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Diffusional transport from structurally variant hydrogels

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Abstract. Diffusional release of solutes from polymer matrices undergoing structural changes has been analysed by incorporating the dependence of solute diffusivity on time. The functional dependence of diffusivity with time has been experimentally verified and its utility and limitations are discussed. Criteria for predicting release characteristics have been arrived at based on two model parameters, K and β. Here K represents the reciprocal of the time required for the structural change and β is the ratio of the solute diffusivity prior to the onset and after the completion of the structural change. The criteria, which are independent of the mechanistic details of the structural change, have been validated by analysing solute release from polymeric matrices undergoing diverse structural changes. The approach should be useful in predicting the relase characteristics of solutes on the basis of the physicochemical characteristics of the polymer-solute systems. It should also help in tailoring the polymers to obtain the desired release kinetics.

Keywords. Diffusional release of solutes; release kinetics; polymer matrices.

1. Introduction

When diffusion of an active ingredient from a matrix device used in controlled release delivery systems is the rate-controlling step and the diffusivity of the active ingredient is constant, it is observed that the rate of release decreases with time (Higuchi 1961). Especially in drug delivery systems, it is important to aim at designing delivery systems, which would release the active ingredient at a constant rate. Swelling-controlled delivery systems based on glassy hydrogels have been extensively investigated towards this end (Hopfenberg 1981; Peppas and Franson 1983; Lee 1987). The criteria for predicting the release of an active ingredient at a constant rate are based on dimensionless numbers, which compare the diffusion time for the solute with the penetration time for the solvent. In these analyses, it is implicit that the penetration of the solvent into the matrix is controlled by case II transport. Lee (1987) recently interpreted the release of an active ingredient from such systems on the basis of time-dependent diffusion coefficients.

Analysing the anomalous sorption of organic vapours in glassy polymers, Petropoulous and Roussis (1978) concluded that solvent uptake can be linear with time even when sorption is not governed by case II transport. Recently Vadalkar *et al* (1993) reported the release of theophylline at constant rates from glassy PHEMA

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hydrogels in water–dioxane, and water–*n*-propanol. Lee and Lum (1992) reported the release of cinnamyl alcohol at a constant rate from polydimethyl siloxane into *n*-heptane. Shah *et al* (1990) extended the analysis proposed by Lee (1987) to explain the release of *p*-nitro benzoic acid from glassy as well as swollen hydrogels. These examples suggest that the release of solutes at constant rates from swellable matrix systems can be achieved even if the solvent penetration is not governed by case II transport.

A feature common to the systems described above is that there is an increase in the swelling of the polymer matrix during release. This results in an increase in the diffusivity of the solute, which compensates for the decreasing concentration gradient with time. Such systems are diverse in nature. For instance, the increase in swelling can be a result of change in the polymer composition due to the hydrolysis in the pendent chains (Shah *et al* 1990), degradation of crosslinks (Vyavahare *et al* 1992) and/or of the polymer backbone (Heller and Baker 1980), effect of change of penetrant composition (Vadalkar *et al* 1993) and so on. Although an enhancement in the diffusivity of the solute in always observed, the release of an active ingredient at a constant rate is not realized in all the cases. It was therefore considered worthwhile to develop a generalized framework to predict the release kinetics from such systems.

This communication provides a framework for the analysis of diffusional release from matrices undergoing structural changes leading to the enhancement of the diffusion coefficient and presents criteria for the solute release at constant rate. The predictions are verified on the basis of the analysis of the experimental data reported in the literature by both our group as well as other investigators, and those generated during the course of this work.

2. Mathematical development

The equation for the diffusion of the active ingredient from a slab geometry in which the diffusion coefficient is a function of time is given by

$$\frac{\partial C}{\partial t} = D_t \frac{\partial^2 C}{\partial x^2}. \tag{1}$$

Here C denotes the concentration of the active ingredient in the slab and x and t are the position and time coordinates, respectively. Equation (1) can be converted to the standard form for the case of constant diffusivity by incorporating the variable

$$\theta = \int_o^t \frac{D_t}{D_\infty} \mathrm{d}t \tag{2}$$

where D_∞ is a constant.

Thus (1) is transformed to

$$\frac{\partial C}{\partial \theta} = D_\infty \frac{\partial^2 C}{\partial x^2}. \tag{3}$$

The solutions of this equation for various boundary conditions have been reported by Crank (1975).

For the case of zero surface drug concentration and uniform initial drug concentration, the fraction of the active ingredient released is M_t/M_∞. Here M_t denotes the amount of the active ingredient released at time t and M_∞ denotes the amount of the active ingredient at time $t \to \infty$. This ratio can be shown to be given by

$$M_t/M_\infty = 2(D_\infty \theta/l^2)^{1/2}[\pi^{-1/2} + 2\sum_{n=1}^{\infty}(-1)^n ierfc(nl/(D_\infty \theta)^{1/2})]. \quad (4)$$

For small times, (4) simplifies to

$$M_t/M_\infty \approx (2/\pi^{1/2})(D_\infty \theta/l^2)^{1/2}. \quad (5)$$

(M_t/M_∞) in this case is a function of θ. The dependence of θ on t will then govern the dependence of M_t/M_∞ on t.

Although the importance and consequences of dependence of the diffusion coefficient on time have been recognized in the literature (Chang 1986; Lee 1987) the exact functional dependence on time has not been investigated. It is obvious that this dependence would be governed by the kinetics of swelling.

Assuming a simple exponential dependence we write

$$D_t = D_t + (D_\infty - D_i)[1 - \exp(-5Kt)]. \quad (6)$$

Here D_t denotes the diffusivity of the active ingredient at time t after the structural change is initiated. D_i and D_∞ denote the values of diffusivity prior to the onset of the structural change and after its completion ($t \to \infty$). K denotes the reciprocal of time in which the structural change is completed. In (6) the term 5 Kt has been used so that $D_t \simeq D_\infty$ at $t = (1/K)$. This equation is analogous to that proposed by Lee (1987). However, in the present case, the physical significance of K is more general. Experimental verification, utility and limitations of (6) will be discussed later.

The exponential dependence proposed by us for diffusivity as a function of time is a representative one. It should be noted that the exact quantitative dependence will depend upon the kinetics of swelling and the size and shape of the solute. We also tried other functional dependencies, of the following form,

$$D_t = D_i + (D_\infty - D_i)Kt, \quad (7)$$

and

$$D_t = D_i \exp(Kt \ln(D_\infty/D_i)). \quad (8)$$

It is obvious that (7) and (8) will be valid only upto $Kt = 1$.

In order that the diffusional release of the active ingredient is modified by the structural changes in the matrix, it is imperative that the two processes take place over comparable time scales. The importance of this concept was illustrated qualitatively by Heller and Baker (1980), who investigated the release of bovine serum albumin (BSA) from acrylamide gels crosslinked with *bis*acrylamide. At low crosslink densities, the equilibrium swelling of the gels was 80%. BSA diffused readily from the gel before the crosslinks were cleaved. On the other hand, at higher crosslink densities BSA was not released even over a period of few weeks. Subsequently, a proprietary hydrogel possessing the desired degradability was developed. BSA was released from the gel at a constant rate as a result of degradation, which we believe not only allowed

the release of BSA by diffusion but also modified the diffusion coefficient in such a way that BSA was released at a constant rate.

