Anomalous sorption of binary solvents in glassy polymers: interpretation of solute release at constant rates

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(Received 29 July 1992; revised 28 January 1993)

Sorption of binary solvents water/dioxane and water/n-propanol in glassy poly(2-hydroxyethyl methacrylate) matrices and concomitant release of theophylline was investigated. The observed sorption profiles of the penetrant as well as the release profiles of theophylline have been explained on the basis of the effect of penetrant concentration on the diffusivity of the penetrant and of theophylline. The model parameters estimated from the release profiles agree well with the values for which an initial burst followed by release at constant rate is predicted.

(Keywords: sorption; binary solvents; glassy polymers; anomalous diffusion; release kinetics)

INTRODUCTION

Sorption of penetrants into glassy polymers and consequent release of active ingredients from the swollen matrices has been extensively investigated[1-4]. The release of active ingredients at constant rate is of particular interest. A number of criteria based on theoretical analysis of penetrant sorption and diffusion of the active ingredient from the swollen polymer matrix have been proposed to predict conditions under which the active ingredient would be released at constant rate. The effect of parameters such as polymer composition and size of the active ingredient has been extensively investigated in the past to examine the validity of these criteria. Although a low-molecular-weight solute is released at a constant rate from a glassy matrix into which the penetrant sorption follows case II transport, the release of a bulkier molecule follows anomalous kinetics because of diffusional limitations[4,5].

Diffusivity of a solute through a hydrogel can be enhanced by enhancing its degree of swelling. This is achieved by incorporating (a) ionizable monomers[6], (b) monomers that complex with the penetrant molecules[7] and (c) crosslinks that erode during release[8]. Release at constant rates from such systems has been reported. Although equilibrium swelling of polymers is enhanced in binary solvents[9], this approach has not been explored.

In this paper we report the sorption of binary solvents comprising water/dioxane and water/n-propanol into glassy poly(2-hydroxyethyl methacrylate) (PHEMA) matrices. The equilibrium swelling behaviour is shown to correlate with the intrinsic viscosity of the polymer. Sorption of solvents has been shown to be linear with time over specific time periods even when not governed by case II transport. Release of theophylline at constant rates into these media has been demonstrated and a possible mechanism is suggested.

EXPERIMENTAL

The 2-hydroxyethyl methacrylate monomer was obtained from Fluka (Switzerland); t-butyl hydroperoxide initiator was obtained from Wilson Laboratory (India); theophylline was obtained from local suppliers.

Bulk polymerization on the 10 g scale was carried out in glass tubes using 0.6% t-butyl hydroperoxide initiator. The solute loading was 1%. Polymerization was carried out at $60 \pm 1°C$ for the first 6 h and then at $70 \pm 2°C$ for another 12 h. The product polymer in cylindrical form was isolated by breaking the test tubes.

The polymer cylinder was machined on a lathe to obtain discs 1.6 cm in diameter and 0.09–0.11 cm in thickness. They were post-polymerized at 50°C for 1 day and stored in a desiccator over fused calcium chloride to prevent moisture absorption during storage. Complete conversion was confirmed from the fact that free monomer never exceeded 0.2% as estimated by u.v. analysis.

Swelling studies

Dynamic swelling studies were carried out for pure PHEMA containing no solute. The discs were weighed and immersed in different compositions of binary mixtures maintained at 37°C. The discs were removed at various time intervals, blotted with a tissue paper and

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0032-3861/93/204300-07

weighed on a Mettler balance ($\pm 1 \times 10^{-4}$ g). This procedure was repeated until no further weight gain was observed. The penetrant uptake of binary solvents of varying compositions as a function of time was measured for glassy as well as rubbery PHEMA discs swollen to equilibrium in water.

The equilibrium swelling was calculated from the equation:

$$\text{Swelling (\%)} = \frac{(W_s - W_d)}{W_s} \times 100 \quad (1)$$

where W_s denotes the weight of the swollen polymer and W_d denotes the weight of the dry polymer.

Measurement of diffusion coefficient

Diffusion coefficients of theophylline at 37°C from the swollen polymer matrices were determined as described by Yasuda *et al.*[10]. There was no change in the equilibrium swelling of the polymer during the measurements. Reproducibility checks indicated that variation in the values of diffusivity was within ±3%.

