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THE SWELLING PROPERTIES OF POLY(2-HYDROXYETHYL METHACRYLATE) HYDROGELS POLYMERIZED BY GAMMA-IRRADIATION AND CHEMICAL INITIATION

J.M. WOOD, D. ATTWOOD and J.H. COLLETT

Pharmacy Department, University of Manchester, Manchester M13 9PL (England)

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SUMMARY

The swelling behaviour of polyHEMA hydrogels in aqueous solutions of various compounds has been investigated. Gels polymerized using a chemical initiator attained a higher equilibrium hydration in aqueous solutions than those polymerized by ionizing radiation. The difference in equilibrium hydration has been explained in terms of the effect of residual initiator on swelling. Aqueous solutions of sodium chloride, sucrose and glucose were found to dehydrate the gels, while solutions of phenol, urea, acetic acid, acetamide, ethanol, sodium acetate and ethyl urea caused swelling. The extent of swelling was a function of the osmotic activity, size, lipophilicity and number of hydrogen bonding groups of the solute molecule. A linear relationship was found between the swelling rate and the concentration of cross-linking agent in the gel.

INTRODUCTION

Poly(2-hydroxyethyl methacrylate) (polyHEMA) gels are the most widely investigated of the acrylic hydrogels, for their applications as polymeric implants in the controlled release of drugs. The gels are usually prepared by free-radical polymerization of 2-hydroxyethyl methacrylate (HEMA) in the presence of water. The radicals may be generated by: (a) chemical catalysts; (b) UV radiation in the presence of a photosensitive chemical; or (c) ionizing radiation. One disadvantage of chemical catalysis and UV irradiation procedures is that the chemicals must subsequently be leached from the gel, since their presence causes problems of biocompatibility with living tissue. A second problem is that chemicals may interact with the polymer chains and affect the gel network structure, thereby altering both the swelling porperties of the gel, and the diffusion characteristics

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of an embedded drug. In this work the swelling characteristics of gels polymerized with a chemical catalyst are compared with those polymerized using γ-radiation. Swelling has been examined following the immersion of gels in solutions of compounds of biological interest, viz. sodium chloride, urea and sucrose. The swelling properties of radiation-polymerized gels have also been investigated in aqueous solutions of structurally related organic compounds, in order to investigate any relationship between the swelling properties of the gel and the structure of the solute.

MATERIALS AND METHODS

2-Hydroxyethyl methacrylate and ethylene glycol dimethyacrylate (EGDMA) (Fluka) has stated purities of 95% and 98% respectively and were used as received. The following reagents were used in hydration experiments: acetamide; ethyl urea; D-glucose, anhydrous (A.R); phenol crystals (A.R); salicylic acid (A.R); sodium acetate; sodium benzoate; sodium salicylate; sucrose (A.R) (BDH Chemicals); acetic acid (SLR); ethanol (A.R); sodium chloride (A.R); urea (SLR) (Fisons Ltd).

Ammonium persulphate (A.R) was obtained from BDH Chemicals.

Preparation of gels

Gels were prepared by copolymerization of HEMA with EGDMA (0.125–0.875%) in the presence of 20–45% (v/v) water. The monomers were mixed with the aqueous phase and the mixture degassed for five minutes.

Chemically polymerized gels

The monomer solutions containing 0.5% (w/v) ammonium persulphate were incubated at 55°C under nitrogen in glass vials for 18 h.

Radiation-polymerized gels

Polymerization was carried out at ambient temperature by γ-irradiation of a solution of monomer in distilled water with a dose of 300 krad from a 2000 Ci ^{60}Co source.

Hydration experiments

Sections of gel of equal size (approximately 3 g and 4 cm^2) were weighed, then immersed in the appropriate solution (0.5 M) at 22°C. They were removed at specified intervals, blotted to remove the superficial liquid, and weighed in closed weighing bottles. The degree of swelling was estimated from the observed percentage increase or decrease in weight.

RESULTS AND DISCUSSION

Swelling in water

As seen from Fig. 1, chemically polymerized gels have a higher equilibrium hydration than gels of the same initial water content which have been polymerized by radiation. The swelling curve of chemically polymerized gels shows a maximum followed by a minimum, and then a gradual reswelling of the gels. This behaviour is ascribed to the presence

