Matrix systems for zero-order release: facile erosion of crosslinked hydrogels*

N. R. Vyavahare, M. G. Kulkarni and R. A. Mashelkar†
Polymer Science and Engineering Group, Chemical Engineering Division, National Chemical Laboratory, Pune 411008, India
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Bioerodible matrices are particularly suited for the systemic administration of drugs over extended time periods. Type I-A bioerodible matrices reported in the past degrade either too slowly or too rapidly. The rate of erosion, therefore, has no influence on the kinetics of release. This paper reports kinetics of release of theophylline from a series of crosslinked glassy/swollen hydrogel matrices based on a novel crosslinking monomer, viz. 2-hydroxyethyl glycolate dimethacrylate. The release of theophylline in an alkaline medium is accompanied by the erosion of the crosslinks. Under appropriate conditions, theophylline is released at a constant rate by the erosion of the crosslinks in the bulk of the swollen polymer as well as by the surface erosion of the glassy polymer. The release behaviour has been explained on the basis of the concept of time-dependent diffusivity of the active ingredient and swelling-controlled zero-order release, respectively.

(Keywords: kinetics; hydrogels; crosslinking; drugs; release; biomaterials)

INTRODUCTION

Bioerodible matrices are preferred for the sustained release of therapeutic agents as their use obviates the need for the removal of the excipient. The kinetics of the release of active ingredient and the mechanistic aspects of release from bioerodible matrices have been extensively reviewed[1,2].

Three-dimensional polymer networks formed by the crosslinking of water-soluble polymers constitute type I-A bioerodible matrices[1] (see *Table 1*). The release of the active ingredient from these matrices is expected to be governed by the degradation of the crosslinks. However, in a number of systems, the erosion of the polymer plays no significant role in the release process and the release is essentially diffusion-controlled[3]. Evidently, the choice of the crosslinking monomer, which would erode over the effective lifetime of the device and bring about the release of the active ingredient in a predetermined manner by influencing the diffusivity, calls for considerable ingenuity.

Surface erosion of the matrix device is also reported to enable the release of the active ingredient at a constant rate[4]. The erosion process could be either mass erosion[4,5] or phase erosion[6]. In the latter case, a glassy hydrogel is transformed into a swollen rubbery hydrogel. The criteria for zero-order release from such systems are such that the penetration of the medium into the matrix must follow case II transport kinetics and the diffusivity of the active ingredient from the swollen hydrogel should be high enough so that the release is penetration-controlled. Although the release of theophylline from glassy poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogels follows anomalous kinetics, the enhanced degree of swelling resulting from a variety of polymer–penetrant interactions has been reported to lead to zero-order release[7–9].

This paper describes the kinetics of release of theophylline from glassy as well as swollen crosslinked hydrogels in aqueous as well as in alkaline media. It is shown that, under appropriate conditions, the release of theophylline in alkaline media follows the coveted zero-order kinetics as a result of the erosion of the crosslinks due to hydrolysis. It is particularly interesting to note that both surface and bulk erosion-controlled zero-order release can be realized.

EXPERIMENTAL

Materials

2-Hydroxyethyl methacrylate (HEMA) was obtained from Fluka and was used as received. Hydroxypropyl methacrylate (HPMA), monochloroacetic acid, methacrylic acid and theophylline were obtained from local suppliers. These chemicals were purified as per standard procedures[10]. t-Butyl hydroperoxide was obtained from Wilson Laboratory (India).

Synthesis of chloroacetyl chloride

Monochloroacetic acid (1 M, 94.5 g) and benzoyl chloride (2 M, 232 ml) were refluxed in an oil bath for 1 h and the chloroacetyl chloride (**1**) formed (b.p. 106°C) was distilled over.

Condensation of chloroacetyl chloride with HEMA

HEMA (0.6 M, 78 g), triethylamine (0.6 M, 61 g) and diethyl ether (500 ml) as solvent were taken in a round-bottomed flask. The reaction mixture was cooled to 0°C in an ice bath and stirred. Then 68 g of 0.6 M chloroacetyl chloride (**1**) was added dropwise to the

* NCL communication no. 4854
† To whom correspondence should be addressed

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Table 1 Classification of bioerodible polymers for controlled release

Type	Nature of polymer	Erosion process	Product of erosion
I-A	Water-soluble polymer insolubilized by crosslinking	Erosion of crosslinks	Water-soluble polymer
I-B	Polymer degradable in backbone	Cleavage of water-soluble polymer chains	Low-molecular-weight molecules
II	Water-insoluble polymer with ionizable groups	Hydrolysis, ionization or protonation of pendant groups	Water-soluble polymer
III	High-molecular-weight water-insoluble macromolecules	Cleavage of labile bonds in polymer backbone	Small water-soluble molecules