Release studies

The kinetics of release was followed by monitoring the absorbance of theophylline released on a Shimadzu 240 u.v.-vis. spectrophotometer at $\lambda_{max} = 272$ nm. The release experiments were carried out in a jacketed vessel maintained at 37°C with constant stirring to maintain perfect sink conditions. The amount of theophylline released at time t (M_t, expressed in grams) was determined from the appropriate calibration curve. The total amount of theophylline released from the disc when it was completely depleted was taken as M_∞. The fraction of theophylline released was expressed as (M_t/M_∞). The release kinetics data are conventionally expressed in terms of the release index n defined as:

$$M_t/M_\infty = Kt^n \quad (2)$$

The release index n was obtained from the slope of the plot of $\ln(M_t/M_\infty)$ vs. $\ln(t)$ (ref. 2). The values of release indices along with 95% confidence limits are summarized in *Table 1*.

RESULTS AND DISCUSSION

Swelling controlled delivery systems

Swelling controlled delivery systems investigated in the past have been largely based on glassy polymers into which the sorption of the penetrant is governed by case II transport. The active ingredient is released at a constant rate from such systems when its diffusivity from the swollen hydrogel is high enough so that the sorption of the penetrant becomes the rate-controlling step[11].

Vyavahare *et al.*[5] recently showed that benzoic acid was released at a constant rate into water from glassy PHEMA hydrogel. This was attributed to the case II transport-controlled penetration of water into the matrix. However, the release of theophylline followed anomalous kinetics as its diffusivity was only one-third of that of benzoic acid. Thus, release of theophylline at a constant rate may be achieved if its diffusivity through the swollen hydrogel were to be enhanced: for example, Siegel *et al.*[6] reported the release of caffeine at constant rate from glassy poly(methyl methacrylate–dimethylaminoethyl methacrylate) (PMMA-DMA) hydrogels at pH 3 and 5 as a result of the protonation of the amino group of DMA, which led to enhanced swelling of the matrix and diffusivity of caffeine.

Analysing anomalous sorption of organic vapours in glassy polymers, Petropoulos and Roussis[12] concluded that solvent uptake can be linear with time even if the sorption of the penetrant does not follow case II transport. Release of carbamezapine and theophylline from glassy poly(2-hydroxyethyl methacrylate–4-carboxystyrene) (PHEMA-4CS) matrices has been shown to be linear with time following an initial burst even though the penetrant sorption did not follow case II transport[13]. It therefore appears that case II transport controlled sorption of the penetrant may not be a prerequisite for either penetrant uptake or the release of the active ingredient to occur at constant rate.

In the following sections, we demonstrate enhanced swelling of glassy PHEMA hydrogels in binary solvents. This has been shown to result in the release of theophylline at a constant rate following an initial burst. In contrast, release from a rubbery hydrogel initially swollen to equilibrium in water and then immersed in the binary solvent follows anomalous kinetics.

Table 1 Summary of systems investigated

Solvent composition (vol/vol)	Equilibrium swelling (%)	Penetration velocity ($\times 10^6$ cm s^{-1})		Diffusion coefficient ($\times 10^7$ cm^2 s^{-1})	Equilibrium swelling interface number, Sw_e	Release index, n	95% confidence limits
		Sorption data	Release data				
Water/dioxane							
100/00	40	2.95	2.78	1.2	2.93	0.66	0.654–0.665
89/11	52	8.00	4.76	6.2	0.79	0.96	0.964–0.972
82/18	62	8.50	4.73	12.6	0.44	0.98	0.977–0.987
75/25	71	11.84	5.39	18.8	0.43	0.96	0.967–0.958
60/40	80	16.58	5.78	25.7	0.47	1.03	1.032–1.046
Water/n-propanol							
60/40	78	12.44	8.08	19.0	0.46	0.96	0.975–0.963
50/50	79	18.43	10.39	18.3	0.69	1.06	1.070–1.058
40/60	80	18.14	9.24	19.5	0.66	1.00	1.005–1.002

Swelling of glassy PHEMA in binary solvents

Swelling behaviour of polymers in binary solvent systems has been investigated in the past to elucidate the mechanism of swelling as well as the preferential solvation of the polymers. Davis and Huglin[9] reported that, in the binary system water/dioxane containing more than 5% water, equilibrium swelling of PHEMA hydrogels was always greater than that in pure water. The maximum (80%) was reached when the medium contained 34% water.

A comparison of the equilibrium swelling curve of PHEMA reported by Davis and Huglin[9] with the solution behaviour reported by Tuzar and Bohdanecky[14] indicates that the intrinsic viscosity of the polymer in the binary solvent also reaches a maximum when the medium contains 34% water. Thus the swelling behaviour of polymers in binary solvents can be correlated with the intrinsic viscosity.