Mathematically, this implies

$$0 < Kt < 1. \tag{9}$$

We now define the parameter

$$\tau = Kt, \tag{10}$$

t in this case denotes the time for release, the parameter τ then denotes the extent of structural change in the matrix. Equation (2) can then be rewritten as

$$\theta = \frac{1}{K}\int_0^{\tau}\left[\frac{D_i}{D_\infty} + \left(1 - \frac{D_i}{D_\infty}\right)(1 - \exp(-5\tau))\right]d\tau. \tag{11}$$

Substituting $D_i/D_\infty = \beta$ and integrating, we have

$$\theta = \frac{1}{K}\left[\beta\tau + (1-\beta)\left(\tau + \frac{1}{5}(\exp(-5\tau) - 1)\right)\right], \tag{12}$$

or

$$\theta = \frac{1}{K}\left[\beta\tau + (1-\beta)\left(\frac{5\tau^2}{2!} - \frac{25\tau^2}{3!} + \frac{125\tau^4}{4!} - \cdots\cdots\right)\right]. \tag{13}$$

We now consider different limiting cases.

Case A: When the time over which release takes place is very small in comparison to K^{-1}, the matrix would have undergone practically no structural change during the release. As a result, the release of the active ingredient will be governed essentially by its diffusion through the matrix characterized by the diffusivity D_i.

For $\tau \to 0$ (say $0 < \tau < 0{\cdot}02$),

$$D_t \approx D_i,$$

$$\theta = (D_i/D_\infty)t,$$

and hence

$$M_t/M_\infty \propto t^{0{\cdot}5}. \tag{14}$$

Case B: When the time over which the release takes place is very large in comparison to K^{-1}, the structural change in the matrix would have been practically over before a significant fraction of solute is released. The release of the active ingredient through the matrix will be governed once again by diffusion characterized by diffusivity D_∞.

For $\tau > 1$,

$$D_t \approx D_\infty,$$

$$\theta = t,$$

therefore

$$M_t/M_\infty \propto t^{0{\cdot}5}. \tag{15}$$

Case C: If during the release of the active ingredient, the extent of the structural change that the polymer matrix undergoes is finite but small, i.e. $\tau \ll 1$,

or more specifically, $0{\cdot}02 < \tau < 0{\cdot}1$, (16)

we could ignore higher order terms in τ and write

$$\theta = \frac{1}{K}\left[\beta\tau + \frac{5(1-\beta)}{2}\tau^2\right]. \tag{17}$$

θ in this case is a quadratic function of τ.

We consider situations under which further simplification is possible.

For

$$\tau \gg \beta/(1-\beta) \tag{18}$$

the change in the diffusion coefficient accompanying the structural change is so large that the first term on the right hand side of (15) can be ignored, so that

$$\theta \propto \tau^2 \tag{19}$$

and

$$M_t/M_\infty \propto t. \tag{20}$$

For

$$\tau \ll \beta/(1-\beta) \tag{21}$$

$$\theta \propto \tau \tag{22}$$

and

$$M_t/M_\infty \propto t^{0.5}. \tag{23}$$

And for

$$\tau \sim \beta/(1-\beta) \tag{24}$$

$$M_t/M_\infty \propto t^n \tag{25}$$

when $0{\cdot}5 < n < 1$, the release kinetics will be anomalous.

Case D: When the extent of structural change in the matrix is fairly large, i.e.

$$\tau - 1, \text{ (say } 0{\cdot}1 < \tau < 1), \tag{26}$$

(13) will have to be used. However, for very small values of β such that,

$$\beta \to 0 \text{ or } \tau \gg \beta/(1-\beta) \tag{27}$$

we have,

$$\theta \approx \frac{1}{K}\left[\frac{5\tau^2}{2!} - \frac{25\tau^3}{3!} + \frac{125\tau^4}{4!} - \cdots\cdots\right], \tag{28}$$

which predicts anomalous release profiles with release exponents closer to 1, especially for relatively small τ (say, $\tau < 0{\cdot}5$), since the first power of τ is no longer involved.

The results of a similar analysis summarized in appendix A indicate that similar criteria emerge when the variation of the diffusivity of solute with time is described by (7). However, when the dependence is governed by (8) explicit criteria do not emerge.

Thus the release of the active ingredient at constant rate can be observed when (a) the release kinetics of the active ingredient is modified by the structural change taking place in the polymer matrix, and (b) the structural change brings about a very large enhancement in the diffusivity of the active ingredient. It is interesting to note that the criteria developed herein are independent of the detailed nature of the

structural changes. In this sense the analysis provided in the foregoing provides a general and unified framework.

3. Experimental work

3.1 *Polymer synthesis*

2-Hydroxy ethyl methacrylate monomer was obtained from M/s Fluka (Switzerland) and *t*-butyl hydroperoxide initiator was obtained from Wilson Laboratory (India). Theophylline was obtained from the local suppliers.

Bulk polymerization 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.

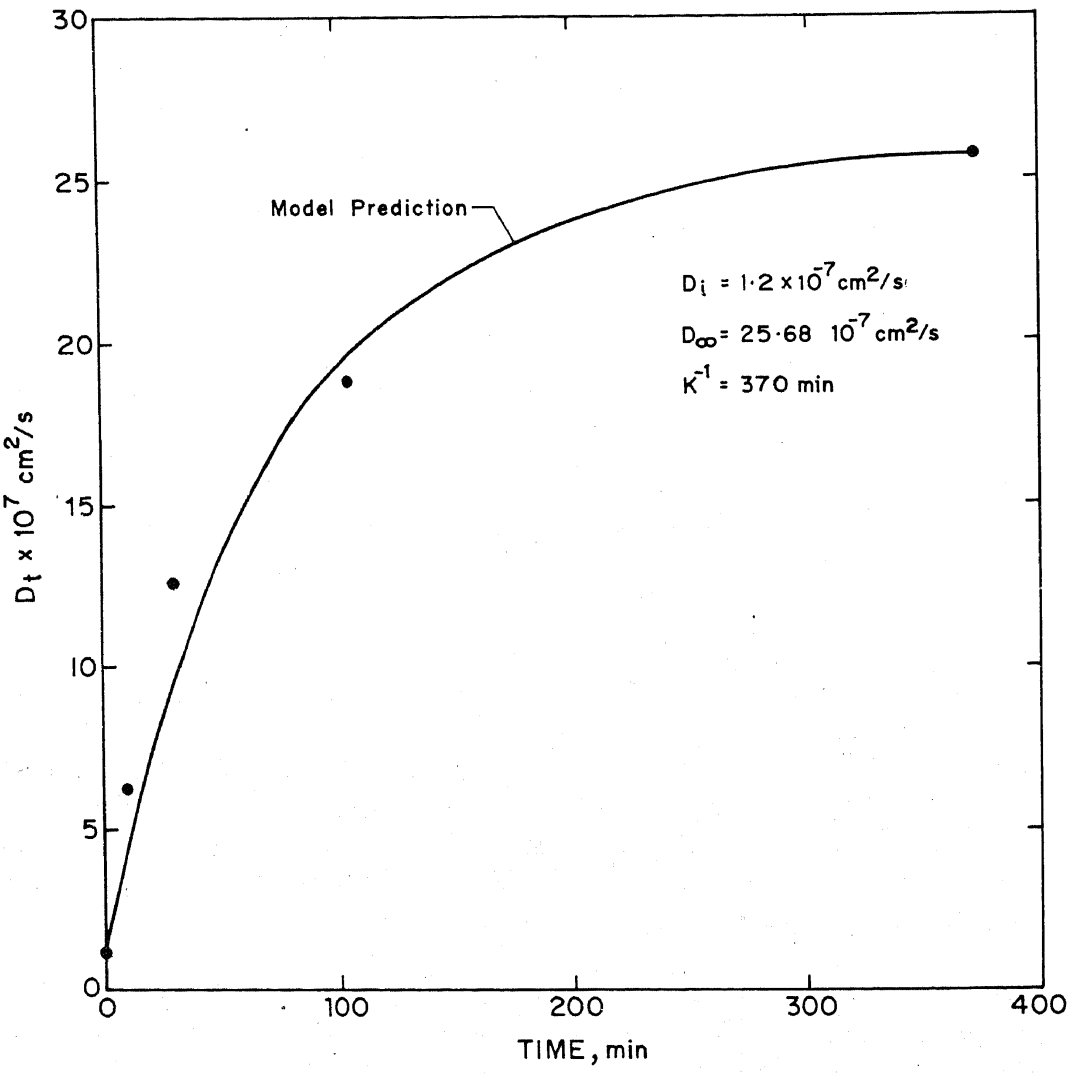

Figure 1. Diffusivity of theophylline in swollen PHEMA in water–dioxane mixture *vs* time [line represents the predictions from (6)].

