A Mechanistic Interpretation of the Zero Order Release from Pendent Chain-Linked Glassy and Swollen Hydrogels*

S. S. SHAH, M. G. KULKARNI, and R. A. MASHELKAR,† *Polymer Science and Engineering Group, Chemical Engineering Division, National Chemical Laboratory, Pune 411008, India*

Synopsis

Zero order release of active ingredients, physically dispersed in the glassy hydrogels has been ascribed in the past to the case II transport of the penetrant medium into the glassy matrix (phase erosion). Surface erosion of the polymer by dissolution has also been shown to result in the zero order release of the dispersed/dissolved active ingredient. This communication reports the zero order release of the pendent chain-linked *p*-nitro benzoic acid and 2,4-dinitro benzoic acid from glassy as well as swollen hydrogel matrices. The results have been elucidated on the basis of increase in the diffusivity of the active ingredient released by hydrolysis and the concomitant increase in the degree of swelling of the polymer matrix. This is the first reported finding of zero order release of an active ingredient from the matrix device as a result of bulk erosion.

INTRODUCTION

Development of controlled-release delivery systems, which would release the active ingredient at a constant rate, continues to attract the attention of a large number of researchers. It is well established that the release of an active ingredient from a rubbery matrix follows the Higuchi relationship.[1] A number of approaches have been explored in the past to develop matrix systems which would deliver the active ingredient at a constant rate. These include: (a) the use of the rate controlling barriers,[2-4] (b) modification of the geometry of the device,[5] (c) establishing a nonuniform concentration distribution profile of the active ingredient across the matrix,[6] (d) development of matrices which undergo controlled rupture during release,[7] and (e) swelling controlled delivery systems based on glassy hydrogels.[8] It has been suggested that the release of the active ingredient from the polymer would follow zero order kinetics as a result of time/position-dependent diffusivities of the active ingredient.[9] Although the form of the functional dependence of diffusivity on time has been debated[10] and the exact structural attributes of the polymer which would result in the time/position-dependent diffusivity are not fully established, the need to develop polymer matrices which would undergo chemical/physical change with time has been emphasized.[11] Preliminary experimental results from our laboratory indicated for the first time that such possibilities may indeed exist.[12,13]

* NCL Commun. No. 4719.

† To whom correspondence should be addressed.

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Extensive studies have been reported in the literature on the release kinetics from the polymer matrices in which the active ingredient is chemically linked to the polymer backbone through the pendent chain.[14-20] Zero-order release of active ingredient has been, however, rarely reported.[21] Besides, very few systematic investigations seem to have been undertaken to elucidate the mechanistic aspects of release.[22]

In an earlier communication, we reported the release of a series of substituted benzoic acids from glassy hydrogels.[23] It was reported that depending on the relative rates of the diffusional transport, the hydrolysis reaction, and the swelling kinetics, a wide range of release characteristics can be realized. It was also reported that the release of *p*-nitro benzoic acid follows zero kinetics for 14 h during which almost 95% of the active ingredient was released. It is obvious that for the long-term delivery of the drugs from implants, the release should continue over at least 6–8 months.

In this communication, we report the release of *p*-nitro benzoic acid and 2,4 dinitro benzoic acid from a series of copolymers in which the active ingredient is chemically linked to the polymer matrix through the pendent chain. It has been shown that the active ingredient is released at a constant rate from both glassy and swollen hydrogels. The release kinetics is shown to be governed by the structural changes accompanying the release, rather than the case II transport of the penetrating medium. An understanding of the mechanism of release would lead to the development of constant-rate delivery systems for the release of the active ingredient over extended time periods.

EXPERIMENTAL

Materials

2-Hydroxyethyl methacrylate (HEMA) was obtained from M/S Fluka (Switzerland) and was purified as described[24] to remove EGDMA and other impurities. *tert*-Butyl hydroperoxide initiator was obtained from the Wilson Laboratory. *p*-Nitro benzoic acid, 2,4 dinitro toluene, thionyl chloride, and triethyl amine were obtained from Loba Chemicals (India). 2,4 Dinitro benzoic acid was synthesized in the laboratory by the oxidation of 2,4-dinitro toluene.[25] These chemicals were purified as per standard procedures.[24]