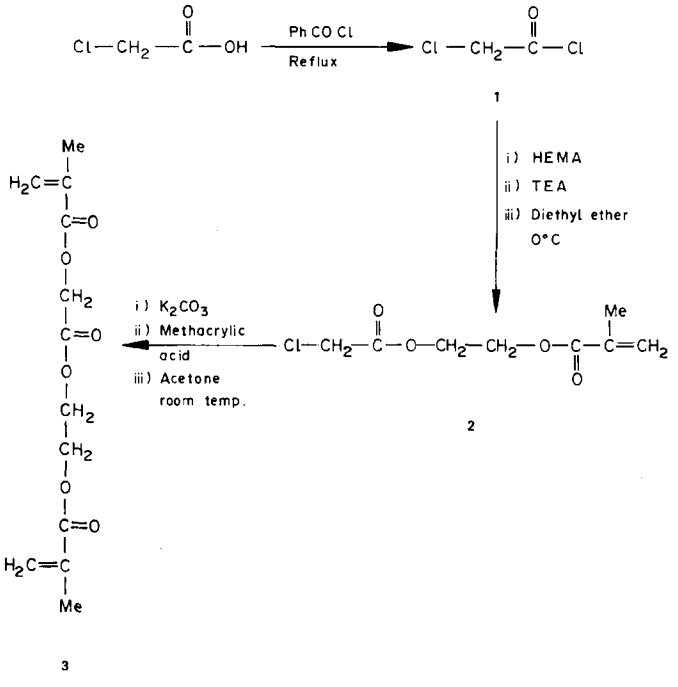

Figure 1 Reaction scheme for the synthesis of 2-hydroxyethyl glycolate dimethacrylate (HEGDMA) (**3**)

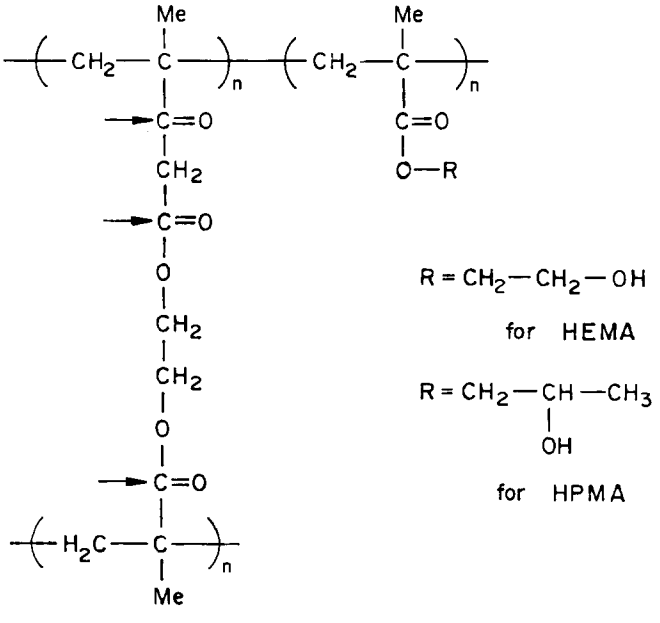

Figure 2 Hydrolysis sites in crosslinked hydrogels

reaction mixture for about 1 h, maintaining the temperature between 0 and 5°C. The reaction mixture was stirred for a further 2 h at 0–10°C and at room temperature overnight. Triethylamine (TEA) salt formed was filtered off and the ethereal solution was washed with cold aqueous sodium bicarbonate solution and water repeatedly to remove unconverted reactants. The ether layer was dried over anhydrous sodium sulphate. Pure product (**2**) was obtained by removing ether under vacuum. The purity and structure of compound **2** were confirmed by thin-layer chromatography (t.l.c.) and spectral analysis.

Molecular formula $C_8H_{11}O_4Cl$; mol. wt. 206.5.

I.r. (nujol): 1630 and 940 cm^{-1} (vinyl C=CH_2); 1715–1730 cm^{-1}, broad band (two ester groups).

^1H n.m.r. ($CDCl_3$): δ = 1.90 ppm (s, 3H); 4.05 ppm (s, 2H); 4.40 ppm (t, 4H); 5.50 ppm (m, 1H); 6.10 ppm (s, 1H).

Synthesis of 2-hydroxyethyl glycolate dimethacrylate (HEGDMA)

First, 110 g of 0.8 M anhydrous potassium carbonate (K_2CO_3) was placed in 500 ml of dry acetone. To this was added 52 g of 0.6 M methacrylic acid in a dropwise manner over 30 min under vigorous stirring at room temperature. The reaction was continued for 2 h to complete the formation of potassium methacrylate. To this stirred suspension of potassium methacrylate in acetone was added 41 g of 0.2 M product **2** in a dropwise manner over 2 h. The reaction was continued at room temperature for 12 h and then at reflux temperature for an additional 4 h. The reaction was followed to completion by the $AgNO_3$ test. The reaction mixture was cooled to room temperature and filtered to remove unreacted potassium methacrylate and potassium carbonate. Acetone was distilled off under vacuum. The crude product (**3**) was dissolved in diethyl ether, and washed repeatedly with water to remove traces of potassium carbonate and potassium methacrylate. The ether layer was dried over anhydrous sodium sulphate. Pure HEGDMA (**3**) crosslinker was obtained as a pale yellow liquid after removing ether under vacuum. The purity and structure of compound **3** were confirmed by t.l.c. and spectral analysis.