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 of the monomer was verified by following the UV spectrum of the monomer.

3.2 *Swelling studies*

Dynamic swelling studies were carried out on PHEMA discs containing no solute. 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.

3.3 *Measurement of diffusion coefficient*

Glassy PHEMA hydrogels were swollen to equilibrium in binary solvents of varying composition. Theophylline was loaded during swelling. Diffusivity of theophylline in

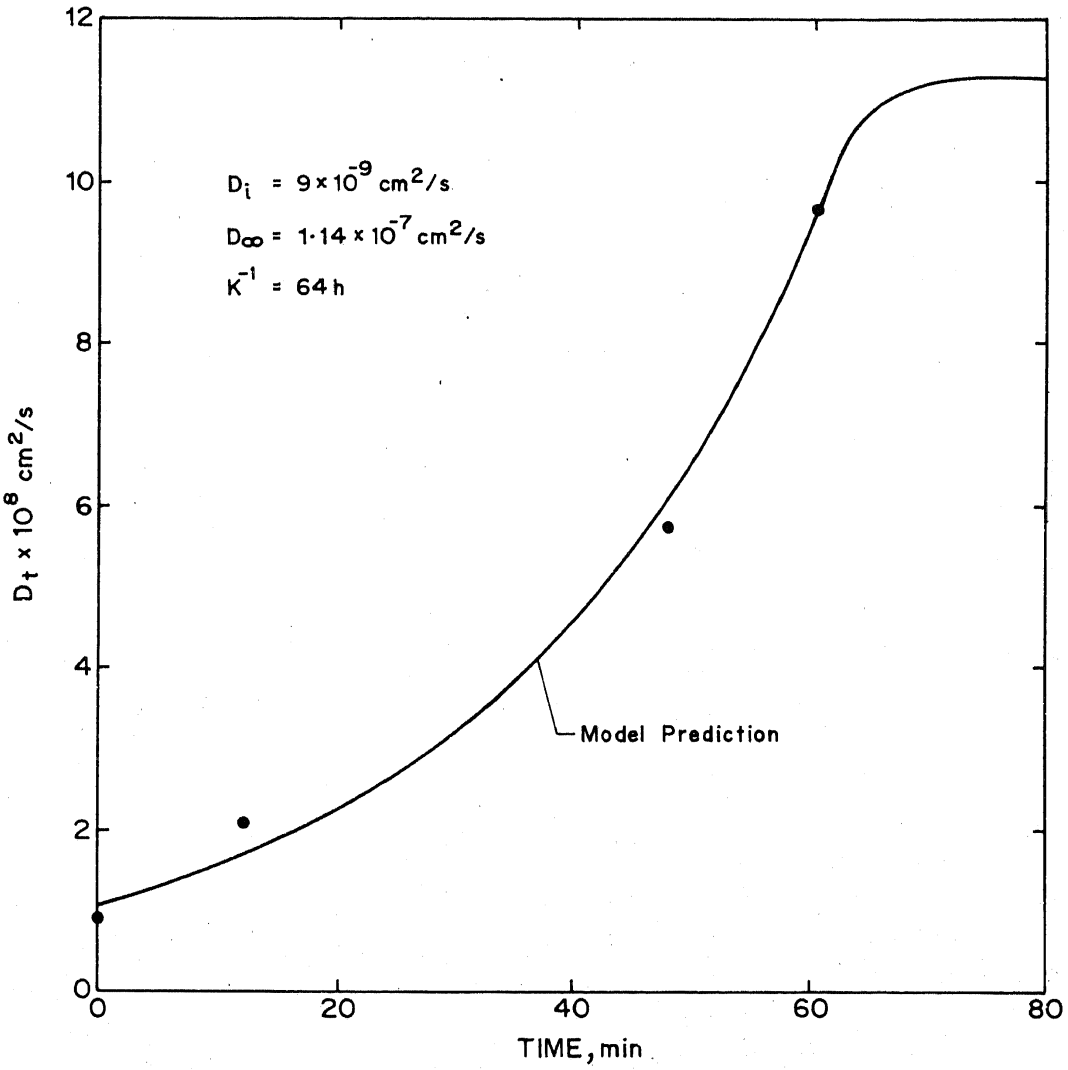

Figure 2. Diffusivity of *o*-nitrobenzoic acid in P(HEMA-PNP) (10:3) *vs* time [line represents the predictions from (6)].

the swollen hydrogels was then determined by following the desorption of theophylline into binary solvents of identical composition as described by Yasuda *et al* (1968). There was no change in the degree of swelling of the matrix during the course of the experiment. A PHEMA hydrogel swollen to equilibrium in water was then immersed in water–dioxane (60:40) and the degree of swelling was followed as a function of time. From the two investigations, diffusivity of theophylline could be correlated with time. A plot of diffusivity of theophylline vs. time so generated is shown in figure 1.

To investigate the functional dependence of solute diffusivity on time in the case of the pendent chain-linked systems, P(HEMA-PNP) hydrogel discs (HEMA:PNP = 10:3) were prepared and hydrolysed in alkali for different time intervals. *p*-nitrobenzoic acid liberated was extracted in acetone. Each disc was freeze-dried and *p*-nitrobenzoic acid was loaded into the disc from solution. The loading was poor because of very low solubility of *p*-nitrobenzoic acid. *o*-Nitro benzoic acid was therefore loaded into the discs and its diffusivity was estimated as described earlier. The results are summarized in figure 2.

