels of PNIPAAm exhibiting similar behavior. In our work, we prepare terpolymeric hydrogels containing blocks of NIPAAm and exhibiting temperature sensitivity even at very low NIPAAm contents.

Experimental

N-isopropylacrylamide (NIPAAm, Eastman Kodak, Rochester, NY) was first dissolved in benzene, filtered and recrystallized in hexane. For the preparation of block terpolymer gels, NIPAAm was first homopolymerized at 25±1 °C in a reaction vessel containing deionized water (at an 1:10 NIPAAm to water molar ratio), using 1 mol% (of the total monomers) ammonium persulfate and 1 mol% sodium metabisulfite as initiators. This mixture was stirred for approximately 10 minutes and until its viscosity increased slightly. In a separate reaction vessel, a mixture containing 80 mol of vacuum-distilled 2-hydroxyethyl methacrylate (HEMA, Aldrich Chemical Co., Milwaukee, WI), 10 mol vacuum-distilled acrylic acid (AA, Aldrich Chemical Co., Milwaukee, WI) and 1 mol ethylene glycol dimethacrylate (EGDMA, Aldrich Chemical Co., Milwaukee, WI) as a crosslinking agent was prepared and added dropwise to the NIPAAm mixture. The molar ratio of NIPAAM:AA:HEMA was 10:10:80. The contents were immediately transferred to 10 mL propylene vials which were sealed and allowed to react for 24 hours in a 37 °C constant temperature water bath. For the preparation of random terpolymers, the reaction of the three monomers was carried out in one step by adding all monomers in one vessel and reacting them under the previous conditions.

Following the polymerization reaction, the hydrogels were removed from the vials and dried in ambient conditions. Thin discs were sliced by the use of the diamond-blade rotary saw, and they were extracted in stirred, 1 liter flasks of deionized water until the absorbance of water at 277 nm was zero. The discs were then dried under vacuum at 37 °C until a constant weight was obtained.

Thin discs (diameter of approximately 14 mm and a thickness of 0.8 mm) of the previously prepared terpolymers were dried to a constant weight in a vacuum oven at 37 °C for approximately 3 days and their dry weights were recorded. The discs were then placed in vials containing a pH=6 buffered solution (prepared by dissolving 43.74 g of $Na_2HPO_4 \cdot 2H_2O$ and 7.11 g of $H_3C_6H_5O_7 \cdot H_2O$ in 1.6 L of deionized water) and immersed in a water bath at 32 °C for at least three days in order to attain their corresponding equilibrium swollen state. The previously equilibrated gel samples (pH=6) were transferred to a pH=5 buffered solution (prepared by adding 50 mL of 0.2 M potassium biphthalate solution to 22.6 mL of 0.2 M sodium hydroxide) at 37 °C for 30 minutes and returned to the pH=6 buffered solution at 32 °C for 30 minutes. This cycle was repeated several times.

Results and Discussion

Figure 1 shows the swelling behavior of the random terpolymer with a 10:10:80 NIPAAM:AA:HEMA molar ratio under conditions of changing pH at a constant temperature of 37 °C. The weight swelling ratio, q, is equal to the swollen weight divided by the dry weight of the polymer sample. The initial equilibrium weight swelling ratio at pH = 6 was approximately 5.6. The inverse of q yielded a polymer weight fraction, w_p, of

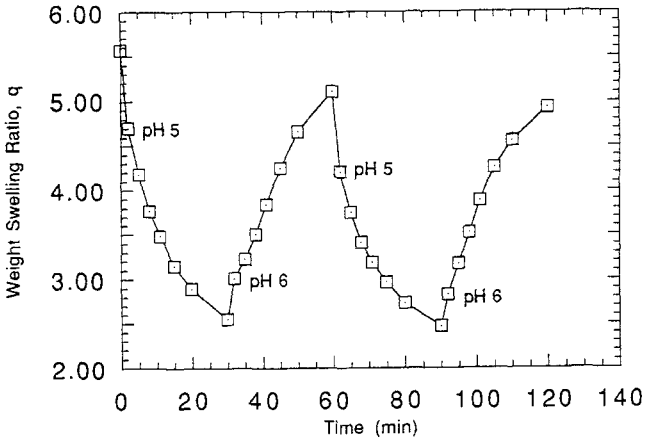

Figure 1. Weight swelling ratio of a random terpolymer of NIPAAm, AA and HEMA (molar ratio 10:10:80) cycled between buffered solutions of pH = 5 and 6 at 37 °C.

