Drug release with simultaneous dimensional changes from a new copolymeric hydrogel

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The diffusional behaviour of sodium salicylate (SSA) from a new chemically crosslinked copolymeric hydrogel of 2-hydroxyethyl methacrylate with *N*,*N*′-dimethyl-*N*-methacryloyloxyethyl-*N*-(3-sulfopropyl)ammonium betaine is reported. The drug release into water was effected under sink conditions and the kinetics at 310 K were followed by continuous measurement of conductivity. A modified form of Fick's second law has been derived to take into account the dimensional changes of copolymer during drug release, which were measured photographically. The procedure was used to evaluate the diffusion coefficient D_s for transport of SSA into water. The value of $D_s = 4.4 \times 10^{-11}\ \mathrm{m^2\,s^{-1}}$ yielded over a range of drug loading is smaller than the load-dependent values obtained when allowance is not made for dimensional changes. The procedure has also been used to determine the diffusion coefficient for water into polymer.

(Keywords: copolymeric hydrogel; drug release; diffusion coefficient)

INTRODUCTION

Synthetic polymers have extensive use as contact lenses, in surgery[1,2] and as matrices for controlled drug release[3,4]. Commonly, the polymers are in the form of hydrogels[5-7]. Such materials are usually crosslinked polymeric or copolymeric networks containing a medium–high quantity of imbibed water[8-10].

As part of a programme on novel polymeric hydrogels, some fundamental swelling, thermodynamic and mechanical characteristics of materials based on 2-hydroxyethyl methacrylate (HEMA) with *N*,*N*′-dimethyl-*N*-methacryloyloxyethyl-*N*-(3-sulfopropyl)ammonium betaine (SPE)[11,12] were established by our polymer group. The zwitterionic SPE component imparts interesting and exploitable properties, including that of a greater affinity for aqueous salt than for pure water. Moreover, perhaps less predictably, the inclusion of SPE in a HEMA/SPE copolymer increases the water uptake compared with that of homopolymer PHEMA alone[13]. However, the value of Young's modulus of the PSPE hydrogel is much smaller than that of PHEMA, and the fragility of the former renders it rather unsuitable as a matrix for the drug-release study considered here. After preliminary tests, one particular copolymer composition was selected. Its hydrogel afforded the best mechanical properties and also possessed a moderately high water content.

Sodium salicylate (SSA) was selected as a convenient model drug because: (i) its solubility in water allows high loading of drug into polymer matrix from concentrated solutions and (ii) its release into water can be followed sensitively by conductivity measurements.

EXPERIMENTAL

Materials

Ultra-pure HEMA (Ubichem Ltd), SPE (Raschig), ethylene glycol dimethacrylate (EGDMA; Aldrich) and SSA (Sigma) were used as received. Distilled and deionized water was employed in swelling and release studies.

Polymerization

The monomer feed composition HEMA/SPE = 0.85/0.15 (mol/mol) was used for preparing the copolymer and a content of 2 wt% crosslinker (EGDMA) based on the total weight of the monomers was chosen, because it afforded a hydrogel of fairly high water content without excessive fragility. Water (40 wt% of the total) was added finally; otherwise, the solution tended to gel at ambient temperature. The mixture was made up gravimetrically and outgassed with nitrogen for 30 min in glass test tubes, which were siliconized previously[14]. After sealing, they were subjected to γ irradiation to a total dose of 10 kGy from a ^{60}Co source at a dose rate of $0.1\ \mathrm{kGy\,h^{-1}}$ measured by Fricke dosimetry. The resultant crosslinked polymer rods were immersed in water for two weeks to remove any possible residual monomer. However, because polymerization was shown to proceed to 100% conversion, the overall composition of the copolymer is the same as that of the initial feed mixture.

Discs, obtained from the hydrogel rods by cutting with a scalpel, were dried at ambient temperature for two days and then at 318 K for one day. Swelling and release experiments were carried out at 310 K.

Swelling of the copolymer in water

The diameter of the dry discs varied between 14 and 16 mm and their thicknesses ranged from 1.5 to 1.8 mm.