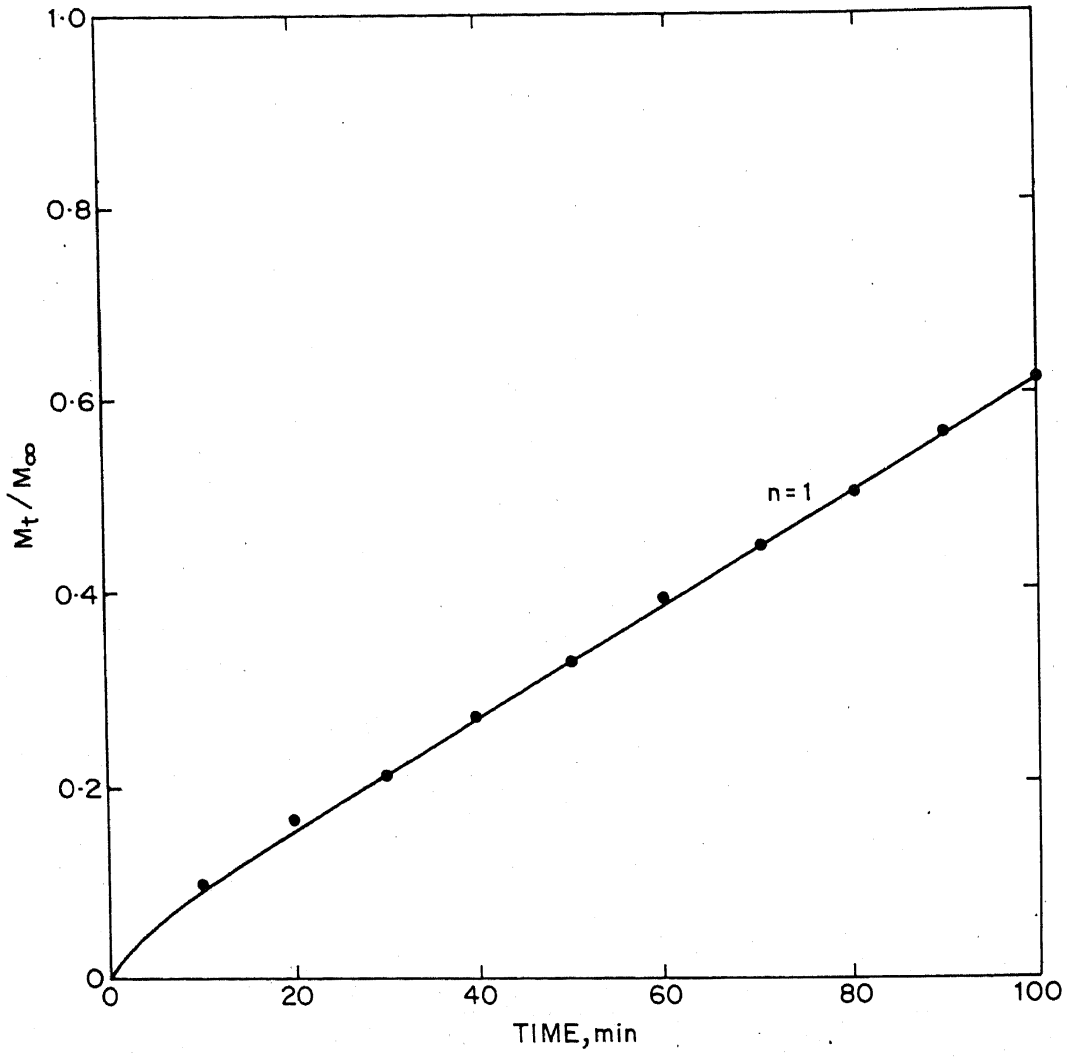

Figure 3. Release profile of theophylline from glassy PHEMA matrix in water: dioxane (89%–11%) [line denotes the statistical fit].

3.4 *Release studies*

The kinetics of release of theophylline was followed by monitoring the absorbance of theophylline released using a Shimadzu 240 UV-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 $t(M_t)$ was determined from the appropriate calibration curve. The total amount of theophylline released from the disc till it was completely depleted was taken as M_∞. The fraction of theophylline released was expressed as (M_t/M_∞). The release exponent (n) was obtained from the slope of the plot of $[\ln(M_t/M_\infty)]$ vs $\ln(t)$. Typical release profiles from glassy and swollen hydrogels are shown in figures 3 and 4 respectively.

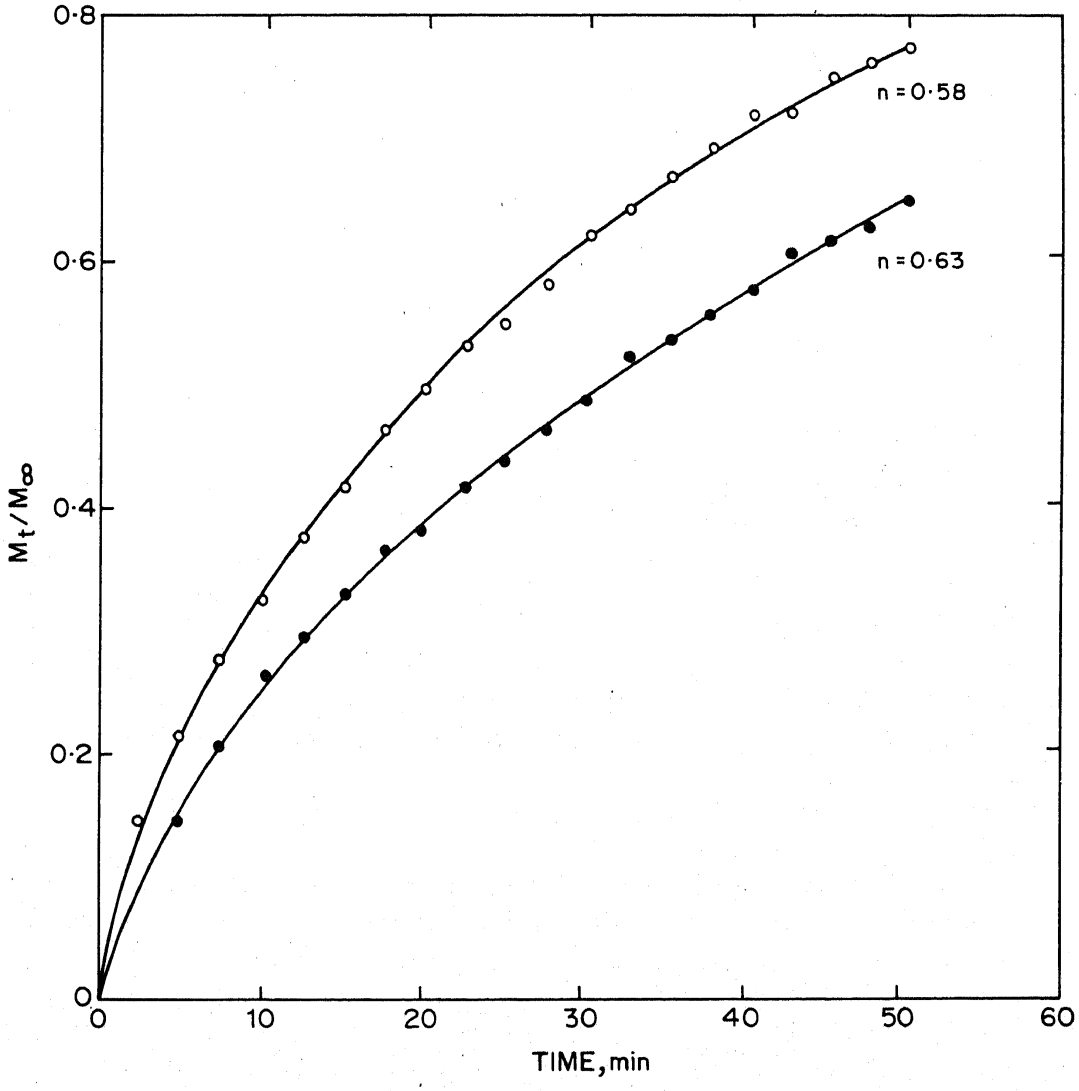

Figure 4. Release profile of theophylline at 37°C from swollen PHEMA matrix hydrogel in water: dioxane 75–25 (●), 60–40 (○).

4. Results and discussion

4.1 *Release of active ingredients from swellable hydrogels*

Swelling controlled delivery systems have been extensively investigated during the last decade. The release of the active ingredient was shown to take place at constant rate, when the penetrant sorption was governed by case II transport and the diffusion time for the solute from the swollen layer was much smaller than the penetration time for the solvent front (Hopfenberg 1981).

A number of communications report the release of an active ingredient at constant rate from glassy as well as rubbery matrices, even when the penetrant sorption does not follow case II transport. These include (a) the release of an active ingredient from pendent chain linked polymers by hydrolysis (McCormick and Fooladi 1980; Shah *et al* 1990), (b) release of bovine serum albumin (BSA) from crosslinked hydrogels undergoing chain scission in the polymer backbone (Heller and Baker 1980), (c) solvent-induced swelling of glassy as well as rubbery polymers (Lee and Lum 1992; Vadalkar *et al* 1993), (d) release of drugs from ionizable hydrogels (Siegel *et al* 1988; Shah *et al* 1991) and (e) release through reversible bilayered membranes created by exploiting volume phase transition in polymers (Kulkarni *et al* 1992).

