J. Pharm. Pharmacol. 1982, 34: 1–4
Received June 5, 1981

0022–3573/82/010001–04 $02.50/0

The influence of gel formulation on the diffusion of salicylic acid in polyHEMA hydrogels

J. M. WOOD, D. ATTWOOD AND J. H. COLLETT*

Department of Pharmacy, University of Manchester, Manchester M13 9PL, U.K.

The influence of solute concentration, gel hydration, and crosslinking density on diffusion rates in polyHEMA hydrogels has been investigated using a radio-tracer technique. At hydrations above 31% water, diffusion is by pore flow, and increases in the crosslinking density of gels bring about a decrease in the diffusion coefficient, D. Below 31% hydration, diffusion is predominantly by solution diffusion and changes in crosslinking density have little effect on the diffusion coefficient. The diffusion coefficient is invariant with solute concentration within the range reported, although at a very high solute concentration, for the gels of lower hydration, the diffusion coefficient is higher than expected. A high value for D may be due to saturation of the binding sites of the diffusant on the polymer chains, leaving a greater proportion of diffusant available for transport.

Considerable interest has recently been shown in the diffusion rates of solutes through hydrogels, in view of their potential use in drug delivery devices (Cardinal et al 1980). Diffusion rates, generally quantified in terms of diffusion coefficients, are used in the determination of factors governing release rates of drugs from these systems.

One non-destructive method available for measuring diffusion coefficients of radio-labelled solutes through a polymer is the double disc method (Park & Van Hoang 1979). This method is particularly suitable for studying diffusion in hydrogels because it avoids contact of the gel with an aqueous solution. Contact with aqueous solutions may result in swelling or dehydration of the gel (Wood et al 1981) which may alter the diffusion characteristics of the solute.

In this work, the double disc method has been used to measure diffusion coefficients of salicylic acid through poly (2-hydroxyethyl methacrylate) (polyHEMA) gels prepared by γ-irradiation. Salicylic acid has been chosen as the diffusant because it is relatively stable to γ-radiation. The effect of the polymer crosslinking density, polymer concentration and diffusant concentration on the diffusion coefficient has been investigated.

MATERIALS AND METHODS

2-Hydroxyethyl methacrylate (HEMA) and ethylene glycol dimethacrylate (EGDMA) (Fluka) had stated purities of 97% and 98% respectively and were used as received.

*Correspondence.

Salicylic acid, AR (BDH), salicylic acid [carboxyl-^{14}C] specific activity 59 mCi mmol^{-1} (The Radiochemical Centre, Amersham and New England Nuclear Corporation).

Preparation of gels

Aqueous solutions of HEMA, EGDMA and salicylic acid were deaerated using a vacuum pump (Edwards 25C20) and bubbled with 'white spot' nitrogen (B.O.C.) for 15 min. The solutions contained 59–67% of total monomer and the diffusant concentration range was 0·05–0·5% w/v. The labelled salicylic acid solution (5 μCi, 0·1 ml) was added to a known volume of monomer solution (approximately 3·5 ml) and the mixture poured into a mould consisting of two glass plates separated by a spacing ring of height 0·4 cm. Polymerization was carried out using γ-radiation from a 2000 Ci ^{60}Co source. Solutions were given a radiation dose of 300 krad at a dose rate of 6·14 krad min^{-1}.

After polymerization, discs of 1·36 cm diameter were cut from the gels. Gels containing no diffusant were prepared in a similar manner. The water contents of the gels were assayed by weighing a gel sample in a closed weighing bottle, then drying it to constant weight in a vacuum oven, and reweighing. The percentage hydration was calculated.

Measurement of diffusion coefficients

A gel containing radiolabelled salicylic acid was placed in face to face contact with a receptor gel containing no diffusant and the whole mounted on a glass scintillation disc (Nuclear Enterprises Ltd) with the receptor gel in contact with the disc. The

disc was placed over the photocathode of a photomultiplier tube (Panax Ltd). The upper surface of the donor gel was covered with an aluminium planchet to promote backscatter of radiation, so increasing the count-rate for any given activity of the sample. Sufficient pressure was applied to the planchet to maintain close and uniform contact between the two gels, without compressing them and squeezing out water. The gel assembly and photomultiplier were enclosed in a light-proof tower. A photomultiplier voltage of 1500V was found to give the highest ratio of the sample count to the background count under the experimental conditions. The count-rate was monitored continuously with a scaler unit (International Design Laboratories, model 7000), to which was attached a pen recorder. The background radiation was measured at the beginning of each experiment. The moment of contact between the two gels was taken as the start of the experiment.