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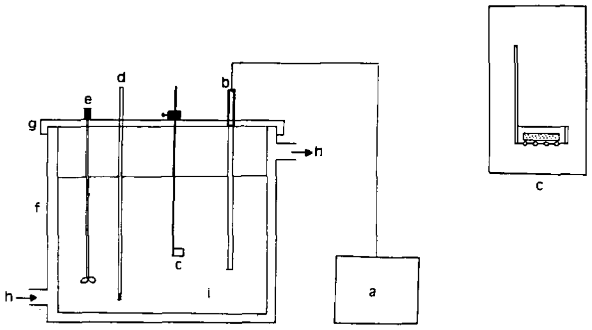

Figure 1 Sketch of the experimental device used: a, conductivity meter; b, conductivity cell; c, disc vessel, glass rod with perforated Teflon base; d, thermometer; e, stirrer; f, double-walled dissolution vessel; g, Teflon lid; h, water to and from recirculating thermostat; i, water. Insert (c): disc vessel showing loaded disc placed in extensively perforated Teflon holder

The xerogel discs (in the absence of SSA) were immersed in water. During swelling in water, the dimensions of the discs increased. The diameter of the discs during the swelling at each time was determined photographically using a Minolta X300 35 mm camera fitted with a Tamron 90 mm f/2.5 lens[9].

The fractional hydration (W_t) at different times was obtained as before[8-10]:

$$W_t = \frac{w_1 - w_0}{w_1} \tag{1}$$

Here w_1 and w_0 are the weights of swollen and dry discs respectively. The equilibrium water content of hydrogel (W_∞) was obtained after 12 h and was found to be 0.55 ± 0.01.

Loading of gels

SSA is very soluble in water (685 kg m^{-3} at 310 K)[15]. To load the drug into the gel, aqueous solutions of it having concentrations between 0.1 and 0.7 M were prepared. The xerogel was immersed in the solution until equilibrium was obtained (one day) and then dried at ambient temperature for two days. Finally, the discs were dried at 318 K and weighed to obtain the xerogel with a known concentration of salt.

The loads of the discs (A) were varied between 191 and 448 kg m^{-3}. The diameters (L_x) of the xerogels with salt were measured (to within ± 0.02 mm) with a micrometer. It should be noted that these loaded discs were difficult to obtain owing to their tendency to break on drying.

Release of SSA from the discs

Release experiments were performed by placing the discs in a perforated Teflon holder (see *Figure 1*, inset). In order to effect release from one surface only, an attempt was made to mask the interface between disc and container by coating one disc face with silicone grease. Unfortunately, this measure did not succeed, because the discs folded during swelling. Consequently, experiments were conducted in which release occurred at both surfaces.

The apparatus used in drug-release experiments is shown schematically in *Figure 1*. The volume of water in the vessel was 0.250 dm^3, the stirring rate was constant at ca. 300 rev min^{-1} (Labstir 12 V Universal Stirrer) and the position of the disc in the vessel was at the same height for all experiments. Sink conditions[15] were maintained. Thus, the amount of release of SSA should not exceed 10% of its solubility in water, which means 17 125 mg taking into account the volume of water in the vessel. The discs were formulated in accordance with this requirement, since the maximum load was 448 kg m^{-3}, which corresponds to 175 mg of released salt.

The release of SSA from the discs was measured continuously with an SM conductivity meter, model AGB-77. A linear dependence of conductivity on concentration was obtained by calibration with standard SSA solutions at 310 K. The weight of drug released at any selected time (M_t) was calculated from the calibration in conjunction with the conductivity. The maximum weight available for release (M_∞) was determined in the same way as M_t. The fractional release (F_s) was then calculated as $F_s = M_t/M_\infty$.

The diameters of hydrogel (L_{Ht}) at any selected time (t) during the release of SSA were determined as indicated in the Experimental section. The release of SSA was examined at different loads of drug using discs of similar thickness at one temperature (310 K).

RESULTS AND DISCUSSION

Diffusion from a gel phase can be considered one-dimensional when the thickness of the disc is not very large. Thus, this assumption has been made for the diffusion of chloramphenicol from PHEMA discs with wet thickness between 1.1 and 2 mm[16], where the drug desorption was linear vs. $t^{1/2}$. Similar considerations applied in the release of theophylline from P(HEMA-*co*-VP) (VP = *N*-vinyl-2-pyrrolidone) discs with 1–3 mm dry thickness[17]. In the same way, this assumption has been made in the determination of diffusion coefficients for release of SSA in this study, since the thickness of dry discs was between 1.5 and 1.8 mm.

Two types of diffusion process were studied here: (i) diffusion of water into the xerogel in the absence of SSA and (ii) diffusion of SSA from the charged xerogel into the swelling medium. The fractional swelling due to water, F_w ($= W_t/W_\infty$), and the fractional release of drug, F_s, are the quantities related to the diffusion processes mentioned. These two quantities may be expressed for diffusion-controlled processes as[18]:

$$F_i = 4\left(\frac{D_i t}{\pi h^2}\right)^{1/2} \tag{2}$$

where i denotes w or s, which correspond to fractional swelling due to water and fractional release of salt respectively. In equation (2), D is the apparent diffusion coefficient (for transport of water into the hydrogel in the case of F_w and for transport of SSA from the hydrogel in the case of F_s), and h is the original thickness of the disc. However, this equation (2) is inadequate in the case considered in this work since, as commented before, the dimensions of the copolymeric hydrogel studied here change significantly with time.