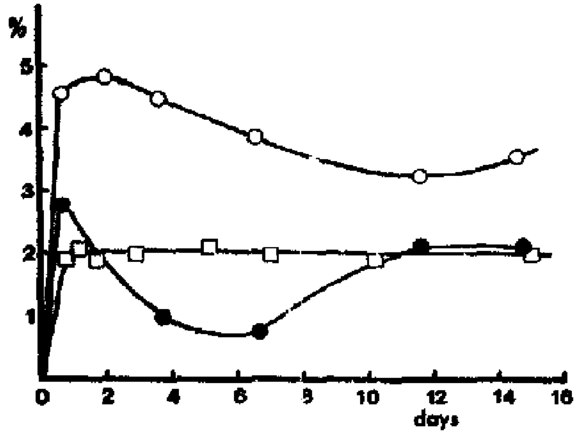

Fig. 1. Percentage weight increase against time for polyHEMA gels immersed in water. Gels contained 0.875% EGDMA, with initial water contents of ○, 40% (chemical polymerization); ●, 45% (chemical polymerization) and □, 40% (radiation polymerization).

of residual chemical initiator in the gels. When a gel is placed in water, the ammonium salt diffuses out of the polymer under a concentration gradient. Dusek et al. (1977) have found that, in general, it is the anion of an electrolyte which governs swelling behaviour. The persulphate ion present in the gel may be adsorbed onto the polymer chains, conferring a negative charge and so causing a mutual repulsion between them. Consequently the network expands and swelling is observed. As the ion diffuses out of the gel, the polymer chains assume their normal alignment and the gel deswells. The magnitude of swelling is smaller for a gel of higher initial water content because of the lower swelling pressure. The magnitude of deswelling is greater, however, because the network has a greater free volume, allowing the salt and water to diffuse out more easily (Yasuda et al., 1968).

The reswelling of the gels after the point of maximum deswelling may be a consequence of a slower diffusion rate of salt within the gel than from the surface layer, which causes a temporary depletion of the part of the network in contact with the surrounding solution. Repletion of the surface layer with salt causes a further expansion of this part of the network and water diffuses in, thus creating the minimum in the swelling curve.

TABLE 1

EQUILIBRIUM HYDRATION VALUES (AS PERCENTAGE WEIGHT CHANGE) OF polyHEMA GELS IN 0.5 M SOLUTIONS

Solute	Method of polymerization	
	Radiation	Chemical
Sucrose	−11.0	−6.8
Sodium chloride	−6.8	−3.2
Urea	9.3	11.0

Diffusion of a salt from the gel centre to the surface occurs more rapidly for a gel of greater free volume, so reswelling occurs after approximately 8 days for gels containing 45% water, as opposed to 14 days for those with 40% water.

Radiation-polymerized gels show a steady weight increase, and equilibrium hydration is reached fairly rapidly. Here, the swelling pressure is governed only by the physical and chemical nature of the polymer.

Swelling in aqueous solutions

Effect of polymerization method on swelling properties

Table 1 shows the hydration rates and equilibrium water contents of radiation- and chemically polymerized gels in 0.5 M solutions of sucrose, urea and sodium chloride. Hydration values of chemically polymerized gels are again higher than those of radiation-polymerized gels, due to the presence of persulphate. Sodium chloride and sucrose caused dehydration of the gels, whereas urea caused swelling. The presence of sodium chloride and sucrose in the solution surrounding the gel causes an imbalance of chemical potential. Equilibrium is restored mainly by the movement of water out of the gel; the diffusion of solute into the gel network also occurs but to a much lesser extent. At equilibrium, the osmotic pressure of the solution is equal to the swelling pressure of the gel which is governed by the contractility of the network.

The effect of urea on polyHEMA gels has been investigated by several workers (Refojo, 1967; Ratner and Miller, 1972; Dusek et al., 1974). The evidence suggests that the mechanism of interaction is dependent on the urea concentration, but that at a concentration of 0.5 M, urea probably exerts its effects by breaking hydrogen bonds in the region of the polymer side-chains (Ratner and Miller, 1972). The cohesion of the polymer network is thereby reduced, the swelling pressure is raised, and the network expands.

Effect of solute structure on swelling

In view of the complex hydration changes caused by residual ammonium persulphate in chemically initiated gels, further studies were restricted to an examination of the swelling characteristics of radiation-polymerized gels in aqueous solutions. Figs. 2 and 3 show the swelling properties of gels immersed in equimolar solutions of several organic compounds which are structurally similar to urea or sucrose, or which have the same functional groups. It can be seen that the gels show a similar pattern of swelling in solutions of most of the compounds under investigation. The exceptions are glucose, phenol and sodium acetate. The magnitude of deswelling is smaller in glucose than sucrose because the molecular size of glucose facilitates its diffusion into the gel network. The gel immersed in sodium acetate shows deswelling prior to swelling, which is at first sight surprising. The acetate ion is less hydrated than the chloride ion, and so might be expected to exert a greater salting-out effect. The change from deswelling to swelling probably reflects penetration of the salt into the gel, which is facilitated by the methyl group on the ion. If the same solute is mainly in the unionized form, as is acetic acid (0.63% ionized at pH 2.5), it is able to penetrate into the gel more easily and swelling then increases markedly. Swelling is probably caused by the solute disrupting the intermolecular bonding, thus affecting the network cohesion, and raising the swelling pressure.