Tuzar and Bohdanecky[14] also reported a maximum in the intrinsic viscosity of the polymer in a series of binary solvent systems such as dioxane/water, ethanol/water, propanol/water, etc. The equilibrium swelling of the PHEMA hydrogels in these systems would be expected to be greater than that in water. Swelling behaviour of PHEMA in water/n-propanol was therefore investigated.

The equilibrium swelling curve of PHEMA in water/n-propanol (*Figure 1*) is similar to the plot of intrinsic viscosity vs. solvent composition (see inset). The equilibrium swelling in the concentration range 40–60% n-propanol remains almost constant. Thus enhanced equilibrium swelling of PHEMA in all the binary solvents reported by Tuzar and Bohdanecky[14] is expected to lead to enhancement in the diffusion coefficient and consequently to the release of theophylline at a constant rate.

Diffusion coefficients of theophylline from swollen hydrogels

Glassy PHEMA discs were immersed in binary solvents till equilibrium swelling was reached. Theophylline

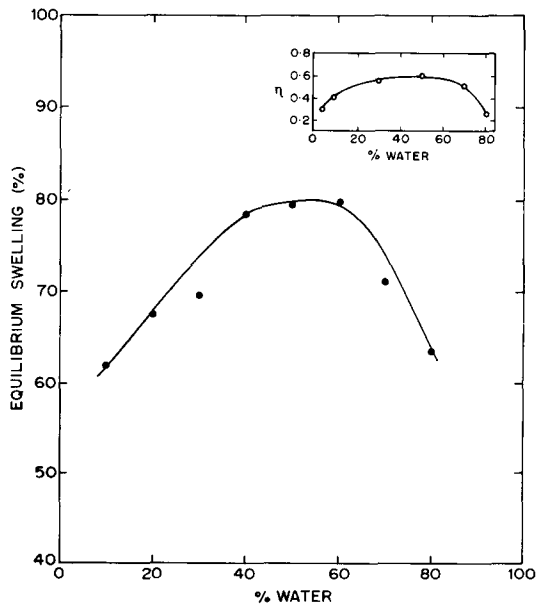

Figure 1 Equilibrium swelling of PHEMA hydrogels in the binary mixture water/n-propanol (inset: data of ref. 14)

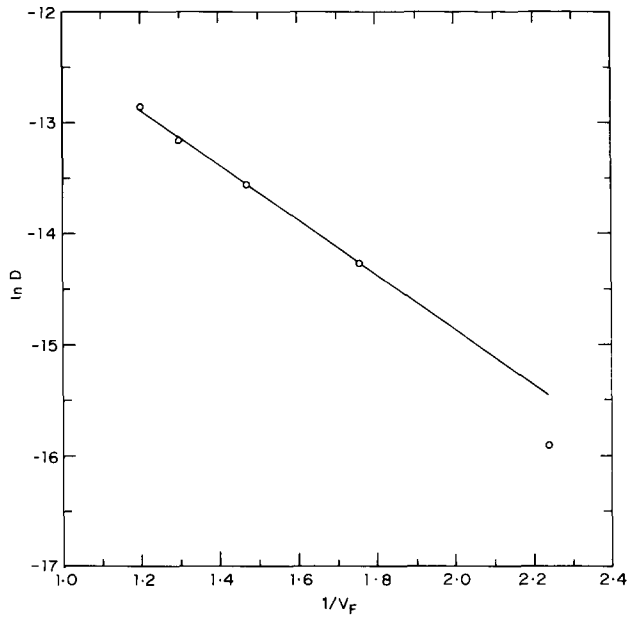

Figure 2 Diffusivity of theophylline in PHEMA hydrogels swollen in water/dioxane mixtures. Test of free-volume theory

was loaded into these discs during swelling. The discs were then immersed in media of identical composition so as to ensure that there was no change in the degree of swelling of the polymer during desorption of theophylline. The amount of theophylline diffusing out was followed as a function of time. The values of the diffusion coefficients obtained are summarized in *Table 1*.