Figure 2 shows the variation of the ratio L_{Ht}/L_x for the different loads including the case $A = 0$ kg m^{-3}. This ratio represents the relative magnitude of the dimensional changes that occur on immersing the xerogels in the swelling medium. It should be noted that, after the loaded gels are immersed in water, two opposite effects occur simultaneously, both due to the existence of a positive

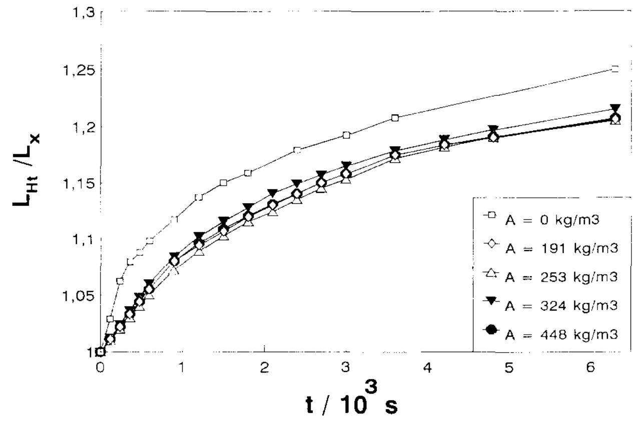

Figure 2 Variation of L_{Ht}/L_x with time for copolymer and copolymer having various loads A in water

osmotic pressure between hydrogel and swelling medium: on the one hand, water diffuses from the swelling medium into the hydrogel and, on the other hand, SSA diffuses from the hydrogel to the surrounding medium. The swelling of the unloaded gel is due to the affinity between the functional groups present in the polymer network and water. It is noteworthy from *Figure 2* that: (i) the dimensional changes associated with the unloaded hydrogel are larger and occur more rapidly than those for the loaded hydrogels and (ii) hydrogels loaded with values of A between 191 and 448 kg m^{-3} all exhibit a similar variation of L_{Ht}/L_x with time.

To take into account the influence of the dimensional change in the release of SSA, an equation has been derived starting from Fick's second law:

$$\frac{dC}{dt} = D\frac{d^2C}{dx^2} \tag{3}$$

Here C is the solute concentration at time t and position x. Solution of equation (3) for a disc of thickness h at short time produces equation (2). This expression is based on a constant diffusion coefficient, D. However, if D is a function of time, i.e. D_t, a dimensionless imaginary time-variable function, $\tilde{T}$, may be defined, in which h_t is the thickness at time t:

$$\tilde{T} = \int_0^t \frac{D_t}{h_t^2} dt \tag{4}$$

Hence,

$$\frac{d\tilde{T}}{dt} = \frac{D_t}{h_t^2}$$

From equation (3), $dC/d\tilde{T}$ may be recast as:

$$\frac{dC}{dt} = \frac{dC}{d\tilde{T}}\frac{d\tilde{T}}{dt} = D_t\frac{d^2C}{dx^2}$$

$$\frac{dC}{d\tilde{T}}\frac{D_t}{h_t^2} = D_t\frac{d^2C}{dx^2}$$

Therefore,

$$\frac{dC}{d\tilde{T}} = h_t^2\frac{d^2C}{dx^2} \tag{5}$$

Equation (5) is similar to Fick's equation, where h_t is the disc thickness at time t. The general solution of this equation at short time is a similar expression to equation (2):

$$F_s = \frac{M_t}{M_\infty} = 4\left(\frac{\tilde{T}}{\pi}\right)^{1/2} \tag{6}$$

If D_t varies because of progressive water uptake to some equilibrium value, then, for a compound that will only diffuse out from a matrix which is hydrated very rapidly, one may assume that:

$$D_t = D_s\frac{\phi_{2t}}{\phi_{2\infty}} \tag{7}$$

Here D_s is the diffusion coefficient of the species in the fully hydrated matrix, ϕ_{2t} and $\phi_{2\infty}$ are the volume fractions of polymer at a specific time and at equilibrium respectively. These volume fractions may be expressed as $\phi_{2t} = (L_x/L_{Ht})^3$ and $\phi_{2\infty} = (L_x/L_{H\infty})^3$, where L_x is the xerogel diameter, L_{Ht} the hydrogel diameter at time t and $L_{H\infty}$ the hydrogel diameter at equilibrium. Substituting D_t from equation (7) into equation (4) affords:

$$\tilde{T} = D_s\int_0^t \frac{\phi_{2t}}{\phi_{2\infty}}\frac{1}{h_t^2} dt \tag{8}$$