Synthesis of Monomeric HEMA Derivatives

The compounds 2-methacryloyl ethyl *p*-nitro benzoate (PNP) and 2-methacryloyl ethyl 2,4 dinitro benzoate (DNP) were prepared by condensing HEMA (0.1 mol) with the respective acid chlorides (0.1 mol) and triethyl amine (0.12 mol) in 100 mL dry benzene. Details of synthesis, purification, and spectral analysis of these derivatives have been described earlier.[23]

Bulk Copolymerization and Preparation of Disks

Bulk copolymerizations for the synthesis of poly(HEMA–PNP) and poly(HEMA–DNP) were carried out in test tubes using 0.8% *tert*-butyl hydroperoxide as initiator. The polymerization was carried out at 60°C for 6 h and then at 80°C for another 12 h. The polymer was obtained in the form of

a cylinder by breaking the test tube. The disks having thickness 0.1–0.13 cm were obtained by cutting the cylinder on a lathe. The disks were post-polymerized at 60°C for 6 h and then stored in the dessicator. Complete conversion of the monomer was confirmed by following UV spectra of the aqueous extracts of the disks.

In Vitro Release Studies

Release experiments were carried out in a jacketed vessel maintained at 37°C. The polymer disk was immersed in 0.01 N NaOH solution with constant stirring. The quantity of *p*-nitro benzoic acid and 2,4 dinitro benzoic acid released was followed by monitoring the absorbance of the release medium at λ_{max} = 274 nm and λ_{max} = 250 nm, respectively on a Shimadzu 240 UV spectrophotometer. The amount of the active ingredient released at time t, (M_t), was determined from the appropriate calibration curves. The total amount of active ingredient incorporated in the disk was taken as M_∞. The fraction of the active ingredient released was expressed as (M_t/M_∞).

Penetration Velocity Measurements

The penetration velocity for each copolymer composition was determined by the weight gain method as described by Peppas and Franson.[8,26] The penetration velocity was calculated from the slope of the initial portion of the penetrant uptake curve from the equation

$$v = (dWg/dt) \times (1/\rho) \times (1/2A^*) \tag{1}$$

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

Measurement of Diffusion Coefficient

Diffusion coefficient of *p*-nitro benzoic acid from poly(HEMA-PNP) copolymers was determined experimentally by the desorption technique reported by Yasuda et al.[27] For diffusivity measurements the copolymers were prepared in the presence of the predetermined quantity of water which ensured that the resulting disks had reached equilibrium swelling. *p*-Nitro benzoic acid (1.0% by weight) was also added during polymerization. After polymerization, slabs of 0.1–0.12 cm thicknesses were cut from the cylinder. Desorption runs were carried out in deionized water to avoid the errors due to the hydrolysis of chemically linked *p*-nitro benzoic acid during the course of measurement.

Diffusion coefficient was calculated from the equation

$$D = (\pi/16)L^2 \tag{2}$$

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

TABLE I
Release Data for the Systems Investigated

Matrix designation	Copolymer composition (g/g)	Equilibrium water uptake (g water/g polymer)	Penetration velocity (cm/s × 10^7)		Diffusion coefficient ($cm^2/s \times 10^8$)	$\frac{D_i}{D_\infty}$ [b]	Release index (n)	
			By weight gain method	From release experiment			For glassy copolymers	For swollen copolymers
				Poly(HEMA-PNP)				
I-A	10 : 1	0.280	20.00	21.80	26.70	0.908	1.08	0.80
I-B	10 : 2	0.211	12.80	[a]	3.52	0.119	0.80	0.88
I-C	10 : 3	0.180	8.80	2.58	2.31	0.078	0.94	1.02
I-D	10 : 5	0.132	6.62	1.48	0.71	0.024	1.03	1.00
I-E	10 : 10	0.053	2.70	0.18	—	—	1.00	1.06
				Poly(HEMA-DNP)				
II-A	10 : 1	0.298	22.10	[a]	—	—	0.55	0.70
II-B	10 : 3	0.192	11.60	3.12	—	—	0.86	0.92
II-C	10 : 5	0.139	7.90	1.49	—	—	1.06	1.04

[a] Velocity of penetration could not be calculated since the zero-order release is not observed.
[b] $D_\infty = 2.94 \times 10^{-7}$ cm^2/s.

the thickness of the disk, and t denotes the time. It was confirmed that there was no additional swelling of the disk during the experiment. The results are listed in Table I.