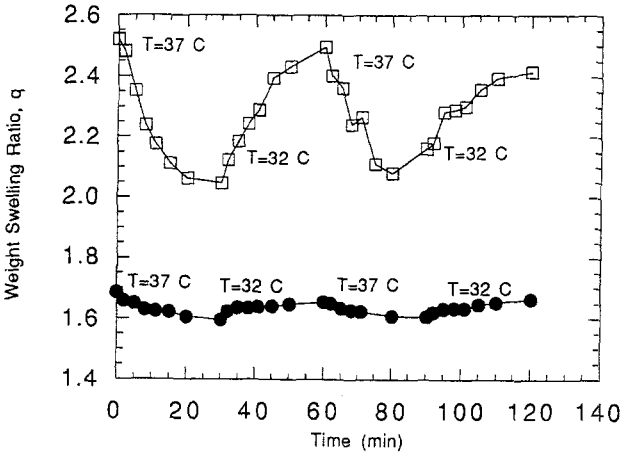

Figure 2. Weight swelling ratio of a block (●) and a random terpolymer (❑) of NIPAAm, AA and HEMA (molar ratio 10:10:80) cycled between temperatures of 32 °C and 37 °C at a constant pH = 5.0.

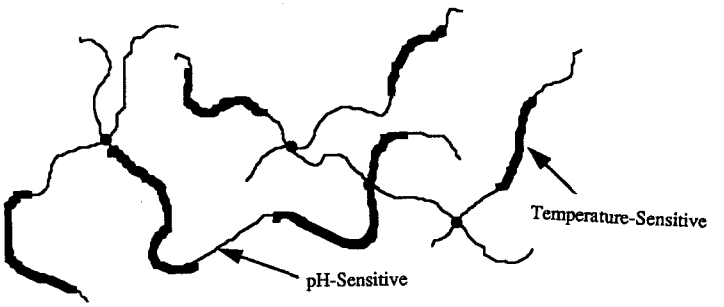

Figure 3. Structure of block terpolymer containing blocks of NIPAAm in a random copolymer of AA and HEMA.

0.18. Upon transferring this swollen disc to a pH=5 buffered solution, q initially decreased rapidly, with initial deswelling rate of 0.44 min^{-1}. Prior to transferring the gel back to the pH=6 buffered solution, the deswelling rate had decreased to 0.034 min^{-1}. The weight swelling ratio fell from 5.5 to approximately 2.5. Upon transferring the polymer sample to the pH=6 buffered solution, the swelling rate was initially 0.23 min^{-1} which is only half of the initial deswelling rate of 0.44 min^{-1} . The weight swelling ratio reached a value of 5.1, which corresponding to a polymer weight fraction of 0.19. This pH-dependent swelling/deswelling behavior was due to the AA repeating units, which ionize as the pH of the gel increased.

However, the temperature sensitivity in these randomly copolymerized gels was low when compared to their pH sensitivity as shown in Figure 2. At a pH = 5, the random terpolymer containing 10% NIPAAm showed a very small change of its weight swelling ratio as a function of time and as the gel was cycled from 37 °C to 32 °C.

The temperature sensitivity of these hydrogels was increased without increasing the mol% of NIPAAm by preparing block terpolymers with the chemical structure shown in Figure 3. In essence, NIPAAm blocks were prepared and were randomly distributed by reaction with other monomers. By increasing local NIPAAm concentrations in this manner, the specific temperature sensitivity of the monomer could be amplified.

The results of the pulsatile temperature swelling study of a block polymer with a 10:10:80 NIPAAm:AA:HEMA molar ratio are shown in Figure 2. With an equilibrium weight swelling ratio of 2.52, or a polymer weight fraction of 0.40 at 32 °C, the block terpolymer gel collapsed in the 37 °C environment to a weight swelling ratio of 2.05, or a polymer weight fraction of 0.49. When comparing block terpolymers with random terpolymers of identical composition the block gel showed a significantly higher degree of

temperature sensitivity. More specifically, the weight swelling ratio of the block polymer changed by 19% when pulsed from its equilibrium weight swelling ratio at 32 °C to 37 °C. In comparison, the weight swelling ratio of the random polymer changed by only 5.3%. Clearly, the block terpolymer gel is a better candidate as a carrier from release of drugs at specific intervals.

Conclusions

Swelling studies performed indicated that hydrogels with AA concentrations of as little as 10 mol% showed sharp swelling changes when the pH of the swelling medium was changed. In order to increase the temperature-sensitivity of the hydrogels without increasing the concentration of NIPAAm, block terpolymers consisting of PNIPAAm blocks distributed within P(AA-co-HEMA) were successfully synthesized. These hydrogels displayed a significantly higher temperature-sensitivity than the random terpolymers.

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