Molecular formula $C_{12}H_{16}O_6$; mol. wt. 256.

I.r. (nujol): 1630 and 940 cm^{-1} (vinyl C=CH_2); 1715–1730 cm^{-1}, broad band (three ester groups).

^1H n.m.r. ($CDCl_3$): δ = 1.9 ppm (s, 6H); 4.1 ppm (s, 2H); 4.45 ppm (s, 2H); 5.6 ppm (m, 2H); 6.1 ppm (s, 2H).

The reaction scheme is shown diagrammatically in *Figure 1*, and the structure of the monomer (HEGDMA) is also shown. The hydrolysis sites in crosslinked hydrogels are shown in *Figure 2*.

Bulk polymerization and preparation of discs

Bulk polymerization of HEMA and HPMA with different crosslinker concentrations (see *Table 2*) was carried out in test tubes using 0.8% t-butyl hydroperoxide as an initiator. Polymerization was carried out at 60°C for 6 h and at 75°C for another 20 h. The polymer was obtained in the form of a transparent cylinder by breaking the test tube. The discs were cut from the cylinder and were 1.4 cm diameter and 0.09–0.11 cm thickness. These were postpolymerized at 50°C overnight and stored in the desiccator over fused calcium chloride to prevent moisture absorption during storage. Complete conversion of the monomer was confirmed by following the u.v. spectra of the extracts of the discs in aqueous medium.

For the systems wherein release of theophylline was carried out from glassy hydrogels, theophylline loading (1% by weight of theophylline on the basis of total monomer weight) was achieved by dissolving theophylline in the monomers before polymerization. For the systems wherein the release of theophylline was carried out from swollen hydrogels, theophylline was loaded by soaking the glassy discs in 0.5% aqueous solution of theophylline until the equilibrium swelling was reached. Typical theophylline loading was 1.05 wt% on the basis of total polymer weight.

'In vitro' release studies

Release studies were carried out in glass-distilled water and in aqueous 0.05 N NaOH solution in a jacketed vessel maintained at 37°C. Discs used for release studies were coated on one side by silicone grease so that release could take place from one side alone. The polymer discs were immersed in water and in aqueous 0.05 N NaOH solution under sink conditions with constant stirring. The quantity of theophylline released with time was followed by monitoring the absorbance of the release medium at $\lambda_{max} = 272$ nm, on a Shimadzu 240 u.v. spectrophotometer. The amount of theophylline released at time t (M_t) was determined from the appropriate calibration curves. The total amount of theophylline released from the disc after keeping it in solution for prolonged periods was taken as M_∞. The fraction of theophylline released was expressed as M_t/M_∞.

Penetration velocity measurements

The penetration velocity for each polymer was determined by the weight gain method in water and in aqueous 0.05 N NaOH solution as described by Peppas and coworkers[11,12]. The penetration velocity was calculated from the slope of the initial portion of the penetrant uptake curve from the equation:

$$v = \frac{1}{2\rho A^*}\frac{dW_g}{dt}$$

where v denotes the penetration velocity, dW_g/dt denotes the slope of the weight gain *versus* time curve, ρ denotes the density of water at 37°C, A^* denotes the area of one face of the disc and the factor 2 accounts for the fact that penetration takes place through both faces. The penetration velocities calculated are listed in *Table 3*.

Measurement of diffusion coefficient

Diffusion coefficients of theophylline from swollen crosslinked PHEMA and PHPMA matrices were determined experimentally by the desorption technique reported by Yasuda *et al.*[13]. For diffusivity measurements in water, polymer discs were soaked in aqueous solution containing 0.5% theophylline until equilibrium was reached. For diffusivity measurements in alkaline medium, polymer discs were soaked in theophylline solution (1%) in 0.05 N NaOH solution until appropriate swelling was reached. The desorption experiments were carried out from the disc with both surfaces exposed.

The diffusion coefficient was calculated from the equation:

$$D = \pi L^2/16$$

where $L = d(M_t/M_\infty)/d(\sqrt{t}/\delta)$, M_t denotes the amount of diffusant released at time t, M_∞ denotes the amount of diffusant released at infinite time, δ denotes the swollen thickness of the disc and t denotes the time. The results are listed in *Table 3*.

