Research Article

pH-Dependent Swelling and Solute Diffusion Characteristics of Poly(Hydroxyethyl Methacrylate–CO–Methacrylic Acid) Hydrogels

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Poly(hydroxyethyl methacrylate–co–methacrylic acid) hydrogels can swell extensively in a high-pH medium where the carboxyl groups are ionized. The swelling equilibrium is a strong function of the methacrylic acid composition of the polymer and pH of the medium. The nonionized gel structure was found to be rather insensitive to the amount of cross-linker, tetraethylene glycol dimethacrylate (TEGDMA), incorporated, within the range of 0.5 to 3%. This result is supportive of the existence of secondary interactions that shield the effect of covalent cross-links. Phenylpropanolamine (PPA) was used as a probe solute to study the diffusion characteristics of the poly(HEMA–co–MA) gels. Its diffusion coefficient in the swollen matrices of different methacrylic acid compositions at various pH’s was measured via a desorption method. It is evident that these diffusion coefficients follow Yasuda’s free volume theory, which expresses an exponential relationship between the solute diffusivity in a swollen polymer membrane and the reciprocal of the membrane hydration. Although interactions exist between PPA and the hydrogel matrix, these interactions are not significant enough to perturb the free volume relationship established. This observation can be explained by the high ionic strength of the system.

KEY WORDS: hydrogel; pH-dependent swelling; diffusion; free volume.

INTRODUCTION

While the release kinetics of swelling polymers have received considerable attention (1–3), the drug release mechanism and kinetics of hydrogel materials whose swelling is pH dependent have not been reported. Potential applications of these systems include delayed and controlled oral delivery, altered gastrointestinal transit following gastric emptying, and site-specific gastrointestinal delivery based on regional pH differences (4,5). In order to access the potential of pH-dependent swelling systems, it is necessary to understand the mechanism of swelling and drug release from these systems.

Cross-linked hydrogels with ionizable side chains can swell extensively in aqueous media. The swelling behavior depends on the nature of the side groups as well as the pH of the medium. In this work, copolymers of 2-hydroxyethyl methacrylate (HEMA) and methacrylic acid (MA) cross-linked with tetraethylene glycol dimethacrylate (TEGDMA) were investigated. This report focuses on the studies of matrix swelling and its subsequent influence on the drug release rate. Phenylpropanolamine (PPA) was chosen to be the model compound for the release study due to its stability and water solubility. Since solute diffusion in hydrophilic polymers depends mainly on the water content of the matrix, the equilibrium swelling will be characterized at various pH’s and copolymer compositions. The release characteristics of PPA from the swelling gel matrix are determined, and the diffusion coefficients of PPA in these swollen gels quantitated and subsequently correlated to the water content of the matrices. It is also anticipated that interactions between PPA molecules and the ionized gel matrix will occur. Therefore, the effect of the charge density on the PPA diffusion coefficient is investigated and the extent of its influence delineated.

MATERIALS AND METHODS

Synthesis of Poly(Hydroxyethyl Methacrylate–co–Methacrylic Acid) Hydrogels

The hydrogels were prepared from monomeric materials via a free radical mechanism. 2-Hydroxyethyl methacrylate⁴ and methacrylic acid⁴ were purified before use, while cross-linker tetraethylene glycol dimethacrylate⁵ was used as received. The detailed procedure of HEMA purification was discussed by Brinkman et al. (6). The HEMA monomer was extracted with hexane and followed by vacuum distillation (250 μHg; 55°C). Cuprous chloride was used as the polymerization inhibitor in the distilling flask. The methacrylic acid

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was relatively pure and was distilled only under vacuum (1.5 mm Hg; 45°C).

The hydrogel slabs were synthesized via solution polymerization. The monomer mixture contained 40% (w/w) water initially. Various monomer and cross-linker concentrations were used to prepare gels of different compositions. The methacrylic acid concentration ranged from 1 to 50% (w/w), and TEGDMA from 0.5 to 3% (w/w) in the monomeric mixtures. The monomer solution was then initiated with a redox couple of ammonium persulfate and sodium metabisulfite. The reacting mixture was injected into a mold made of two glass plates spaced 1.8 mm apart by a silicone rubber gasket. The reaction was allowed to run for 2 hr at 60°C. The resultant polymer was removed and washed in portions of fresh distilled water for at least 1 week before use to purify the residual reactants from the gel.