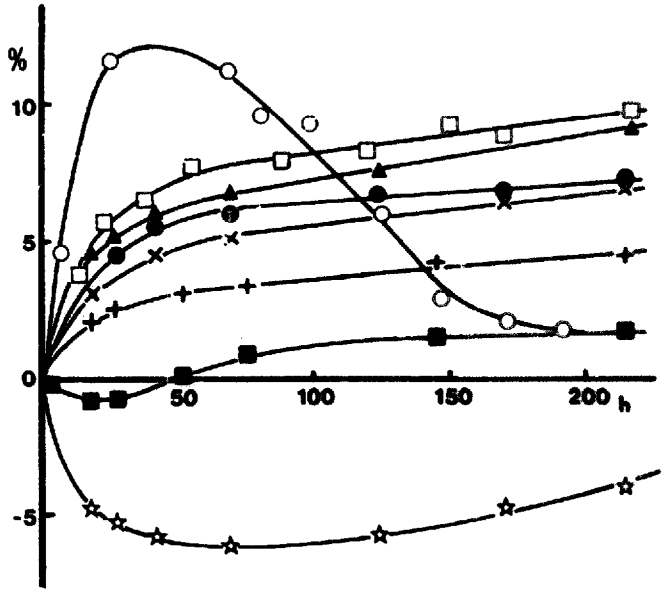

Fig. 2. Percentage weight increase against time for radiation polymerized polyHEMA gels (40% water, 0.875% EGDMA), when immersed in 0.5 M solutions of ○, phenol; □, ethyl urea; ▲, urea; ●, acetic acid; X, acetamide; +, ethanol; ■, sodium acetate; ☆, glucose.

Swelling of gels in acetamide is slightly lower than that of gels in urea, whilst the swelling in ethyl urea is higher than that in urea. It is evident that swelling is increased both by an increase in the number of hydrogen bonding sites and in the lipophilicity of the molecule. Acetic acid causes virtually identical swelling behaviour to acetamide, which would be expected from the similarity of their structures and molecular sizes. Ethanol has a smaller effect, probably because the absence of a carbonyl group reduces the possible number of polymer–solute interactions.

The very high swelling in solutions of sodium benzoate and salicylate compared with

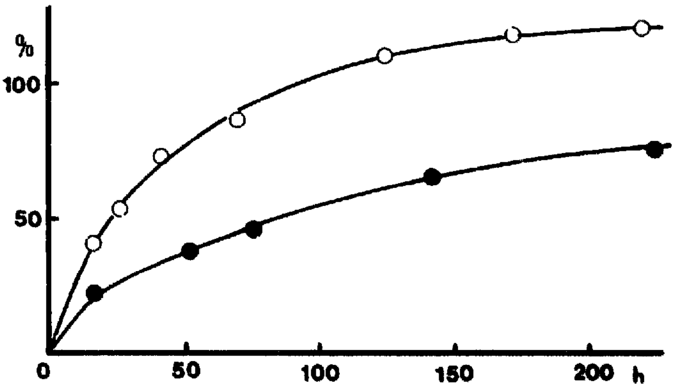

Fig. 3. Percentage weight increase against time for radiation-polymerized polyHEMA gels (40% water, 0.875% EGDMA), when immersed in 0.5 M solutions of ○, sodium salicylate and ●, sodium benzoate.

that in sodium acetate (Fig. 3) suggests that these compounds interact in a different way with the polymer, or with a different part of the network. The aromatic ring of the benzoate and salicylate ions may disrupt the hydrophobic bonding between the methyl groups or chain backbones of the polymer. In addition, the hydroxyl group of sodium salicylate may allow more water molecules to penetrate into the regions of the network into which the compound is sorbed, or it may cause the molecules to be more effective in disrupting the hydrophilic regions of the network.

In 0.5 M phenol, the gel shows maximum swelling at 26 h, after which time it deswells (Fig. 2). It was observed that placing the gel in a phenolic solution caused the gel surface to become opaque almost immediately. The opacity gradually progressed from the outer region into the centre of the gel over a period of days, with the outer region becoming clear again. Turbidity, or microsyneresis, generally occurs when more solvent is incorporated into the gel than can be solvated by the hydrophilic polymer side-chains (Refojo and Yasuda, 1965). The rate of diffusion of phenol into the gel is high and as it penetrates, phenol disrupts the hydrophilic regions in the gel, allowing water to diffuse in. Thus the swelling rate up to 26 h is very high. Although phenol might be expected to partition into the hydrophobic regions of the gel, the ionic character of the molecule is much lower than that, for example, of sodium salicylate, so it will probably not break down the structure of the hydrophobic regions and allow water to penetrate evenly throughout the network. Thus the gel separates into two phases, resulting in turbidity. As the network contracts to bring about a more homogeneous system, some of the excess solution in the gel is expelled, and so deswelling occurs after the maximum weight increase.