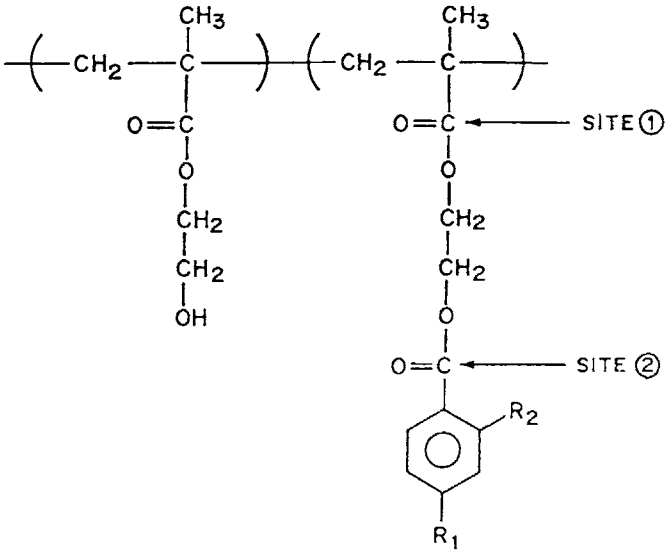
RESULTS AND DISCUSSION

Mechanism of Hydrolysis

In order to explain the release kinetics of pendent chain-linked active ingredient, an understanding of the mechanism of hydrolysis is essential. Rate of hydrolysis of pendent chain-linked active ingredient from the copolymers depends upon the nature of the functional group undergoing hydrolysis, steric hindrance, and the hydrophobicity of the polymer.

In the alkaline medium, hydrolysis of ester linkage takes place by the attack of hydroxyl group (OH^-) on the electron-deficient carbonyl carbon. For the copolymer systems reported in this work there are two hydrolyzable sites, 1 close to the polymer backbone and the other relegated to the pendent chain end by the spacer group (Fig. 1). For steric reasons the hydrolysis of the latter is more facile than that of the former.

In a prior communication[23] we have reported release kinetics of a series of substituted benzoic acids (SBA) from poly(HEMA–HEMASBA) in acidic as well as in alkaline medium. It was shown that depending upon the nature of the substituents on benzoic acid, the release kinetics could be either swelling controlled, diffusion controlled, or hydrolysis controlled.



FOR (PNP) = $R_1 = NO_2$, $R_2 = H$

(DNP) = $R_1 = R_2 = NO_2$

Fig. 1. The copolymer structure and sites of hydrolysis.

The release of *p*-nitro benzoic acid from poly(HEMA–PNP) essentially follows swelling controlled zero order kinetics. This is because the introduction of a nitro group in *p*-position to the —COOH— group significantly enhances the rate of hydrolysis of the ester link. Although introduction of nitro groups in 2- and 4- position as in the case of poly(HEMA–DNP) further enhances the rate of hydrolysis, the release of 2,4-DNBA is found to be diffusion controlled ($n = 0.5$, for matrix II-A) as it is a bulkier molecule. The substitution of $-OCH_3$ or $-NH_2$ groups in *p*-position suppresses the rate of hydrolysis. As a result, the hydrolysis becomes the rate controlling step.

Penetration Velocity Measurements

The penetration velocities for poly(HEMA–PNP) and poly(HEMA–DNP) copolymers were calculated from the initial weight gain curve.[8,26] The equilibrium water content and penetration velocities are listed in Table I.

For the copolymers poly(HEMA–PNP) and poly(HEMA–DNP), the equilibrium water content and penetration velocity decrease as the hydrophobic monomer content of the copolymer increases. This trend is in good agreement with that observed in the past.[8,28] The penetration velocities calculated from the release data[29] for the copolymers which exhibit zero order release are listed in Table I.

Hopfenberg and Hsu[29] have shown that when the release of an active ingredient from a glassy hydrogel follows swelling controlled zero order release, the values of the penetration velocity calculated from release data are in good agreement with those measured experimentally. In our earlier communication we have shown that such is indeed the case for the release of *p*-nitro benzoic acid from the glassy poly(HEMA–PNP) hydrogel I-A.[23] In the present case, however, the penetration velocities calculated from release data differ significantly from with those arrived at from the weight gain experiments even when the release of the active ingredient follows zero-order kinetics. The apparent discrepancy between the two values suggests that although the release follows zero order kinetics it may not be swelling controlled as in the case of the matrix I-A. This aspect is later discussed in detail.