The hydrogel cylinders were fabricated in the polyethylene tubing (3-mm i.d.) via bulk polymerization. The methacrylic acid compositions used in monomeric mixtures were 10 and 30% (w/w), and the TEGDMA concentration was fixed at the level of 0.2% (w/w). The monomeric solution was initiated with 1% 2,2'-azobisisobutyronitrile (AIBN) and then injected into a straight polyethylene tubing. The two ends were then sealed and the entire enclosure was maintained in a 60°C water bath for 12 hr. The polymer cylinder was removed and cut into segments 3 cm in length. The polymer gels were washed in portions of fresh distilled water for a period of at least 1 week before further use. Structural identification was not performed with these gels since the polymerization procedure for the methacrylate monomers was well established and documented (8–11). For the rest of the discussion, whenever methacrylic acid composition is described, it is intended to mean the composition of the monomeric solution from which the polymer is made.

Equilibrium Swelling Study

In the swelling study, only the hydrogel slabs made via solution method were used. Gels of different compositions were cut into squares of 1.8 × 1.8 cm² and equilibrated in 0.1 M HCl solutions until the weight was stabilized. The gels were then transferred to pH 7 buffers of 0.1 M ionic strength. Sample weight was followed and sufficient time was allowed to reach swelling equilibrium. The experimental procedure was maintained at 37°C throughout. Two indices, SR and H, were used to represent the equilibrium swelling behavior. The swelling ratio (SR) was defined by

\[
SR = \frac{\text{equilibrium weight at pH 7}}{\text{equilibrium weight at pH 1}}
\]

The matrix hydration (H) was defined by

\[
H = \frac{\text{equilibrium swollen gel weight} - \text{dry gel weight}}{\text{equilibrium swollen gel weight}}
\]

Drug Release and Measurement of Diffusion and Partition Coefficients

Phenylpropanolamine was used as obtained without further purification. Gels of different methacrylic acid compositions were used in these experiments. Drug loading was carried out by equilibrating the gel sample in a 2% drug solution at a proper pH. The ionic strength for both loading and extracting media was kept at 0.2 M. If the gel slab was used, a sample 3 cm in diameter was used. The loaded sample was clamped between a circular plexiglass ring and a base permitting release over one surface, and the composite was anchored in the extracting medium by a plexiglass rod. If the gel cylinder was used, the sample was held in a stainless-steel wire basket. The volume of the extracting fluid was 200 ml, and the stirring speed 120 rpm. PPA samples were assayed by an ion-pairing high-performance liquid chromatographic (HPLC) method.

The mathematical analysis employed in calculating diffusion and partition coefficients from the desorption experiments is based on a diffusion model developed by Lee (7). The advantage of this model is that the analysis allows the external bulk concentration to increase with time via a mass balance at the gel/bulk fluid interface. Experimentally, one then can use any bulk volume for extraction and the sink condition is not required. In addition, partition coefficient can be determined based on the initial loading and final equilibrium drug concentrations. The working equation for evaluating the diffusion and partition coefficients for planar geometry is

\[
\tau = \frac{3\Lambda^2}{4} \left[ \ln \frac{C_b - C_{bl}}{C_{b2} - C_{b1}} + \frac{1}{2} \left( \frac{C_{b2} - C_{bl}}{C_b - C_{bl}} \right)^2 - \frac{1}{2} \right] = \frac{Dt}{a^2}
\]

where

\[
\Lambda = \frac{C_{bo} - C_{bl}}{C_{b2} - C_{bo}} = \frac{V}{2KAa}
\]

and for cylindrical geometry,

\[
\tau = \frac{3}{40} \left[ \ln \left( \frac{C_{b2} - C_{bl}}{C_b - C_{bl}} \right) - 1 \right]^3 + \frac{3(3\Lambda + 5)}{160} \left[ \frac{C_{b2} - C_{bl}}{C_b - C_{bl}} - 1 \right]^2 \frac{3\Lambda^2(5 - 3\Lambda)}{80} \ln \left( \frac{C_{b2} - C_{bl}}{C_b - C_{bl}} \right)
\]

where,

\[
\Lambda = \frac{C_{bo} - C_{bl}}{C_{b2} - C_{bo}} = \frac{V}{kMr^2L}
\]

The diffusivity can be calculated from the slope of the \( \tau \) versus \( t \) plot, and \( k \) from the equilibrium concentration data using Eq. (2) or (4). Please refer to the Nomenclature for the definitions of various quantities involved in these equations.

RESULTS AND DISCUSSION

Swelling Equilibrium

Experimental SR values determined from gels of dif-