A plot of $\ln D$ vs. $1/V_F$, where V_F denotes the volume fraction of the solvent mixture in the gel, is linear (*Figure 2*). This is in agreement with the predictions of the free-volume theory for solute diffusion in hydrogels[10]. The value of the diffusivity of theophylline predicted from the plot of diffusivity vs. equilibrium swelling in water/dioxane blends at equilibrium swelling ($V_F = 0.4$) is $1.89 \times 10^{-7}\ cm^2\ s^{-1}$. This value is higher than the diffusivity of theophylline ($1.2 \times 10^{-7}\ cm^2\ s^{-1}$) in the PHEMA hydrogel swollen to equilibrium in water ($V_F = 0.4$). This can be explained as follows. Increase in the swelling of the PHEMA hydrogel in the binary solvents is due to the disruption of hydrogen bonding in water, which enhances its interaction with the polymer. This would enhance the free volume and the solute diffusivity. As the solvent composition tends towards pure water, the sudden increase in hydrogen bonding and the close packing of the water structure would lower the free-volume contribution and subsequently the solute diffusivity.

Release kinetics from glassy and swollen hydrogels

Prior efforts to achieve release of active ingredients from glassy hydrogels have focused on the manipulation of the polymer composition: for example, Peppas and Franson[2] investigated the release of theophylline from poly(2-hydroxyethyl methacrylate–methyl methacrylate) (PHEMA-MMA) copolymers. The variation in the penetrant velocity and solute diffusivity was such that the release index did not vary widely. In the present investigation binary solvents comprising 60–89% water were used as penetrants. The results of variation in solvent composition on the penetrant velocity and theophylline diffusivity are summarized in *Table 1*. For instance, in

the case of the penetrant containing 11% dioxane, the penetrant velocity was 8.0×10^{-6} cm s^{-1} and diffusivity of theophylline was 6.24×10^{-7} cm^2 s^{-1} as compared to the corresponding values of 2.66×10^{-6} cm s^{-1} and 1.2×10^{-7} cm^2 s^{-1} in the case of water. Equilibrium swelling interface number now decreases to 0.794 from $\simeq 3.0$ (ref. 5). Theophylline is released at a constant rate following an initial burst (*Figure 3*).

In order to investigate further the effect of equilibrium swelling on release, we investigated the release of theophylline from glassy PHEMA hydrogels in media containing increasing proportions of dioxane. In all these cases, the release of theophylline was found to be linear with time following an initial burst. The rate of release increased with increasing equilibrium swelling of the swollen hydrogel.

Although the values of the equilibrium swelling interface number for release in binary solvents are lower than that for release in water ($\simeq 3$) (see *Table 1*), the values of penetration velocity experimentally determined are higher than those predicted from the release data. The difference between the two values increases with increasing equilibrium swelling of the polymer.

In order to investigate if theophylline is released at constant rate from the rubbery hydrogel as well, discs loaded with theophylline and saturated to equilibrium in water were immersed in water/dioxane media of increasing dioxane content. The release profiles shown in *Figure 4* are distinctly different from those for the release of theophylline from the glassy hydrogels. The release kinetics are anomalous ($n=0.6$). Unlike the case of the release from glassy hydrogels, the release cannot be considered to be linear following the burst.

In the previous section we showed that, in the case of the solvent system water/n-propanol, the equilibrium swelling of the PHEMA hydrogel is constant over a wide range of compositions. It was therefore expected that penetration velocities for these systems would be identical and the release profiles would superpose. The release data summarized in *Figure 5* illustrate that, while for the systems comprising 40% and 50% water, the release

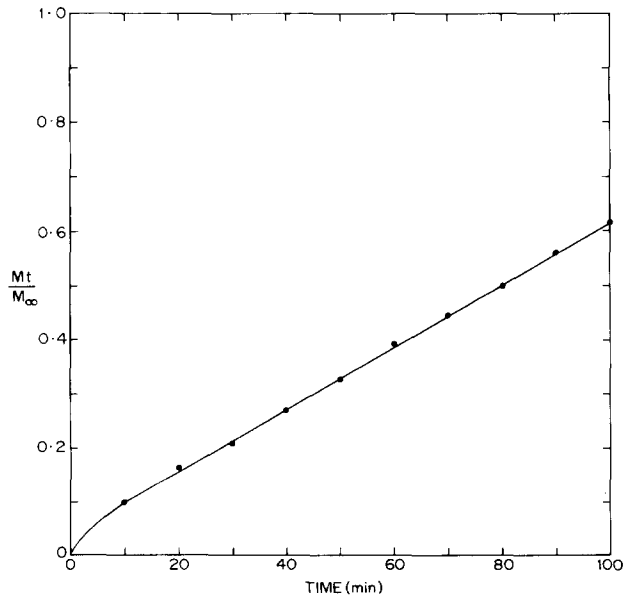

Figure 3 Release profile of theophylline from glassy PHEMA matrix in water/dioxane (89/11); line denotes the statistical fit