In the following sections, we show how the criteria developed in the foregoing can be satisfactorily used to predict the release characteristics of diverse matrix systems. In each case the rationale behind the dependence of diffusion coefficient on time has been explained and the predictions compared with experimental results.

4.2 *Time-dependent diffusion coefficients*

In the past, diffusivity of a solute from the polymer penetrant system has often been modelled as a function of penetrant concentration on the basis of the free volume theory (Davidson and Peppas 1986). However, this approach, although sound in principle, poses some difficulties during its application. First, the exact dependence of diffusivity on concentration cannot be *a priori* determined. Second, it requires a numerical solution for the coupled partial differential equations often incorporating a moving boundary. This, therefore, does not yield simple, predictive criteria. Finally, the analysis is further complicated when an increase in the hydrophilicity of the polymer causes an increase in the swelling. In this context, it was thought reasonable to consider a time-dependent diffusivity involving model parameters which could be experimentally determined.

A wide range of structural changes can take place within the polymer matrix during the course of solute release, which can lead to an increase in the degree of swelling of the matrix with time. Since the solute diffusivity is also a function of the degree of swelling of the polymer, it follows that the solute diffusivity would also be a function of time. The exact functional dependence would be governed by the structural changes involved and the kinetics of swelling. However, this has not been experimentally established. Since it is not possible to determine the diffusivity of the solute from a dynamically swelling system, this dependence was investigated by us indirectly as described earlier.

The plot of diffusivity of theophylline as a function of time is shown in figure 1. The values of the parameters D_i and D_∞ represent the diffusivity of theophylline from

PHEMA hydrogels swollen to equilibrium in water and the solvent, water: dioxane (60:40), respectively. K denotes the reciprocal of time required for swelling. It can be seen from figure 1 that the diffusivity of theophylline as a function of time predicted from (6) is in fair agreement with the values experimentally determined.

In the case of initially glassy hydrogels similar verification is difficult, since the diffusivity of solutes from glassy polymers cannot be readily measured. As the solvent penetrates the glassy polymer and a critical solvent concentration is reached, the glassy polymer is transformed into a rubbery one. The degree of swelling of P(HEMA) at this stage is close to 10% (Korsmeyer *et al* 1986b). However, measurements of the diffusivity of theophylline by the desorption method from water–dioxane compositions in which the equilibrium swelling was 10%, did not yield consistent results. The value of diffusivity of *p*-nitrobenzoic acid from the copolymer of PHEMA having 13% degree of swelling was taken as D_i. The actual value of diffusivity of theophylline would be lower than this value and the criteria defined by (18) would

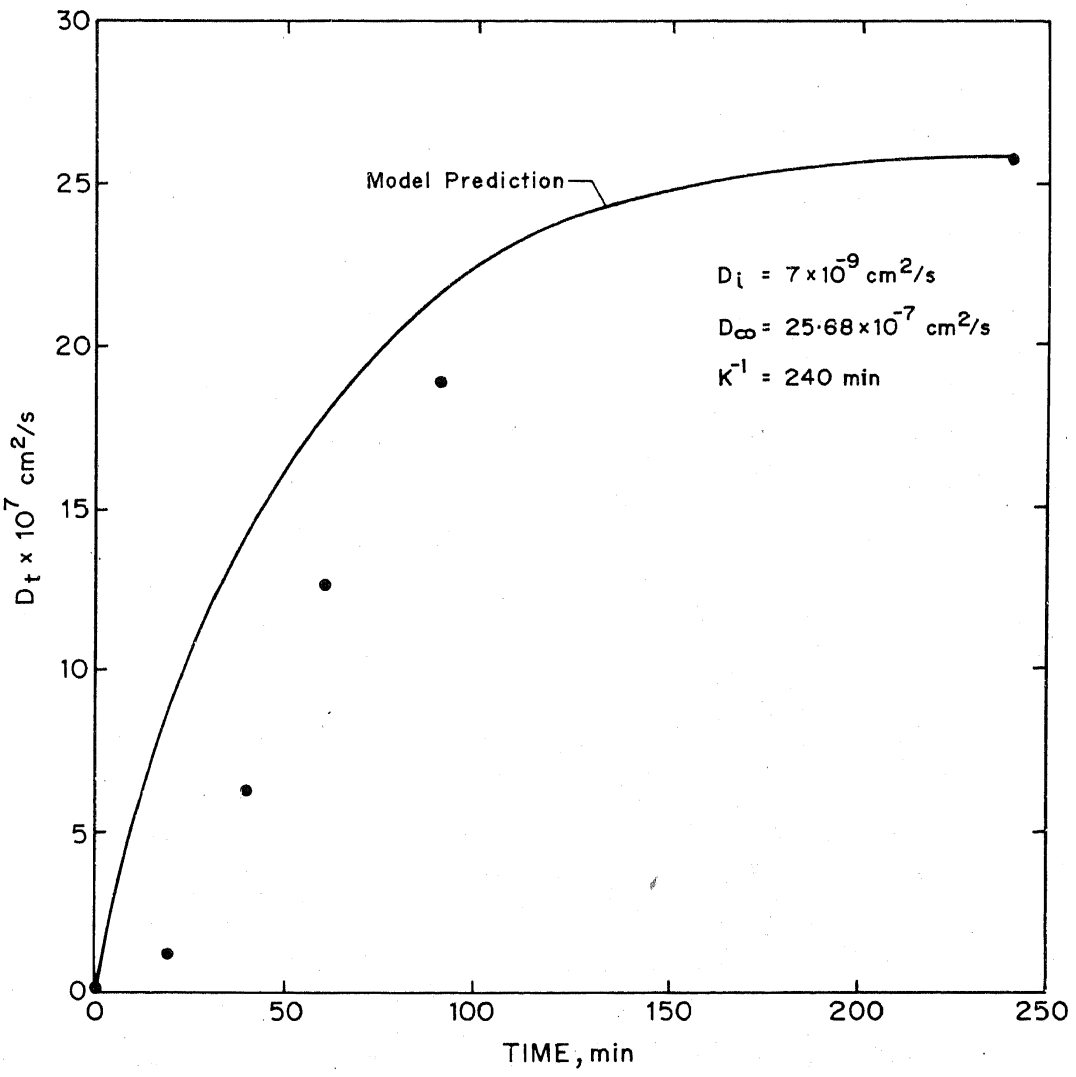

Figure 5. Diffusivity of theophylline in glassy PHEMA in water-dioxane mixture *vs* time [line represents the predictions from (6)].

always be valid. Further it was observed that the predictions based on (6) are not as sensitive to D_i as to K.

The predictions for the diffusivity of theophylline based on (6) are shown in figure 5. It is obvious that the fit is not as good as in the preceding case. In view of the complexities in the relaxation process, which govern the transition from the glassy to the rubbery state, such a simplistic functional dependence is unlikely to hold. It, however, provides a reasonable basis for arriving at the criteria for release under limiting conditions (Lee 1987).

4.3 *Release of solutes from glassy hydrogels*

4.3a *P(HEMA-MMA) copolymers*: Davidson and Peppas (1986) investigated the release of theophylline from glassy as well as swollen hydrogels based on P(HEMA-MMA) copolymers. The relevant physicochemical data for release are summarized in table 1. The parameter β strictly represents the ratio of diffusivity of theophylline in glassy polymers to that in the equilibrium swollen polymer. The diffusivity of solutes in the glassy phase is very low ($\simeq 10^{-10}$ cm^2/s). The solute will be able to diffuse through the matrix at a finite rate only when the matrix has undergone transition from a glassy phase to a rubbery phase. The solvent composition for the PHEMA hydrogel at which glass–rubber transition occurs, is in the range of 10% (Korsmeyer *et al* 1986). On the basis of the values of diffusivities of various solutes in PHEMA hydrogel and the copolymers of varying degrees of swelling (Shah *et al* 1990; Vyavahare *et al* 1990), the maximum possible value of D_i for theophylline can be assumed to be 7×10^{-9} cm^2/s.