RESULTS AND DISCUSSION

Release of theophylline in aqueous media

Swollen hydrogels. The kinetics of release of theophylline from the crosslinked swollen PHEMA hydrogels (A and B; see *Table 2*) in water is depicted in *Figures 3* and

Table 2 Release kinetics of theophylline from swollen hydrogels

Polymer[a]	Equilibrium swelling (g H_2O/ g polymer)	Release index, n	Remarks
In aqueous medium			
A	0.4063	0.501 ± 0.0015[b]	Diffusion-controlled release
B	0.3662	0.512 ± 0.0018	Diffusion-controlled release
C	0.1864	–	–
In alkaline medium			
A	0.6521[c]	0.590 ± 0.0007	Bulk erosion occurs, increase in diffusivity not adequate
B	0.6208[c]	0.590 ± 0.0009	Bulk erosion occurs, increase in diffusivity not adequate
C	0.4633[c]	0.974 ± 0.0061	Bulk erosion occurs with adequate increase in diffusivity and hence zero-order kinetics

[a]A, P[(96)HEMA-*x*-(4)HEGDMA] wt% basis;
B, P[(92)HEMA-*x*-(8)HEGDMA] wt% basis;
C, P[(96)HPMA-*x*-(4)HEGDMA] wt% basis
[b]Calculated for 95% confidence limits
[c]Equilibrium swelling up to the release period

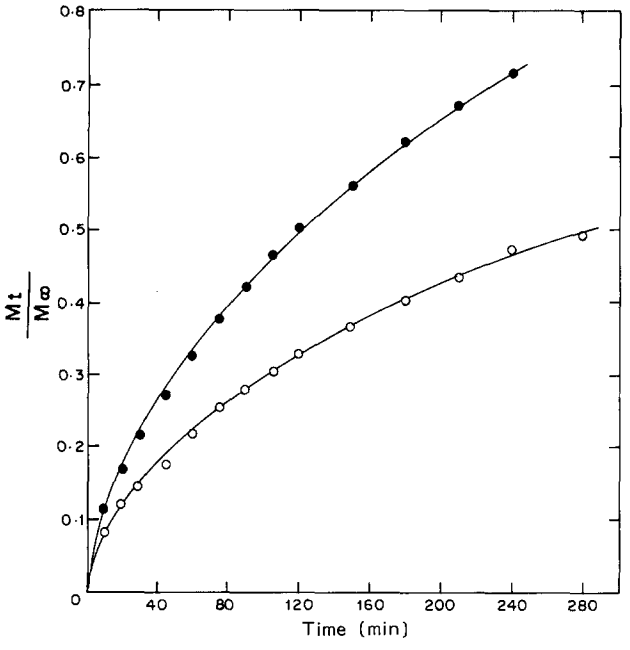

Figure 3 Fractional release of theophylline from swollen polymer A in water (○) and in alkaline medium (●) at 37°C

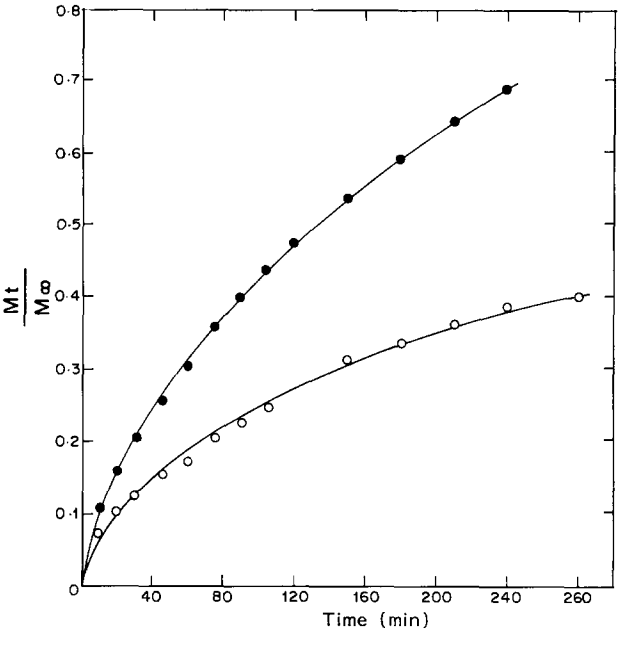

Figure 4 Fractional release of theophylline from swollen polymer B in water (○) and alkaline medium (●) at 37°C

4. It is evident that the fractional release is not linear with respect to time. This is to be expected since the polymer matrices are in the rubbery phase and do not undergo any structural change during the release period. Further, the release rate of theophylline from the matrix containing higher loading of crosslinking monomer is lower. This can be explained on the basis of the lower diffusivity of theophylline from the matrix, as a result of the lower equilibrium degree of swelling (see *Table 2*). Hosaka *et al.*[14] reported the diffusivities of erythromycin in hydrogels based on methyl methacrylate, ethyl methacrylate and *N*-vinylpyrrolidone. The diffusivity from the swollen hydrogel was found to be proportional to the square of the water content of the hydrogel. It thus follows that the release rate of theophylline would decrease with increasing degree of crosslinking.