Here $h_t^2 = h^2(L_{Ht}^2/L_x^2)$, where h is the original thickness of the disc. Hence from equation (8), the imaginary time-variable function is given by:

$$\tilde{T} = \frac{L_x^2}{h^2} D_s (L_{H\infty})^3 \int_0^t \frac{dt}{(L_{Ht})^5} \tag{9}$$

Substituting for $\tilde{T}$ from equation (9) into equation (6) yields:

$$F_s = \frac{M_t}{M_\infty} = \frac{4}{\pi^{1/2}}\frac{L_x}{h} D_s^{1/2}(L_{H\infty})^{3/2}\left(\int_0^t \frac{dt}{(L_{Ht})^5}\right)^{1/2} \tag{10}$$

F_s *versus* $\{\int_0^t [dt/(L_{Ht})^5]\}^{1/2}$ should yield a linear plot, from the slope of which D_s may be obtained. This equation (10) is also applicable to the case $A = 0$ kg m^{-3} ($F_w = W_t/W_\infty$ instead of F_s, and D_w instead of D_s).

The integral was solved here by fitting the curves (*Figure 3*) of the variation of $1/L_{Ht}^5$ (determined experimentally) with time (in seconds) to polynomials (of coefficients a_i). A boundary condition must be considered to solve the integral in equation (10), viz. the integral equals zero for $t = 0$. For the uptake of water ($A = 0$) the curve was best-fitted to an eight-order polynomial, but polynomials of fifth order were sufficient to fit the curves for dimensional changes of loaded discs. The correlation

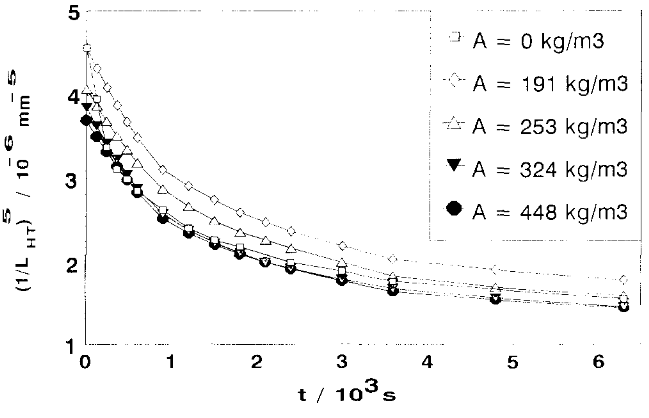

Figure 3 Change of $1/L_{Ht}^5$ with time for copolymer and copolymer having various loads A in water

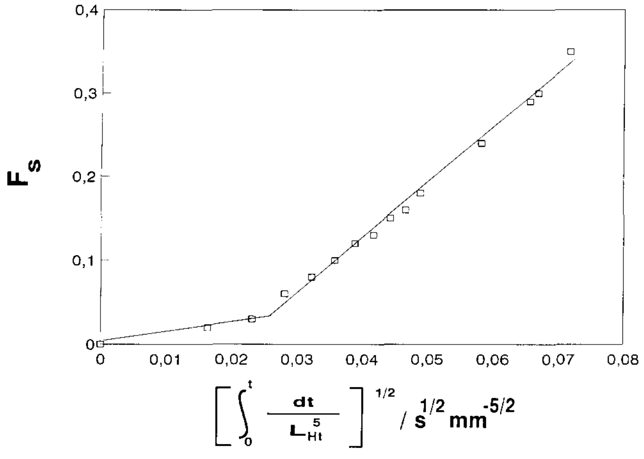

Figure 4 Fractional release of SSA from a P(HEMA-*co*-SPE) disc into water as a function of $[\int_0^t (dt/L_{Ht}^5)]^{1/2}$ for $A = 191\ kg\,m^{-3}$

coefficients were better than 0.999 in all cases. By way of illustration, the values of the polynomial coefficients are quoted here for only one example, viz. the system having a load $A = 191\ kg\,m^{-3}$: $a_0 = 4.57 \times 10^{-6}\ mm^{-5}$, $a_1 = -2.34 \times 10^{-9}\ mm^{-5}\,s^{-1}$, $a_2 = 1.07 \times 10^{-12}\ mm^{-5}\,s^{-2}$, $a_3 = -2.68 \times 10^{-16}\ mm^{-5}\,s^{-3}$, $a_4 = 3.32 \times 10^{-20}\ mm^{-5}\,s^{-4}$, $a_5 = -1.58 \times 10^{-24}\ mm^{-5}\,s^{-5}$.