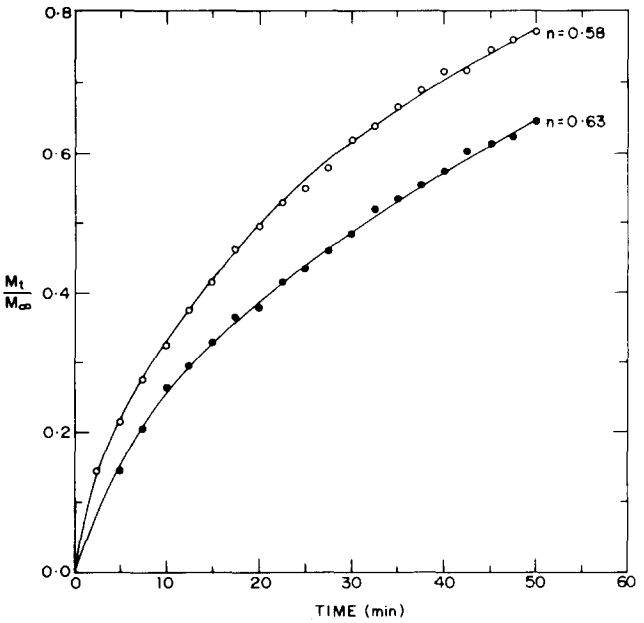

Figure 4 Release profiles of theophylline at 37°C from swollen PHEMA hydrogel in water/dioxane 75/25 (●) and 60/40 (○)

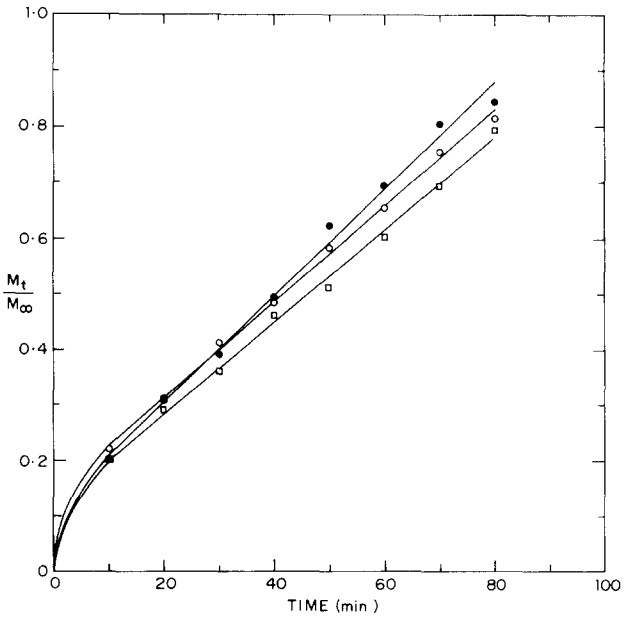

Figure 5 Release of theophylline at 37°C from glassy PHEMA hydrogels in water/n-propanol 40/60 (○), 50/50 (●) and 60/40 (□)

profiles do almost superpose, the rate of release from the medium containing 60% water is slightly lower. Solvent penetration measurements showed that, while the penetration velocities in the first two cases were very similar (18.43×10^{-6} and 18.14×10^{-6} cm s^{-1}), the velocity in the latter case was lower (12.44×10^{-6} cm s^{-1}). It is difficult to explain why the penetration velocity in this case is low.

It is thus seen that theophylline is released from the glassy PHEMA hydrogels into binary solvents at a constant rate except for the initial burst. However, the release at constant rate cannot be attributed to case II transport controlled sorption of the penetrant. We therefore investigated the penetrant sorption in detail.

Swelling kinetics of glassy and rubbery hydrogels

To investigate the kinetics of swelling of the glassy PHEMA in the mixed solvent systems, polymer discs were immersed in respective solvents and the weight gain of the disc was measured as a function of time. A typical plot of the fractional penetrant uptake vs. time shown in *Figure 6* indicates a rapid uptake followed by a linear relationship and subsequently negative deviations from linearity. It needs to be emphasized here that the linear dependence observed is not a consequence of case II transport controlled sorption of the penetrant.