Glassy hydrogels. The kinetics of release of an active ingredient from a glassy hydrogel depends upon the relative contributions of the velocity of penetration of the surrounding medium (v), and the diffusivity of the active ingredient (D), from the swollen hydrogel. The criteria for swelling-controlled zero-order release have been discussed by us earlier in detail[15]. The release of theophylline from crosslinked glassy PHEMA matrix A is shown in *Figure 5*. The release index ($n = 0.71$) is consistent with the values reported in the literature[11,15]. The kinetics of release of theophylline from the glassy hydrogel matrix follows anomalous kinetics since the diffusivity of theophylline from the swollen hydrogel matrix is low (see *Table 3*). In fact further decrease in the equilibrium degree of swelling results in a diffusion-controlled kinetics for the release of theophylline from the crosslinked glassy PHPMA (polymer C) ($n = 0.55$).

Release of theophylline in alkaline media

Erosion of crosslinks: choice of the crosslinking monomer. In order to understand the kinetics of release of theophylline from the crosslinked glassy as well as swollen hydrogels, an understanding of the mechanism of hydrolysis is essential. The rate of hydrolysis depends upon the nature of the functional group undergoing hydrolysis, steric hindrance, hydrophobicity of the polymer and the medium in which hydrolysis takes place. Indeed, if the kinetics of release is to be influenced, it is imperative that the erosion of the crosslinks takes place over the same time-scale as the release. Based on the study of the release of active ingredient from the polymeric hydrogels crosslinked by methylenebisacrylamide, Heller and Baker[3] concluded that these hydrogels are not suitable candidates for the release of active ingredients by matrix erosion. When the crosslink density is low enough for erosion to occur, the active ingredient is released at a very high rate as a result of high diffusion coefficient. In contrast, in the case of highly crosslinked polymers, erosion does not take place over the lifetime

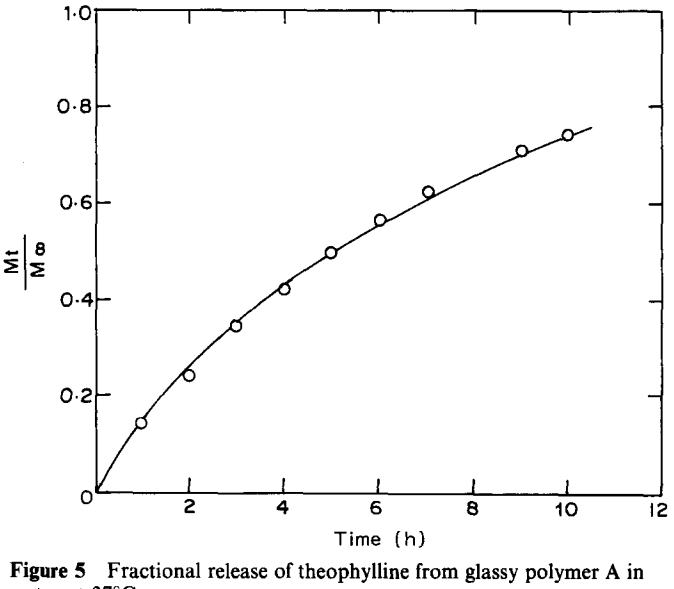

Figure 5 Fractional release of theophylline from glassy polymer A in water at 37°C

Table 3 Release kinetics of theophylline from glassy hydrogels

Polymer[a]	Equilibrium swelling (g H_2O/ g polymer)	Penetration velocity ($\times 10^{-6}$ cm s^{-1})	Theophylline diffusivity ($\times 10^{-7}$ cm^2 s^{-1})	Release index, n	Remarks
In aqueous medium					
A	0.4063	2.42	0.79	0.71 ± 0.028[b]	Anomalous release kinetics
B	0.3662	2.13	0.53	0.71 ± 0.012	Anomalous release kinetics
C	0.2047	0.53	0.08	0.55 ± 0.015	Diffusion-controlled release
In alkaline medium					
A	0.8172[c]	3.94	3.83	0.98 ± 0.002	Swelling-controlled zero-order release due to surface erosion
B	0.8154[c]	4.19	4.04	0.98 ± 0.003	Swelling-controlled zero-order release due to surface erosion
C	0.4816[c]	–	1.02	0.87 ± 0.0006	Anomalous release kinetics

[a]See *Table 2*
[b]Calculated for 95% confidence limits
[c]Equilibrium swelling up to the release period

of the device. In both cases, therefore, the release of the active ingredient follows the conventional Higuchi relationship and the erosion of the crosslinks plays no significant role in the release process.