Diffusion Coefficient Measurements

Diffusion coefficients of *p*-nitro benzoic acid from poly(HEMA–PNP) of varying copolymer compositions were evaluated by the method described earlier.[27] The values are listed in Table I.

A logarithmic plot of diffusivity of *p*-nitro benzoic acid and equilibrium water content is shown in Figure 2. The diffusivity of *p*-nitro benzoic acid is given by the equation

$$D = 6.2 \times 10^{-8} W^{3.2} \tag{3}$$

Hosaka et al.[30] reported the diffusivity of erythromycin in hydrogels based on methyl methacrylate, ethyl methacrylate, and *N*-vinyl pyrrolidone. The diffusivity of erythromycin from the swollen hydrogel was found to be proportional to the square of the water content of the hydrogel and was given by the equation

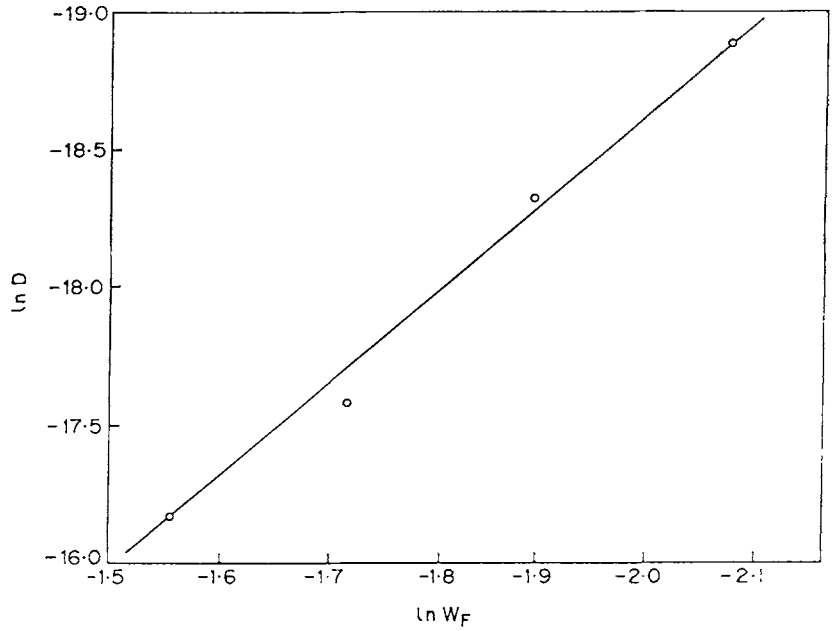


Fig. 2. Diffusivity of *p*-nitro benzoic acid from swollen poly(HEMA-PNP) hydrogel matrices.

$$D = 3.03 \times 10^{-10} W^{2.03} \tag{4}$$

where D denotes the diffusivity and W denotes the weight fraction of water at equilibrium. Similarly the diffusivity of benzoic acid varies with 1.56*th* power of equilibrium water content of the hydrogel.[31] The diffusivity of the active ingredient in the polymer is governed not only by its molecular size and shape, but also the polymer structure and its degree of swelling as well. Since in the present case both the active ingredient and the equilibrium swelling of the polymer matrix are changing simultaneously, it is not possible to compare either the preexponential factors and/or the exponents of release in eqs. (3) and (4).

It can be shown, however, that both expressions stem from the same mechanistic considerations. The diffusive transport in the polymer diluent system is governed by the free volume which in turn is governed by the structure of the polymer as well as the degree of swelling.[32] Kulkarni and Mashelkar[33] have shown that the diffusivity of a solute in the polymer diluent system defined by the volume fraction of the diluent $\varnothing_2$ is given by

$$D_{\varnothing_2} = RTA_d \exp \frac{-B_d}{f_1(\varnothing_2, T)} \tag{5}$$

where $D_{\varnothing_2}$ denotes the diffusivity of the solute in the polymer diluent system comprising volume fraction of the diluent $\varnothing_2$, R denotes the gas constant, $f_1(\varnothing_2, T)$ denotes the free volume of the polymer diluent system containing volume fraction of the diluent $\varnothing_2$, and A_d and B_d denote the constants in the free volume theory related to the size and shape of the diffusant. It can be seen

that the eqs. (3) and (4) can be brought to the same form as eq. (5) by taking the logarithms of both sides, expanding the term $\ln(W)$ and ignoring higher terms in W. The empirical terms in eqs. (3) and (4) can then be correlated with the constants in the free volume equation which bear definite physical significance.