From the data summarized in table 1, it is apparent that in the case of the glassy P(HEMA-MMA) polymer (1D), $\tau > 1$. As a result a significant fraction of theophylline is released after equilibrium swelling is reached. The release kinetics, therefore, is governed by the diffusion of theophylline from the swollen matrix. The release index observed ($n = 0{\cdot}55$) is thus in agreement with the predictions of case B, (15). For the release of theophylline from the matrix 1E also, $\tau > 1$. The release index in this case is therefore expected to be 0·5. Although this is not in agreement with the value of the release index reported by Davidson and Peppas (1986), the value is in agreement with the value reported earlier by Peppas and Franson (1983). The deviation of the

Table 1. Release of theophylline from glassy P(HEMA-MMA) hydrogels*+.

No.	Fraction of HEMA	$D_\infty \times 10^7$ (cm^2/s)	$\frac{\beta}{(1-\beta)}$	τ	n	
					Predicted	Experimental
1A	1·0	1·700	0·0427	0·500	Anomalous	0·65
1B	0·9	0·511	0·1580	0·625	Anomalous	0·62
1C	0·8	0·188	–	3·000	0·5	0·60
1D	0·7	0·059	–	3·167	0·5	0·56
1E	0·5	0·328	–	1·600	0·5	0·94 (0·5)**

*$D_i = 7{\cdot}1 \times 10^{-9}$ cm^2/s; +(Davidson and Peppas 1986); **(Peppas and Franson 1983).

observed release index from the predicted value for polymer 1C, although small, cannot be presently explained.

In the case of the polymers 1A and 1B, the value of the parameter τ is close to 0·5 (case D) which indicates that the release is influenced by the relaxation process. On the basis of (13), the release of theophylline is expected to follow anomalous kinetics which is indeed the case.

4.3b *pH induced swelling*: Shah *et al* (1991a) reported the release of theophylline and carbamezapine from glassy P(2-hydroxyethyl methacrylate-*p*-carboxy styrene) P(HEMA-4CS) matrices in media of increasing *p*H. Penetration of the alkaline medium is accompanied by the transition of the glassy polymer into a rubbery one and ionization of the carboxylic acid.

At *p*H = 11, theophylline as well as carbamezapine were released at constant rate following an initial burst (see figure 6 and table 2). However, this could not be attributed to the case II transport controlled sorption of the penetrant. As water permeates into the glassy P(HEMA-4CS) matrix, it causes swelling of the glassy polymer, which in the absence of the alkali, would be only 26% because of the hydrophobic nature of 4CS. In the presence of alkali, further swelling of the matrix

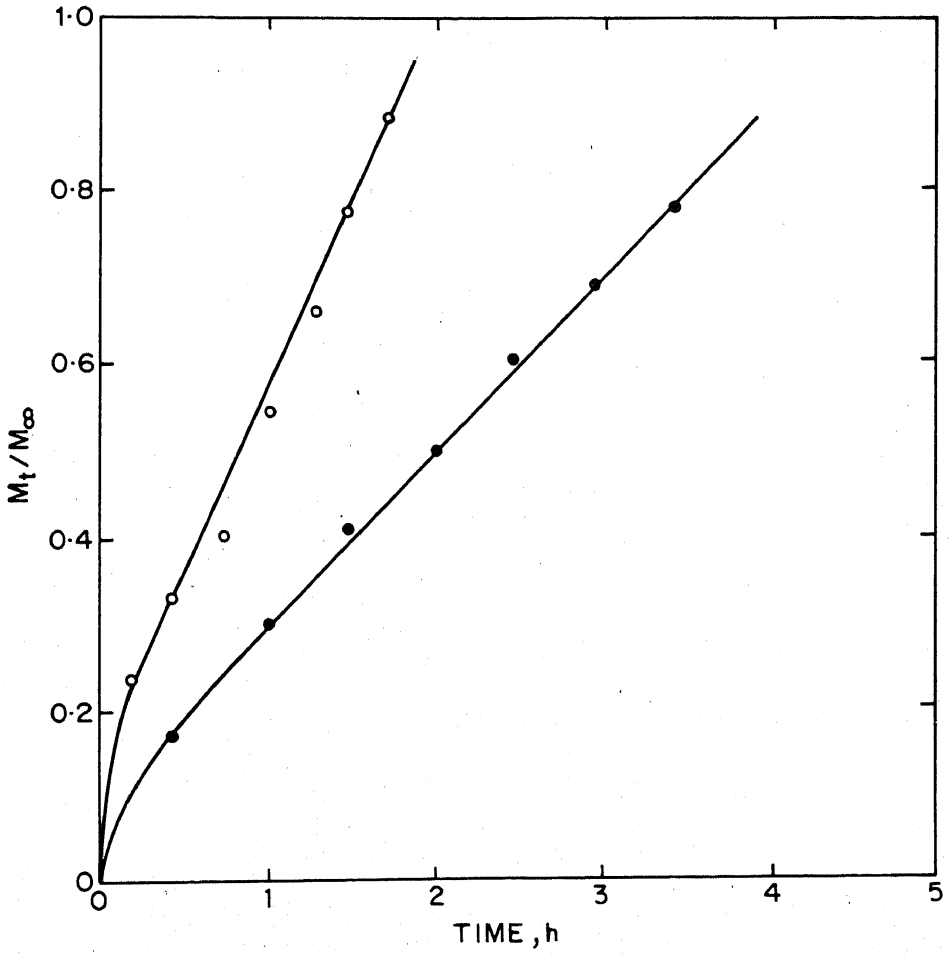

Figure 6. Release profiles of theophylline (○) and carbamezapine (●) from P(HEMA-4CS) matrix *vs* time.

Table 2. Comparison of model predictions and experimental data for P(HEMA-4CS)$^{+}$.

No.	pH	$\frac{\beta}{(1-\beta)}$	τ	n	
				Predicted	Experimental
(a) Release of carbamezapine					
1	8	0·0370	0·16	Anomalous	0·65
2	11	0·0370	0·28	1·00	0·96
(b) Release of theophylline					
1	8	0·0072	0·075	Anomalous	0·64
2	9	0·0072	0·100	Anomalous	0·77
3	11	0·0072	0·125	1·00	1·00

†(Shah *et al* (1991a)

takes place as a result of the ionization of carboxyl group. The rate of this step is governed by the interdiffusion of H^+ and Na^+ ions. Thus, as a result of ionization of 4CS, the degree of swelling of the matrix P(HEMA-4CS) increases with time, which results in an increase in the diffusivity of the solute. The relevant parameters were obtained from the swelling and release data reported by Shah *et al* (1991).

For the release of carbamezapine, $\tau > 0{\cdot}1$ (case D), anomalous release kinetics is anticipated on the basis of (13). This is borne out in the case of release of carbamezapine from P(HEMA-4CS) matrix at $p\text{H} = 8$. For release at $p\text{H} = 11$, the term $\beta/(1-\beta)$ decreases in relation to τ and the release index tends towards unity as predicted by (27).

The release of theophylline from P(HEMA-4CS) matrix at pH 8 and 9, $\tau \to 0{\cdot}1$ (case C). The anomalous release kinetics observed is in agreement with the predictions of (24). For the release at $p\text{H} = 11$, $\tau > 0{\cdot}1$ (case D). Since the inequality defined by (26) is satisfied, the release is expected to proceed at a constant rate, which is the case.