Effect of gel formulation on swelling

The effect on swelling with changing the gel formulation was examined. Fig. 4 shows that there is a linear relationship between the swelling rate in 0.5 M urea and the concentration of the cross-linking agent (EGDMA). The slope of this plot is -0.55×10^{-2} h^{-1} g^{-1} dl. The slope of a similar plot for gels in 0.5 M sodium salicylate is -3.48×10^{-2}

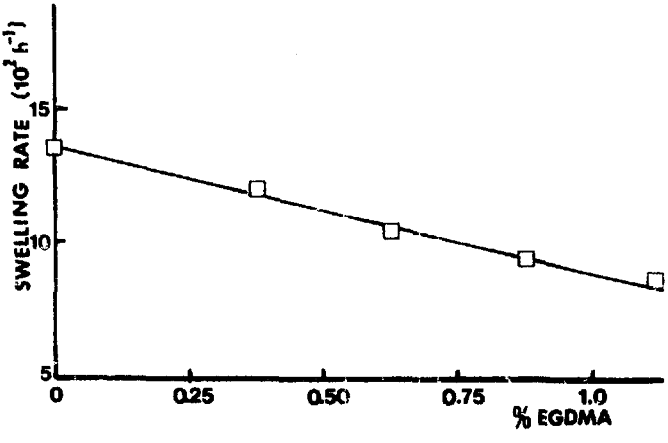

Fig. 4. Effect of the concentration of cross-linking agent (EGDMA) on the initial swelling rate of radiation-polymerized polyHEMA gels (40% water, 0.875% EGDMA) immersed in 0.5 M urea.

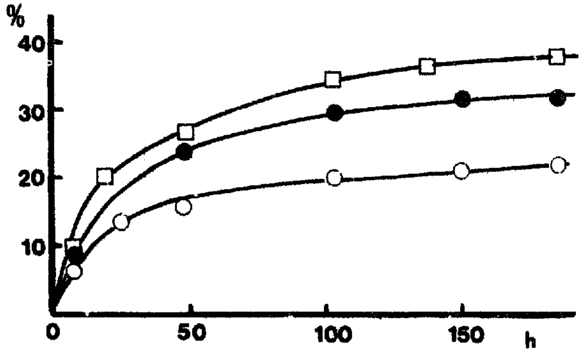

Fig. 5. Percentage weight increase against time for radiation-polymerized polyHEMA gels (20% water, 0.875% EGDMA) immersed in ○, water and 0.5 M solutions of ●, glucose and □, urea.

h^{-1} g^{-1} dl indicating a much greater dependence of swelling on the covalent cross-linking density when more of the non-covalent intermolecular bonds have been broken. Fig. 5 shows the swelling characteristics of gels of a higher polymer concentration. It can be seen that increasing the polymer concentration from 60% (Fig. 2) to 80% causes an increased swelling of the gel in 0.5 M glucose. The swelling here is explained in terms of: (1) a substantial reduction in the amount of unbound (freely diffusing) water in the polymer network at high polymer concentrations. Lee et al. (1975) have found that most of the water in an 80% polymer gel is bound water, i.e. it is bonded to the polar groups on the polymer side-chains and is not easily removed; and (2) the tendency of the gel network to expand and imbibe solvent until the polymer chains are maximally solvated (at approximately 40% in water). A gel of only 20% water will have a high swelling pressure; evidently higher than the osmotic pressure of 0.5 M glucose. Swelling in 0.5 M glucose is higher than that in water, indicating that glucose interacts with the polymer, and the contractile properties of the network are affected.

CONCLUSIONS

(1) Gels produced by chemical initiation and γ-irradiation had different swelling characteristics, and this could be attributed to the presence of the initiator in chemically polymerized gels. (2) The equilibrium hydration of polyHEMA gels is determined by the nature of the solute in the solutions in which they are immersed. (3) An inorganic electrolyte and the sugars, glucose and sucrose dehydrated the gel. (4) Organic solutes with hydrogen bonding polar groups generally caused swelling. (5) The degree of swelling appeared to be a function of solute molecular size, lipophilicity and hydrogen bonding capacity. (6) The swelling rate was proportional to the cross-linker concentration. It can be inferred that the swelling rate is directly related to the contractility of the network.

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