In the past, we have demonstrated that the kinetics of release of the active ingredient from glassy as well as swollen hydrogel matrices can be influenced by the appropriate choice of comonomers that undergo hydrolysis in either acidic or alkaline media[16,17]. The mechanistic aspects of release have been explained quantitatively by Shah *et al.*[18] on the basis of the concept of time-dependent diffusivity reported by Lee[19] to model zero-order release from swelling-controlled systems. During hydrolysis, a hydrophobic monomer is converted to a hydrophilic one, thereby enhancing the equilibrium degree of swelling of the polymer and hence the diffusivity of the active ingredient. The ideal crosslinking monomer for the bioerodible system I-A has to satisfy the following criteria: (a) it should be a hydrophobic divinyl monomer; (b) it should undergo hydrolysis over time-scales comparable to the release period; (c) the hydrolysis should lead to hydrophilic sites which would enhance the overall degree of swelling of the polymer matrix; and (d) no low-molecular-weight solute should be released during hydrolysis. Diethylene glycol dimethacrylate (DEGDMA) is widely used as a crosslinking monomer for acrylates and methacrylates. However, the monomer is highly resistant to hydrolysis. To overcome the problem, a new crosslinking monomer, which has a similar structure to that of DEGDMA but is more susceptible to hydrolysis, has been synthesized. The crosslinking monomer used in this work has three possible sites (*Figure 2*) where hydrolysis could take place. For steric reasons, the ester link in the centre of the molecule is most susceptible to hydrolysis. It may be noted that the crosslinking monomer HEGDMA hydrolyses to generate a hydroxyl group and a carboxyl group, which is converted to its sodium salt, and no low-molecular-weight solute is released. The degree of swelling of the polymer is thus significantly enhanced as the hydrolysis proceeds.

Glassy hydrogels. In a prior communication[15] we have shown that the release of benzoic acid from glassy PHEMA hydrogels follows zero-order kinetics. The release of theophylline, however, follows anomalous kinetics since the diffusivity of theophylline from the swollen matrix is low (1.2×10^{-7} cm^2 s^{-1}) compared to that of benzoic acid (3.45×10^{-7} cm^2 s^{-1}). Shah *et al.*[18] reported the release of *p*-nitrobenzoic acid from a glassy P(HEMA–PNP) matrix containing 4.9% *p*-nitrobenzoic acid (PNP = *p*-nitrophenol). Although there is no significant increase in the degree of swelling as the comonomer content of *p*-nitrobenzoic acid is low, the rate of hydrolysis of the ester link is enhanced by the NO_2 group in the *para* position. Since the diffusivity of *p*-nitrobenzoic acid through the swollen matrix (2.67×10^{-7} cm^2 s^{-1}) is sufficiently high, the release followed zero-order kinetics.

It therefore follows that if the hydrolysis of the crosslinking monomer from the glassy hydrogel were to be rapid in comparison with the rate of penetration of alkaline medium into the matrix, and the equilibrium degree of swelling of the matrix could be enhanced so that the diffusion of theophylline could be rapid, zero-order release of theophylline from the glassy PHEMA hydrogel could be achieved. A wide range of polymer–penetrant interactions have been reported in the literature which lead to increased degree of swelling of hydrogels. These include formation of charge-transfer complexes between the functional groups of the polymers and the release medium[7], ionization of the polymer[8] and polymer–solvent interactions[9]. In the present case, the hydrolysis of the hydrophobic crosslinking monomer HEGDMA leads to (a) decrease in the crosslink density, (b) generation of hydroxyl and carboxyl groups which are hydrophilic and (c) ionization of the carboxyl group in alkaline media. Each of these factors would lead to enhanced swelling and enhanced diffusivity of theophylline.

The release of theophylline from the crosslinked glassy PHEMA hydrogels A and B is shown in *Figure 6*. The release follows zero-order kinetics as anticipated. The penetration velocity of the medium into the glassy matrix determined experimentally ($v = 3.94 \times 10^{-6}$ cm s^{-1}) compares fairly well with the values computed from the release data ($v = 3.17 \times 10^{-6}$ cm s^{-1}). Similar results were reported by Shah *et al.* for the release of *p*-nitrobenzoic acid[20]. This further confirms that the release of theophylline from the glassy hydrogel is indeed controlled by the case II transport of the penetrant. In our prior communication[15] it was shown that the