Figure 4 shows a plot of F_s vs. $[\int_0^t (dt/L_{Ht}^5)]^{1/2}$ according to equation (10) for one of the loads. The behaviour found for the other loads is similar and all comments given hereafter are equally applicable to them. It is apparent that the plot is linear up to $F_s \approx 0.30$. At higher values of F_s, there is a break and the slope of the curve increases. This behaviour may be attributed to a significant erosion of the hydrogel surface due to the movement of the solvent in the disc. This could produce a greater surface area for drug release, resulting in a progressive increase in release rate. More fundamentally, however, it is important to note that equation (2) represents an approximate, but adequate, solution to the full diffusion equation restricted to low fractional release. There is no rigid criterion of 'low', but $F_i \lesssim 0.4$ is adopted commonly. (In the region restricted to higher fractional release, the relevant approximation leads to a dependence of F_i on time that is of an exponential form[19] rather than a linear one with respect to $t^{1/2}$.) The restriction mentioned applies equally to equation (6) and hence also to the final expression used, equation (10). Consequently, the diffusion coefficient associated with each load is determined here from data for values of F_s between 0.02 (due to the small lag) and 0.3 in all cases. The values obtained are listed in *Table 1* which shows that:

(i) The diffusion coefficient for ingress of water is much greater than that for release of SSA.

(ii) The diffusion coefficient for release of SSA is concentration-dependent in the concentration range studied here as determined via equation (2). Values of D_s practically independent of load concentration are obtained by means of equation (10), the mean value being $4.4 \times 10^{-11}\ m^2\,s^{-1}$.

(iii) The method described in this paper provides a value of D_w that is 15% bigger than the value obtained by means of equation (2), whereas the values of D_s obtained using equation (10) are smaller than the values calculated through equation (2). The difference between these values depends on the hydrogel load and varies from 14% for the lowest load to 100% for the highest.

Table 1 Values of diffusion coefficients obtained via equations (2) and (10)

	D_w ($10^{-10}\ m^2\,s^{-1}$)		D_s ($10^{-11}\ m^2\,s^{-1}$)	
A ($kg\,m^{-3}$)	Via eq. (2)	Via eq. (10)	Via eq. (2)	Via eq. (10)
0	1.1	1.3	–	–
191	–	–	5.8	4.3
253	–	–	6.6	4.3
324	–	–	7.7	4.3
448	–	–	9.4	4.7

(iv) The value of D_w obtained via equation (2) is of the same order of magnitude as the value reported for PHEMA hydrogels at 294 K, e.g. $1.25 \times 10^{-10}\ m^2\,s^{-1}$ (ref. 18).

Considering the experiments on drug release, the differences found on applying the two methods used could be explained by making the following considerations: From the results given, the water front within the hydrogel advances much faster than the salt front (focusing attention on the results obtained via equation (10), approximately three times faster). This faster penetration of water produces two significant effects: (i) a change of the gel dimensions and (ii) a thermodynamic effect, viz. a change of the medium in which salt diffuses (not only polymer but polymer and water). Equation (10), of course, considers only dimensional changes and discussion must be constrained to the first effect. Accordingly, these dimensional changes yield a change in the distance that any single salt molecule must travel to leave the hydrogel and consequently a delay in the release rate, which is only detected when these dimensional changes are considered.

In summary, failure to account for the finite swelling of the hydrogel during release was shown in this system to affect the value of the diffusion coefficient obtained. The effect is not dramatic in absolute terms, but is on a relative basis. Good[20] has adopted a procedure similar to the present one in order to take account of a concentration dependence of D_s, but his treatment did not allow for dimensional changes. Leanirith-Yean *et al.*[16] studied the slow release of chloramphenicol from crosslinked PHEMA and also noted a small but significant difference between the values of the diffusion coefficient of the drug obtained by the two procedures. In the experiments of Good, there was virtually no change in the dimensions during the release. Moreover, although there was a 10% increase in polymer thickness in the experiments of Leanirith-Yean *et al.*, this was primarily due to swelling and possible dimensional changes thereafter during the very slow drug release were not mentioned by these authors. As far as we are aware, no previous workers have employed a scheme whereby the actual dimensional changes during release were measured and utilized in order to obtain a corrected diffusion coefficient.

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