During the initial stages of sorption of the penetrant through the glassy hydrogel, diffusion in the glassy region is the rate-controlling step. The slope of the plot of (M_t/M_∞) vs. $t^{1/2}$ can therefore be interpreted as the diffusion coefficient of the penetrant in the glassy region[3]. Vrentas *et al.*[15] predicted pseudo-Fickian diffusion in glassy polymers at low penetrant concentrations, as the Deborah number for diffusion is very large ($Deb_D \gg 1$). Penetrant diffusion in such situations takes place in a medium in which polymer structure does not vary during diffusion. A comparison of the relaxation time for the glassy PHEMA as reported by Davidson and Peppas[3] and the characteristic diffusion time calculated using the values of diffusivities determined in this work shows that the diffusional Deborah number is 2.7. The evaluation of diffusion coefficient on the assumption of the pseudo-Fickian behaviour is further justified by the linearity of the plot of penetrant uptake vs. (time)$^{1/2}$.

For the penetrant containing 11% dioxane, the value of the diffusion coefficient (9×10^{-8} cm^2 s^{-1}) calculated from the data in the range wherein fractional solvent uptake was linear with respect to (time)$^{1/2}$ (see *Figure 7*) is in good agreement with that reported by Kabra *et al.*[16] ($(9 \pm 2) \times 10^{-8}$ cm^2 s^{-1}) for the penetration of water in the glassy PHEMA. With increasing concentration of dioxane in the binary mixture, the diffusivity decreases, which could be attributed to the higher molecular weight as well as molecular size of dioxane in comparison to that of water.

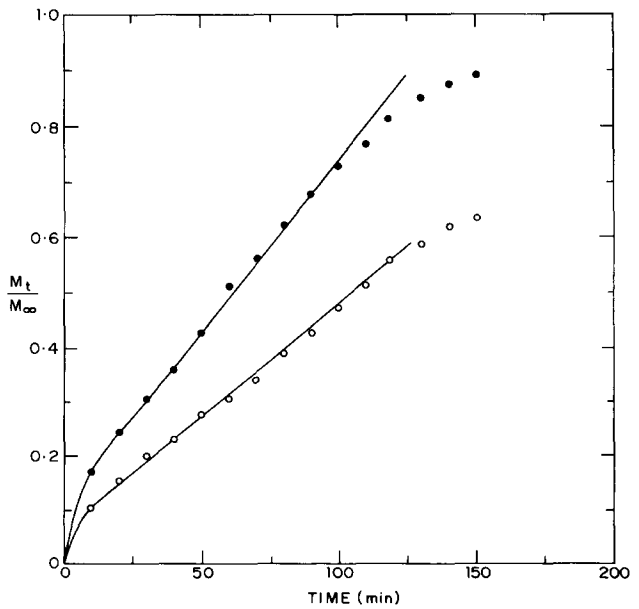

Figure 6 Sorption in glassy PHEMA: water/dioxane 82/18 (●) and 75/25 (○)

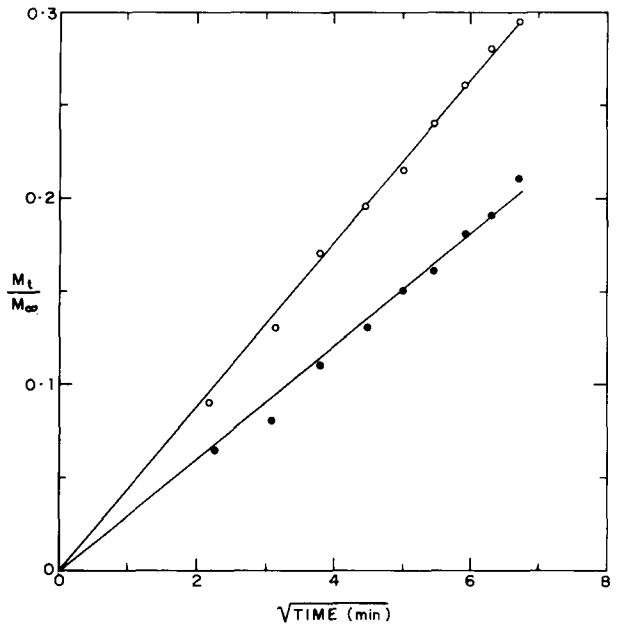

Figure 7 Estimation of diffusion coefficient of water/dioxane 89/11 (○) and 60/40 (●) in glassy PHEMA