4.3c *Mixed solvent systems*: The release of theophylline from glassy PHEMA hydrogels in media containing increasing proportions of dioxane was investigated. In all the cases, the release of theophylline was found to be linear with time following an initial burst (Vadalkar *et al* 1993). Sorption of binary solvents in the glassy PHEMA matrix does not follow case II transport. The swelling is slow enough so that the diffusivity of the solute does not reach its equilibrium value instantaneously but increases over a period of time. From the values of τ (see tables 3 and 4) it is apparent that solute release and swelling take place over comparable time scales. Since it is not possible to determine the solute diffusivity under dynamic swelling conditions, the swelling behaviour of the glassy hydrogel was investigated as a function of time. Diffusivity of theophylline was determined from equilibrium swollen hydrogels and then plotted as a function of time as shown in figure 1.

The release data for the theophylline from glassy PHEMA (table 4) fall under case D ($0{\cdot}1 < \tau < 1$). Since the inequality defined by (27) is satisfied, the release of theophylline is expected to proceed at a constant rate. The experimental findings are in agreement with the predictions.

The release of theophylline from initially swollen hydrogels (table 3) belongs to case C (s. no. 1 and 2) or case D (s. no. 3 and 4). Since in both cases, the parameters

Table 3. Effect of solvent composition on the release of theophylline from rubbery PHEMA hydrogels*+.

No.	Water: dioxane	$D_\infty \times 10^7$ (cm²/s)	$\frac{\beta}{(1-\beta)}$	τ	n	
					Predicted	Experimental
1	60:40	25·68	0·0482	0·078	Anomalous	0·58
2	75:25	18·81	0·0684	0·097	Anomalous	0·63
3	82:18	12·61	0·1049	0·181	Anamalous	0·56
4	89:11	06·24	0·2376	0·305	Anomalous	0·54

*$D_i = 1{\cdot}2 \times 10^{-7}$ cm²/s; +Vadalkar *et al* (1993)

Table 4. Effect of solvent composition on the release of theophylline from glassy PHEMA hydrogels*+.

No.	Water: dioxane	$D_\infty \times 10^7$ (cm²/s)	$\frac{\beta}{(1-\beta)}$	τ	n	
					Predicted	Experimental
1	60:40	25·68	0·0028	0·300	1·00	1·03
2	75:25	18·81	0·0038	0·388	1·00	0·96
3	82:18	12·61	0·0050	0·463	1·00	0·98
4	89:11	06·24	0·0115	0·544	1·00	0·96

*$D_i = 7{\cdot}1 \times 10^{-9}$ cm²/s; +Vadalkar *et al* (1993)

$\beta/(1-\beta)$ and τ are of the same magnitude, anomalous release kinetics is observed in accordance with the predictions.

4.4 *Release from rubbery polymers*

Lee and Lum (1992) synthesized polydimethyl siloxane microspheres, into which cinnamyl alcohol was loaded. Since the polymer is rubbery at room temperature and does not undergo swelling in water, release of cinnamyl alcohol from these matrices was governed by diffusion ($n = 0{\cdot}53$). In contrast, PDMS is swollen extensively in *n*-pentane. The release of cinnamyl alcohol is not only accelerated as a result of swelling but takes place at constant rates ($n \sim 1{\cdot}0$) over extended time periods. It was noticed that the criteria developed above for planar geometry hold good in the case of spherical geometry as well when $D_\infty \theta / a^2 \ll 1$ (as in (5)) where a is the radius of the

Table 5. Cinnamyl alcohol release from PDMS microspheres*+.

No.	System	$D_\infty \times 10^5$ (cm²/s)	$\frac{\beta}{(1-\beta)}$	$\tau = \frac{D_{avg}}{Ka^2}$	n	
					Predicted	Experimental
1	16·7% Pentane	1·77	0·0075	0·895	1·00	1·27
2	21·3% Pentane	2·15	0·0062	1·085	1·00	1·02

*$D_i = 1{\cdot}34 \times 10^{-7}$ cm²/s, $a = 0{\cdot}05$ cm; +Lee and Lum (1992)

particle. In this context, a comparison of the swelling as well as the release profiles of cinnamyl alcohol indicates that $0{\cdot}1 < \tau < 1$ (case D). However, the values of the diffusivity of cinnamyl alcohol in PDMS in water and PDMS swollen in *n*-pentane illustrate (see table 5) that the inequality in (27) is satisified.

4.5 *Release of p-nitrobenzoic acid from P(HEMA-PNP) hydrogels*

A number of researchers have reported the release of the active ingredient, which is chemically linked to the polymer backbone through the pendent chain. The active ingredient is released as a result of hydrolysis and diffusion through the matrix. The release of the active ingredient at constant rate was earlier attributed to the enhancement in the rate constant for hydrolysis due to the neighbouring group effect (McCormick and Fooladi 1980).

Shah *et al* (1990) linked *p*-nitrobenzoic acid to 2-hydroxyethyl methacrylate (HEMA). The resulting monomer, 2-methacryloyl ethyl *p*-nitrobenzoate (PNP) was copolymerized with HEMA in different proportions. Planar glassy hydrogel discs were exposed to 0·01 N NaOH. As the alkali penetrated into the matrix and hydrolysed the ester link, *p*-nitrobenzoic acid diffused out of the matrix. The release continued over extended time periods at constant rate even after the disc was fully saturated with alkali. The release of *p*-nitrobenzoic acid from hydrogels swollen to equilibrium in water and then immersed in alkali also proceeded at constant rate.

The monomer 2-methacryloyl ethyl *p*-nitrobenzoate is hydrophobic as compared to 2-hydroxy ethyl methacrylate. The equilibrium degree of swelling of the copolymer and consequently the diffusivity of *p*-nitrobenzoic acid decreases as the HEMA content of the polymer is decreased (Shah *et al* 1990) (see table 6). As the ester linkage in PNP is hydrolysed to release *p*-nitrobenzoic acid, the HEMA content of the copolymer increases. This leads to an increase in the degree of swelling of the hydrogel as well as the diffusivity of *p*-nitrobenzoic acid. Since it was not possible to measure the diffusivity of *p*-nitrobenzoic acid due to its very low solubility, the diffusivity of

Table 6. Comparison of model predictions with experimental data for pendent chain-linked and cross-linked hydrogels*+.

No.	System	$D_\infty \times 10^8$ (cm²/s)	$\frac{\beta}{(1-\beta)}$	τ	*n*	
					Predicted	Experimental
Pendent chain-linked system						
1	P(HEMA-PNP) 10:2	3·52	0·135	0·455	Anomalous	0·80
2	P(HEMA-PNP) 10:3	2·31	0·085	0·577	1·00	0·94
3	P(HEMA-PNP) 10:5	0·71	0·025	0·600	1·00	1·03
Erodible cross-links						
1	P(HEMA-HEGDMA)	7·90	0·250	0·346	Anomalous	0·59
2	P(HPMA-HEGDMA)	0·80	0·082	0·600	1·00	0·97

*$D_i = 2{\cdot}94 \times 10^{-7}$ cm²/s,+

o-nitrobenzoic acid was measured as described earlier. The diffusivity increases exponentially with time in agreement with (8) as shown in figure 2.

The relationship between θ and τ, when the dependence of diffusivity on time is governed by (8) is given in the appendix, (A5). This relationship does not lead to explicit criteria for predicting the release kinetics. It can only be said that the release indices anticipated on the basis of (A5) would be in general higher than the predictions for various cases which follow from (13). However, these should not matter since the objective of the analysis is to distinguish between Fickian and anomalous release, of which the zero order release ($n = 1$) is a special case, just as case II transport-controlled penetrant sorption at constant rates ($n = 1$) is a special case of anomalous sorption.