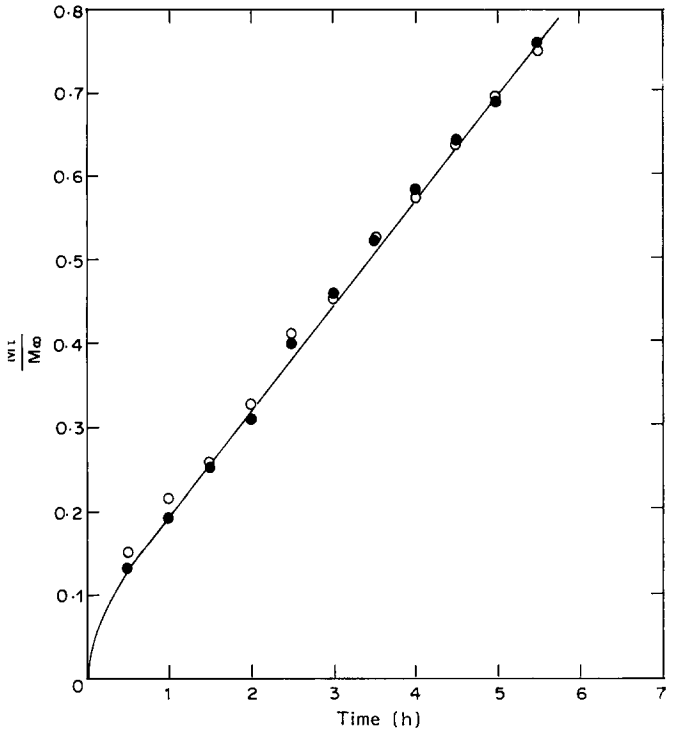

Figure 6 Fractional release of theophylline from glassy polymer A (●) and polymer B (○) in alkaline medium at 37°C

dimensionless parameter $\sqrt{Dt}/vt$ correlates well with the release index. It was shown that, for values of the parameter which were greater than 1.3, swelling-controlled zero-order release would be expected. The value of the parameter in the present case turns out to be 1.533. This further proves that the release in alkaline medium is essentially penetration-controlled. It is interesting to note that the swelling behaviour of two polymers containing 4% and 8% crosslinking monomer is identical. As a result, the release profiles for the two are also superimposed (*Figure 6*). The kinetics of release of theophylline from crosslinked glassy PHPMA hydrogel-based matrix C is shown in *Figure 7*. It is clear that the release in this case follows anomalous kinetics ($n = 0.87$). Although the release of theophylline in this particular case is accompanied by the erosion of the crosslinks, the equilibrium degree of swelling in this case is much lower (0.48 g water/g polymer). As a result, the diffusivity of theophylline is not adequate to ensure zero-order release. The anomalous kinetics observed is thus not unexpected.

Swollen hydrogels. The release profiles of the theophylline from the swollen crosslinked PHEMA matrices in alkaline media are shown in *Figures 3* and *4*. In both the cases, the release index is close to the Higuchi relationship ($n = 0.6$). The release rate in both cases is greater than that observed during release in aqueous media. During the release of theophylline in alkaline medium, the alkali penetrates the matrix and brings about erosion of the crosslinks by hydrolysis. As a result of the decrease in the degree of crosslinking, the generation of more hydrophilic sites and the ionization of the carboxyl group generated, there is an increase in the swelling of the polymer as the release proceeds. However, this increase in swelling is not reflected in a corresponding increase in the release index of theophylline. This is in contrast with the observations made by Shah *et al.*[18], who reported an increase in the release index of *p*-nitrobenzoic acid from swollen PHEMA-based hydrogels ($n \rightarrow 1$) as a result of increase in the swelling of the polymer matrices. This can be explained on the basis of the enhancement in the diffusivity brought about by increased swelling in the two cases and the criteria for zero-order release proposed by Lee[19]. In the present case the equilibrium degree of swelling of the polymer matrices during the course of release is enhanced from 40% to 60%. There is a corresponding increase in the diffusivity of theophylline such that $D_i/D_\infty = 0.33$. On the other hand, the polymers investigated by Shah *et al.*[18] were highly hydrophobic, and during the course of release the degree of swelling increased from 13% to 40%. As a result, there was a significant increase in the diffusivity of *p*-nitrobenzoic acid so that ($D_i/D_\infty = 0.025$). The latter is in better agreement with the criterion proposed by Lee for zero-order release, viz. $D_i/D_\infty \rightarrow 0$. It therefore appears that although the PHEMA matrices investigated in this work undergo a bulk erosion process during the time-span of release, the enhancement in the diffusivity is not large enough to lead to zero-order kinetics. Thus, it is important not only that the erosion of the polymer structure takes place during the time-span of release, but also that the corresponding increase in the swelling of the polymer should result in substantial increase in the diffusivity of the active ingredient. It therefore appears that a polymer matrix having a low degree of swelling at the beginning of the experiment would be capable of releasing the active ingredient at a constant rate.