Penetrant sorption in the later stages is accompanied by significant dimensional changes. (a) In the initial stage, a swollen shell layer is formed, which envelops the glassy core. During this stage, swelling results in an increase in the thickness of the disc. Increase in the diameter is comparatively insignificant as it is constrained by the presence of the glassy core. As the thickness of the glassy core decreases, the disc undergoes shape changes in response to the stresses developed as a result of the differential swelling between the core and the shell. (b) As the penetration continues and the glassy core disappears, the stresses are relieved and the diameter increases substantially. (c) Subsequent swelling takes place isotropically. Stage (b) is completed in a much shorter time span as compared to stages (a) and (c). Similar observations have recently been reported by Kabra *et al.*[16] except that the swelling during the initial stage was assumed to take place at a constant rate.

Non-Fickian sorption of penetrants in polymers, which results in sigmoidal sorption profiles, was first demonstrated by Crank[17] to result from the effect of the transverse differential swelling stresses on the diffusion coefficient of the penetrant. Subsequent modification of the model was proposed by Petropoulos and Roussis on the following lines[12]. Diffusion of the penetrant leads to an increase in the thickness of the disc and an increase in the diameter. The latter, however, is constrained by the presence of the glassy core. This leads to the development of stresses within the shell and the core. The diffusion coefficient of the penetrant is now governed by the stress and the penetrant concentration. The equation for change in local stress with time was solved along with the diffusion equation, strain generated and the stresses set up as a result of the concentration gradient. Plots of penetrant uptake vs. time were then obtained. The uptake was linear with time and then deviated towards the time axis. The sorption profiles shown in *Figure 6* are qualitatively similar to the predictions of this model[12].

Korsmeyer *et al.*[18] proposed an alternative approach wherein the effect of stresses developed due to differential swelling was neglected. Swelling was considered to cause

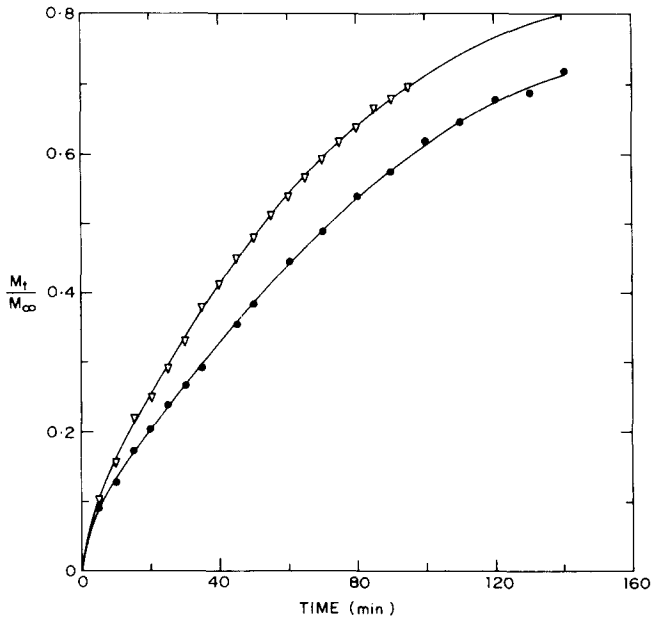

Figure 8 Sorption in swollen PHEMA: water/dioxane 82/18 (●) and 60/40 (▽)

only an increase in thickness till the glassy core disappeared. Swelling thereafter was considered to be isotropic. An exponential dependence of the diffusion coefficient on concentration was incorporated in the diffusion equation. Penetrant concentration at which the glass–rubber transition occurred was denoted by C_g. Penetrant uptake profiles under these conditions were shown to be linear with time following an initial fast uptake. The linear solvent uptake with respect to time observed by us is in qualitative agreement with these predictions[18]. Sorption plots for the rubbery hydrogels swollen to equilibrium in water (*Figure 8*) indicate that the fractional uptake is no longer linear with time.

Interpretation of release kinetics

It has been shown in the preceding sections that theophylline is released at constant rates from glassy PHEMA hydrogel in water/dioxane or water/n-propanol, even though the penetrant sorption does not follow case II transport. In view of the complex penetrant sorption and structural and dimensional changes, a semiquantitative interpretation of the observed release profiles is presented.