Evaluation of the diffusion coefficients was made using the mathematical solutions of the diffusion equation applicable to diffusion in a plane sheet (Crank 1975). The time dependence of C, the concentration of radiolabelled diffusant at a distance x from the outer radioactive face in the double disc experiment can be expressed as:

$$C = C_0\left[\frac{h}{L} + \frac{2}{\pi}\sum_{n=1}^{n=\infty}\frac{1}{n}\sin\frac{n\pi h}{L}\exp(-Dn^2\pi^2t/L^2)\cos\frac{n\pi x}{L}\right]$$

where C_0 is the initial concentration of diffusant in the radioactive disc, h is the thickness of the radioactive disc, L is the composite thickness of the two discs, D is the diffusion coefficient, and n is an integer.

The above equation has been modified (Park & Van Hoang 1979) assuming β particle absorption is exponential, to give:

$$(A_0 - A_L) = \frac{4LA_\infty}{\pi h}\cdot\frac{[1+\exp(-\mu L)]}{[1-\exp(-\mu L)]}\sum_{n=1}^{n=\infty}\frac{\sin[(2n-1)\pi h/L]\exp[-(2n-1)^2\pi^2Dt/L^2]}{(2n-1)[1+(2n-1)^2\pi^2/L^2\mu^2]}$$

where A_0 is the activity at the originally active face after time t, A_L is the activity at the originally inactive face after time t, A_∞ is the activity at this face after infinite time, and μ is the β-particle absorption coefficient (cm^{-1}) for the polymer gel, given by:

$$\mu = \frac{22\rho}{E_{max}^{4/3}}$$ (Westlake & Johnson 1975)

E_{max} is the maximum emission energy of ^{14}C β particles (0·156 MeV) and ρ is the density of the polymer. Gel densities were measured using a Beckman Air Pycnometer.

Radiation stability of salicylate

To assess the degree of degradation of salicylic acid under the irradiation conditions used for the polymerization of HEMA, aqueous solutions of salicylic acid were irradiated and the concentration of salicylate assayed before and after irradiation. Four solutions, of concentrations 56, 80, 102 and 160 mg% were prepared, deaerated and bubbled with nitrogen as described previously, then irradiated under nitrogen. Samples were given a dose of 300 krad at a dose rate of 7·25 krad min^{-1} and a temperature of 25 °C. After irradiation, salicylate degradation was measured by measuring u.v. absorption intensities at 298 nm. Dilutions were made in 0·1 M HCl.

RESULTS AND DISCUSSION

Radiation stability of salicylate

Table 1 shows the percentage salicylate remaining unchanged after γ-irradiation of the aqueous solutions. The maximum percentage breakdown is approximately 6%. The percentage breakdown is less at high salicylate concentrations, as expected, and is probably due to increased protection from radiation damage afforded by the aromatic rings at high concentrations.

Table 1. Percentage salicylate remaining unchanged after gamma irradiation of aqueous solutions under nitrogen. Radiation dose = 300 krad.

Salicylate concn (mg %)	Percentage unchanged
56	93·76
80	96·14
102	96·82
160	98·50

Effect of gel hydration on diffusion coefficients

The influence of gel hydration on the diffusion coefficient of salicylic acid is shown in Table 2. There is an increase in values of D with increase in hydration. It has been found (Yasuda et al 1968) that for solutes which diffuse through the aqueous phase of the gel, D is a function of the reciprocal hydration according to the following equation:

$$\log D = \log D_0 - K\left(\frac{1}{H} - 1\right)$$

where D_0 is the diffusion coefficient of the solute

in water, H is the volume fraction of diluent in the polymer, and K is a constant. A plot of log D vs. 1/H

Table 2. Diffusion coefficients (D) in gels of different hydration H = volume fraction of water in gel.

D ($\times 10^8$ cm^2 s^{-1})	H
12·4	0·400
10·9	0·350
8·72	0·336
7·39	0·328
6·65	0·310
6·52	0·299
6·31	0·290
6·70	0·270
5·85	0·241

is expected to be linear for solutes which permeate through the pores of the polymer matrix.

Fig. 1 shows a linear relationship between log D and 1/H in the hydration range 0·31–0·40 (1/H = 2·5–3·23). Several workers have reported linear plots of log D vs. 1/H for several different polymers and diffusants (Yasuda et al 1968; Yasuda et al 1969; Olanoff et al 1979). The linear relationship is generally thought to be indicative of a decreasing average pore size and increasing percentage of bound water with increasing polymer concentration (Flynn et al 1974) and suggests therefore that diffusion is occurring mainly by pore flow in this region. There is a change of slope in Fig. 1 at a hydration value of 0·31 (31%). This suggests that a different mechanism of diffusion is occurring at low hydrations. Another accepted diffusion mechanism in polymers is solution-diffusion, which involves the dissolution and diffusion of the solute within the polymer segments.