Kinetics of Release

Poly(HEMA–PNP): The kinetics of release of a chemically linked active ingredient from the glassy hydrogel depends on the relative contributions of the penetration velocity (v), diffusion coefficient of the active ingredient through the swollen matrix (D_∞), and the rate of hydrolysis of the pendent chain (R_h). The rate-controlling step could be identified by evaluating the three dimensionless numbers viz. thiele modulus (θ), equilibrium swelling interface number (SW_e) and the reaction penetration number (PR_e). Figure 3 shows the release profiles of p-nitro benzoic acid from a series of glassy poly(HEMA–PNP) copolymer matrices. The relevant physicochemical data are summarized in Table I. It can be seen that the release index of p-nitro benzoic acid tends to unity as the PNP content of the copolymer increases. Hopfenberg and Hsu[29] showed that when the release of an active ingredient is swelling controlled, the values of the penetration velocity of the surrounding medium calculated from the observed release rate agree well with the experimentally determined ones. It can be seen from the Table I that in the case of the matrix I-A, the penetration velocity estimated agrees very well with the value experimentally observed. It can, therefore, be concluded that the release of p-nitro benzoic acid in this case

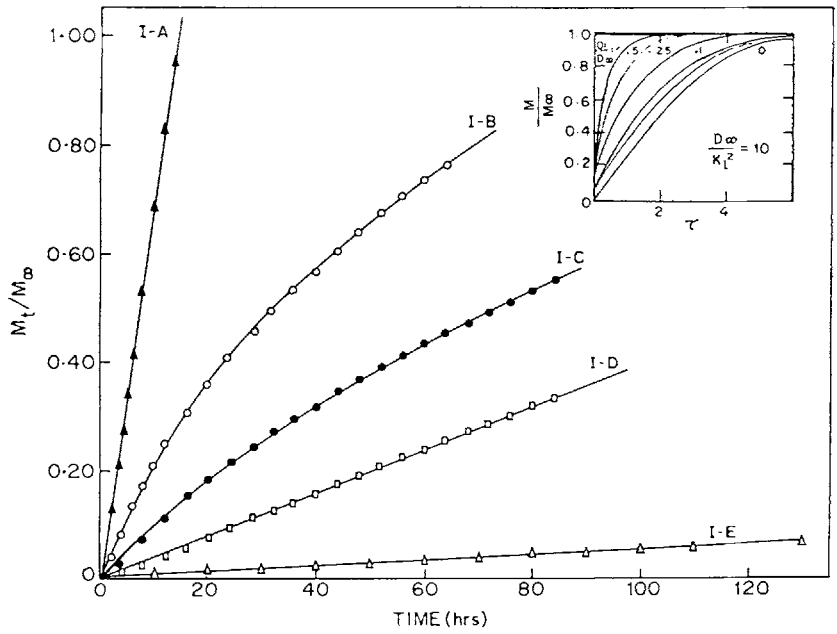


Fig. 3. Kinetics of release of p-nitro benzoic acid from glassy poly(HEMA–PNP) hydrogel matrices (inset model prediction Ref. 35).

is controlled by the penetration velocity of the medium. In the case of the polymer matrices I-C to I-E, however, although the zero order release is observed, the penetration velocity values estimated from the observed release rates are substantially lower than those experimentally observed. Moreover, the ratio (v_{obs}/v_{exp}) decreases with increasing PNP content of the copolymers. This implies that the release of *p*-nitro benzoic acid continues at a constant rate even after the penetrating fronts have met. Clearly, the release of *p*-nitro benzoic acid in these cases is not controlled by the velocity of the penetrating front.