The diffusivity ratio (D_i/D_∞) used in the analysis corresponds to the ratio of diffusivity of *p*-nitrobenzoic acid in the hydrogel P(HEMA-PNP) (D_i) to that in P(HEMA) hydrogel (D_∞). The time corresponding to 60% release of *p*-nitrobenzoic acid was obtained from the release data. The time required for complete exhaustion of *p*-nitrobenzoic acid was taken as the time required for the structural change to be completed (K^{-1}).

The predictions presented in table 6 are based on the mathematical analysis presented in § 2. Since τ is greater than 0·1, the data for the release of *p*-nitrobenzoic acid are analysed under the framework of case D. The predictions for the system P(HEMA-PNP) (nos. 1 and 3 in table 6) are in agreement with the model predictions. Since the ratio $[\beta/(1-\beta)]/\tau$ for the polymer P(HEMA-PNP) (no. 2 in table 6) is much smaller as compared to that for polymer 1, it is obvious that the release index should be greater than 0·8, which is the case.

An interesting feature of the pendent chain-linked systems is that the time required for the release and for the structural change to be completed is always comparable. Release of the active ingredient at constant rate will therefore be observed if the inequality defined by (18) is satisfied. The release of active ingredient at constant rate can thus be ensured by increasing the hydrophobicity of the polymer matrix. Systems, which can release the active ingredient up to six months, have been developed using this approach (Shah *et al* 1991).

4.6 *Matrix systems containing erodible crosslinks*

The utility of the pendent chain-linked systems described above is restricted to the active ingredients, which have the appropriate functional groups so as to conjugate with the monomers which could then be polymerized. Matrix systems, in which the structural changes can be brought about without the loss of a low molecular weight solute, and in which a physically dispersed solute is released by diffusion, would significantly broaden the applicability of such systems. Since the two processes are now decoupled, it is possible to observe a wide range of release characteristics. The importance of developing hydrogels in which the erosion of crosslinks takes place over the same time as the release of the active ingredient has been discussed earlier (Heller and Baker 1980).

Vyavahare *et al* (1992) investigated the kinetics of release of theophylline from glassy as well as swollen PHEMA hydrogels crosslinked by 2-hydroxyethyl glycolate dimethacrylate (HEGDMA). In contrast to the widely used crosslinked monomer diethylene glycol dimethacrylate, which is highly resistant to hydrolysis, HEGDMA is susceptible to hydrolysis, which leads to the generation of a hydroxyl group and

a carboxyl group. The latter is converted to its sodium salt and leads to a further increase in swelling due to ionization. The degree of swelling of the polymer is significantly enhanced as the hydrolysis proceeds and yet the release profiles observed vary significantly.

Release of theophylline from P(HEMA-HEGDMA) hydrogels (case D) deviates slightly from the Fickian behaviour ($n = 0{\cdot}59$). This is because during the course of hydrolysis, the equilibrium degree of swelling in enhanced from 40 to 65%. During the same time period there is a five-fold increase in the diffusivity i.e., $(D_i/D_\infty) \simeq 0{\cdot}20$. The values of parameters τ and $(\beta/(1-\beta))$ are comparable. The release of theophylline, therefore would be expected to follow anomalous kinetics in accordance with (28). This is indeed the case. It, therefore, appears that although erosion of crosslinks and consequent increase in the swelling as well as the diffusivity do take place in the case of PHEMA matrices as well, increase in the diffusivity of theophylline is not adequate so as to lead to the release of theophylline at a constant rate. P(HPMA-HEGDMA) has an initial degree of swelling of 0·18 g/g. As the HEGDMA crosslinks are hydrolysed during the course of release of theophylline, the degree of swelling is enhanced to 0·46 g/g. This results in an almost fourteen-fold increase in the diffusivity of theophylline. Thus, although diffusional release of theophylline is influenced by the structural changes in the matrix so that $\tau \simeq 1$ (case D) in the case of both P(HEMA-HEGDMA) and P(HPMA-HEGDMA) hydrogels, the ratio $[\beta/(1-\beta)]/\tau$ in the case of P(HPMA-HEGDMA) matrices ($= 0{\cdot}14$) is much smaller than in the case of P(HEMA-HEGDMA) matrices ($= 0{\cdot}70$). The release index for theophylline although expected to be anomalous is also expected to shift towards unity, as a special case of anomalous kinetics. This is observed to be true (table 6).

5. Concluding remarks

In a number of situations, release of solute from hydrogels is accompanied by structural changes, which lead to an increase in the degree of swelling of the hydrogel. Although the origin of the structural changes which lead to increase in the degree of swelling could be rather diverse, such systems have common characteristics in that there is an increase in the diffusivity of the solute with time.

In this communication, the effect of an increase in the diffusivity of the solute as a result of the structure changes has been investigated by incorporating the dependence of diffusion coefficient on time in the release kinetics. The validity of the functional relationship assumed and its limitations are discussed. It has been shown that depending upon the relative rates of structural changes, solute release and the effect on the solute diffusivity, a wide range of release profiles can be realized. This analysis thus provides a unified framework for tailoring polymers to obtain the desired release kinetics.

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Appendix A

As discussed in § 2, the dependence of D_t on time can assume different functional forms depending upon the mechanism of structural change and kinetics of swellings. In this context (7) and (8) were also analysed on the same lines as (6).

Substituting (7) in (2), we obtain,

$$\theta = \frac{1}{K}\left[\beta\tau + \frac{(1-\beta)\tau^2}{2}\right]. \tag{A1}$$

Hence, apart from cases A and B which also hold good here, we get the following criteria when $0{\cdot}02 < \tau < 1$:

For $\tau \gg \beta/(1-\beta)$, $M_t/M_\infty \propto t$. (A2)

For $\tau \ll \beta/(1-\beta)$, $M_t/M_\infty \propto t^{0.5}$. (A3)

For $\tau \sim \beta/(1-\beta)$, $M_t/M_\infty \propto t^n$, $0{\cdot}5 < n < 1{\cdot}0$. (A4)

Note that criteria (A2), (A3) and (A4) compare well with the criteria under case C of § 2. However, τ is not limited to values less than 0·1.

On the other hand, for (8)

$$\theta = \frac{\beta}{K}\left[\tau + \frac{\tau^2}{2!}\ln\left(\frac{1}{\beta}\right) + \frac{\tau^3}{3!}\left(\ln\left(\frac{1}{\beta}\right)\right)^2 + \cdots\cdots\right]. \tag{A5}$$

However, this functional form does not permit development of criteria for specific release exponents to be observed except for cases A and B. In general, anomalous release kinetics are likely to be observed with n approaching one for small β and small τ. Another interesting feature of this functional form is that it can account for release exponents greater than 1 for very low values of β and very high values of τ.

List of symbols

C	concentration of the active ingredient in the polymer matrix (mol/cm^3);
D_{avg}	average diffusivity of the active ingredient (cm^2/s);
D_i	diffusivity of the active ingredient before the onset of structural changes (cm^2/s);
D_t	diffusion coefficient of the active ingredient at time t (cm^2/s);
D_∞	diffusivity of the active ingredient after the completion of structural change (cm^2/s);
K	reciprocal of time in which the structural change is completed (s^{-1});
l	half length of the slab (cm);
M_t	amount of active ingredient released at time t (mol);
M_∞	amount of active ingredient released at time $t \to \infty$ (mol);
n	release exponent;
t	time (s);
t_{60}	time for 60% release (s);

x position coordinate (cm);
β ratio of D_i to D_∞;
τ extent of structural change in the matrix;
θ transform as defined by (2).

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