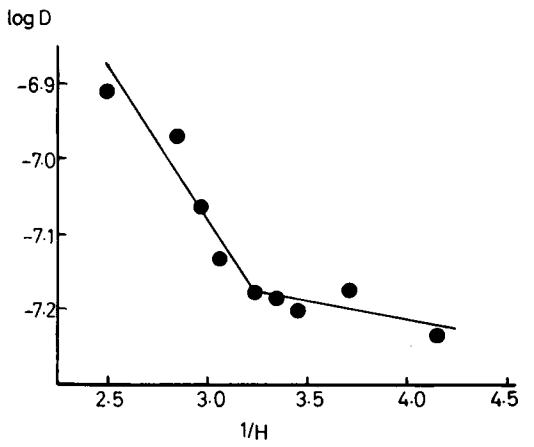

FIG. 1. Plot of log diffusion coefficient (D) as a function of reciprocal hydration (1/H)

Zentner et al (1978, 1979) have found that at small pore sizes, solution-diffusion is the predominant mechanism of diffusion through polyHEMA gels. The small decline in D after the change in slope may be due to decreasing segmental mobility of the chains.

Effect of Polymer crosslinking density on diffusion coefficient

Fig. 2 shows a linear decrease of D with increasing concentration of the crosslinking agent (EGDMA) in gels containing 35% water. The effect of crosslinking on the diffusivity may be interpreted in terms of (a) polymer chain mobility, (b) average pore size, and (c) mobility of the solvent in the gel. The reduction in polymer chain mobility caused by crosslinking will reduce the range of pore sizes present at any one time, and may reduce the average pore size. If diffusion of salicylic acid is occurring through the pores of the polymer matrix, the effect of these changes would be to reduce D. Reduction of the average pore size with increase of crosslinking density might be expected to result in a limiting value for D at high concentrations of crosslinking agent, as the pore diameter approaches the solute diameter (Chen 1974; Wisniewski et al 1976). A limiting value is not seen in Fig. 2, probably because the crosslinking density is not sufficiently high.

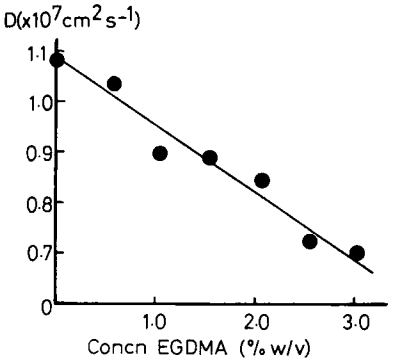

FIG. 2. Plot of diffusion coefficients (D) of salicylic acid in gels containing different concentrations of crosslinking agent.

An alternative explanation for the reduction in D with increasing crosslinking density is that the solvent mobility within the gel is being reduced. Crosslinking is thought to decrease the percentage of bulk water in the gel, and increase the percentage of bound and interfacial water (Lee et al 1974; Andrade et al 1975). Hydrophilic solutes are thought to diffuse mainly through the bulk water (Zentner et al

1979), so the effect of increasing the crosslinking density is to reduce the effective free volume of the polymer. Brown & Chitumbo (1975) found that the main factor limiting the diffusivity of small solutes in polyacrylamide gels was the mobility of the solvent in the gel.

Table 3. Diffusion coefficients of salicylic acid through polyHEMA gels containing 27% water and different concentrations of crosslinking agent.

EGDMA concn (% total monomer)	D ($\times 10^8$ cm^2 s^{-1})
0	6·60
1·49	6·64
2·24	6·59
2·98	6·74
3·73	6·75
4·48	6·77

If diffusion is occurring by solution-diffusion in gels containing less than 31% water, the crosslinking density would not be expected to have a significant effect on the diffusion coefficient. Table 3 shows the effect on D of changing the crosslinker concentration in gels of 27% water. It can be seen that the diffusion coefficient does not change significantly with crosslinker concentration, supporting the view that diffusion is not occurring by pore flow in these gels.

Table 4. Diffusion coefficients in gels containing 27% water (D27) and 35% water (D35), and different concentrations of diffusant.

Concn Diffusant (mg %)	D27 ($\times 10^8$ cm^2 s^{-1})	D35 ($\times 10^8$ cm^2 s^{-1})
126	6·36	10·23
200	6·46	9·96
275	6·17	8·79
400	6·74	10·42
500	7·22	8·81

Effect of diffusant concentration on D

Table 4 shows values of the diffusion coefficient at different diffusant concentrations, for gels of 35 and 27% water. It can be seen that within the range of concentrations 126–400 mg % the diffusion coefficient does not change significantly with concentration. The higher value of D for a solute concentration of 500 mg % and gel hydration 27% possibly indicates a saturation of the binding sites of the solute on the polymer chains. Consequently a greater proportion of solute molecules are available for transport. This effect is less noticeable in a gel of higher water content where diffusion is occurring by pore flow.

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