To test this hypothesis, poly(hydroxypropyl methacrylate) (PHPMA) was chosen as the polymer matrix. The kinetics of release of the theophylline from the swollen crosslinked PHPMA matrix C is shown in *Figure 8*. Indeed, the release of theophylline from this matrix follows zero-order kinetics ($n = 0.94$), barring the initial

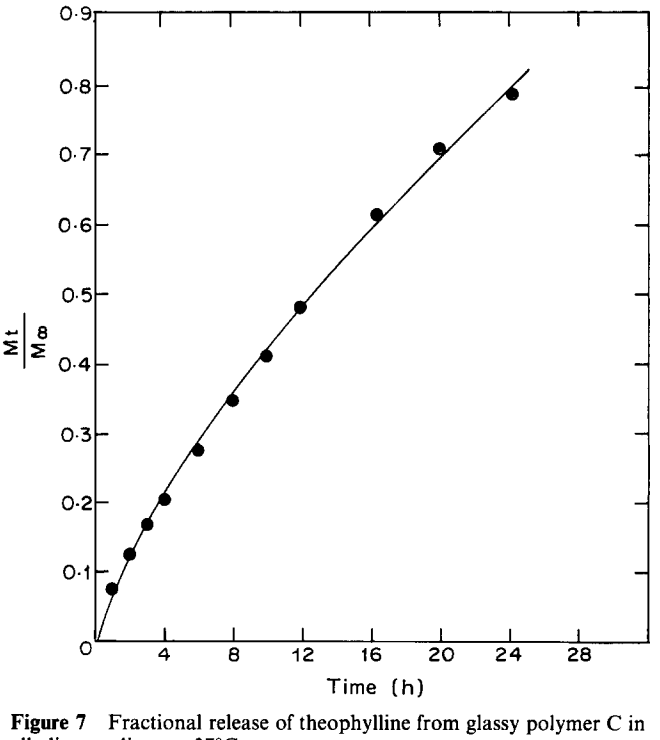

Figure 7 Fractional release of theophylline from glassy polymer C in alkaline medium at 37°C

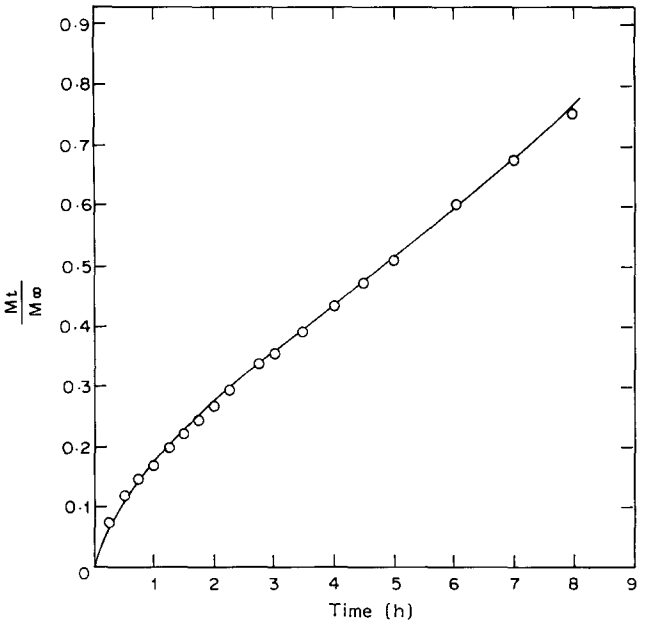

Figure 8 Fractional release of theophylline from swollen polymer C in alkaline medium at 37°C

burst effect. This is because the polymer has very low initial degree of swelling at the start of the experiment (0.18 g water/g polymer) which increases over the release period to 0.46 g water/g polymer. The corresponding increase in the diffusivity of theophylline is such that $D_i/D_\infty = 0.07$ whereas the corresponding value in the case of the PHEMA matrix is 0.33. Zero-order release of theophylline thus results owing to the increase in the diffusivity of the theophylline from the matrix over the release period and is consistent with the criterion proposed by Lee[19].

CONCLUSIONS

This paper highlights the kinetics of release of theophylline from crosslinked swollen and glassy hydrogel matrices in aqueous as well as in alkaline media. It has been shown that, in alkaline media, a wide range of release profiles are manifested as a result of the erosion of the crosslinks. Zero-order release of theophylline from the glassy PHEMA matrix in alkaline medium results from case II transport-controlled relaxation of the medium and the enhanced swelling brought about by the erosion of the crosslinks in the surface layer. On the other hand, zero-order release of theophylline from swollen PHPMA hydrogels is a result of significant enhancement in the diffusivity of theophylline due to the erosion of the crosslinks in the bulk of the polymer. This paper thus shows that it is possible to develop erosion-controlled matrix systems for the zero-order release of the active ingredient by the appropriate choice of the crosslinking monomer. Although the matrices used in this work are not water-soluble and can therefore not be strictly classified as type I-A bioerodible systems, it should be possible to develop such matrices by copolymerizing the water-soluble monomers which constitute type I-A systems with the novel crosslinking monomer reported in this work.

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