In the initial stages of penetrant sorption when the Deborah number for the penetrant diffusion is large, diffusion is Fickian. However, as the penetrant concentration increases, the polymer undergoes the glass transition and stresses due to differential swelling set in. Swelling results predominantly in an increase in the thickness of the disc with only marginal increase in the diameter till the glassy core disappears. Subsequently swelling takes place isotropically, resulting in an increase in the diameter as well as the thickness. The solute molecules dispersed in the glassy polymer matrix would diffuse out only when the polymer has undergone transition to the rubbery phase. Further increase in the penetrant concentration results in an increase in the diffusion coefficient of the solute.

The effect of the dependence of diffusion coefficient of the solute on penetrant concentration and its release from a glassy, swellable hydrogel matrix was investigated by Korsmeyer *et al.*[18] by taking into account the dependence of diffusion coefficient of the penetrant on its concentration of the form:

$$D_1 = D_{1s}\exp(\beta_1)(1 - C_1) \quad (3)$$

and that of the solute (D_2) on the penetrant concentration to be:

$$D_2 = D_{2s}\exp(\beta_2)(1 - C_1) \quad (4)$$

in accordance with the free-volume theory.

D_{1s} and D_{2s} denote the diffusivities of the penetrant and the solute at equilibrium swelling and C_1 denotes the normalized penetrant concentration. β_1 and β_2 denote the concentration dependence of diffusion coefficients of the two species. The penetrant and solute diffusion equations were set up in terms of normalized concentrations, dimensionless time and dimensionless position coordinate along with appropriate boundary conditions and then integrated to obtain the fraction of solute released as a function of time. It was shown that, for a polymer having equilibrium swelling $\simeq 90\%$ and for $\beta_1 = 5$ and $\beta_2 = 4$, solute release profiles are linear with time following an initial non-linear dependence. Release profiles can be similarly generated for various parametric values of D_{2s}, D_{1s}, β_1, β_2, equilibrium swelling and penetrant concentration at which the glass transition takes place (C_g).

The diffusivity of theophylline in PHEMA hydrogels swollen in water/dioxane mixtures of varying compositions has been reported in earlier sections. Analysis of the diffusivity data in the solvent concentration range 50–70% leads to $\beta_2 = 4$. Although we have not been able to determine β_1, $\beta_1 = 5$ is justified in view of the range of values of β_1 reported by Korsmeyer *et al.*[19]. We therefore conclude that the release profiles of theophylline observed by us can be attributed to the dependence of solute and the penetrant diffusion coefficients on the penetrant concentration.

Lee[20] recently interpreted the release of an active ingredient from glassy polymers in which the penetration of the solvent follows case II kinetics in terms of a time-dependent diffusion coefficient. Shah *et al.*[21] extended the framework to explain the release of *p*-nitrobenzoic acid from glassy as well as swollen hydrogels. The approach could also be used to explain solute release from rubbery silicone matrices[22]. A feature common to these systems is an increase in the swelling of the polymer matrix and hence an increase in the diffusivity of the solute with time during the course of release. The sorption of the binary solvent has already been shown to be influenced by the penetrant concentration, which increases with time. Analysis of the release profiles of theophylline from glassy as well as rubbery PHEMA hydrogels based on this concept is presented elsewhere[23].

CONCLUDING REMARKS

Case II transport of penetrants in glassy polymers has been investigated in the past to develop swelling-controlled delivery systems that would release the solute at constant rates. Anomalous release kinetics has often been encountered because of the diffusional limitations. In binary solvents, equilibrium swelling of PHEMA hydrogels is enhanced due to the cosolvency effect, which can be predicted *a priori* from the solution behaviour

of the polymer. This results in an almost 20-fold enhancement in the diffusivity of theophylline. However, the sorption of binary solvent does not follow case II transport kinetics.

It has been shown that sorption of water/dioxane as well as release of theophylline at constant rate from glassy PHEMA hydrogels is a result of the effect of penetrant concentration on the penetrant as well as the solute diffusivity. The model parameters evaluated from the release data agree well with the parametric values for which the solute release at constant rate is predicted. Systems based on water/dimethylsulfoxide could find applications in transdermal delivery systems. The framework developed in this work would be useful for the design of such systems as well as others wherein similar enhancements in swelling can be brought about by other mechanistic means.

ACKNOWLEDGEMENTS

V. S. Vadalkar would like to acknowledge the financial support received from the Council of Scientific and Industrial Research, New Delhi, in the form of a Research Fellowship. S. S. Bhagwat was a visiting fellow at NCL under the Chimanlal Choksi award. The work reported here represents NCL Communication No. 5567.

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