In order to verify if this was indeed so, the poly(HEMA–PNP) matrices were saturated with water. During this period no hydrolysis, and hence, no release of *p*-nitro benzoic acid is anticipated. The swollen hydrogel disks were then immersed in 0.01 N NaOH solution and the release of *p*-nitro benzoic acid was followed. The results shown in Figure 4 indicate that the release of *p*-nitro benzoic acid follows zero order kinetics even from the swollen hydrogel matrices. This leads to the conclusion that in the case of the polymer matrices I-C to I-E, the differences in the penetration velocities experimentally determined and those calculated from the observed release rates are not due to experimental error in the estimation of either of them. While the polymer matrix is in the glassy state when the penetration velocities are measured by the weight gain method, it is not in the glassy state during the entire period over which the release is monitored, although release continues at a constant rate for reasons unknown until now.

To elucidate the mechanism of zero-order release from the swollen hydrogel matrices, we examine the Higuchi equation. The release of an active ingredient from a rubbery polymer matrix of constant area of cross section is given by

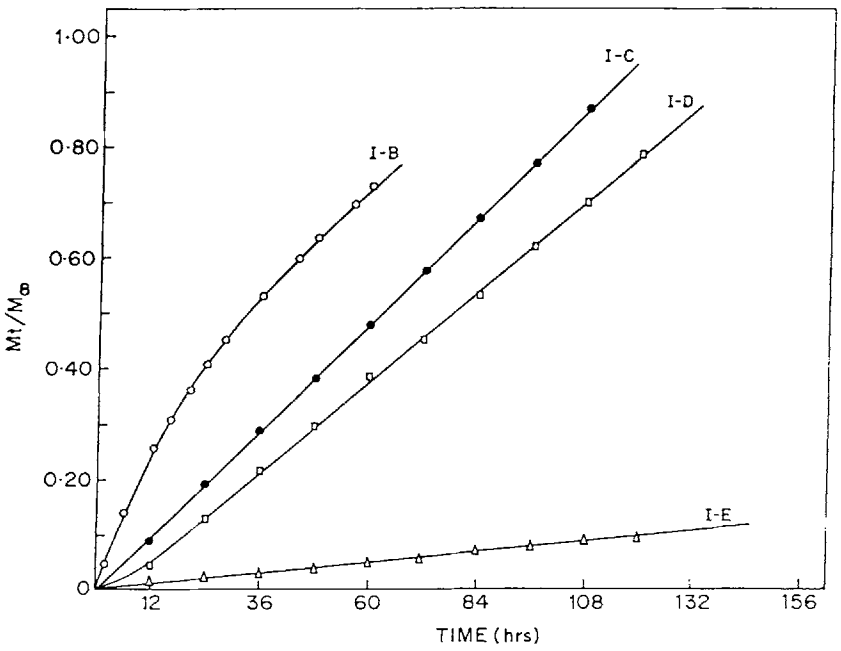


Fig. 4. Kinetics of release of *p*-nitro benzoic acid from swollen poly(HEMA–PNP) hydrogel matrices.

$$Q = [(2A - C_p) \cdot C_p \cdot D_m t]^{1/2} \tag{6}$$

where Q denotes the amount of active ingredient released in time t, A denotes the initial loading, C_p denotes the solubility of the active ingredient and D_m denotes the diffusivity of the active ingredient from rubbery matrix. For an active ingredient physically dispersed in the rubbery matrix A, C_p and D_m are constant and the release rate decreases with time since the diffusion time increases. Here it may be noted that the derivation of eq. (6) was based on the pseudo-steady-state analysis. As a result, the predictions of release rates are in error in the limit $A \rightarrow C_p$ by up to 11.3%. Paul and McSpadden[34] subsequently offered an exact analysis for the release of an active ingredient physically dispersed/dissolved in the polymer matrix. When the release kinetics is matrix controlled

$$M_t = \frac{2C_p}{\text{erf}(\eta^*)} \sqrt{\frac{D_m t}{\pi}} \tag{7}$$

where

$$\eta^* = \xi / 2\sqrt{D_m t} \tag{8}$$

and

$$\sqrt{\pi}\,\eta^* \exp(\eta^*)^2 \text{erf}(\eta^*) = \frac{C_p}{A - C_p} \tag{9}$$

ξ denotes the thickness of the region within which the concentration of the active ingredient decreases from A on the surface of the undissolved solute core within the matrix to zero at the surface of the matrix. When the active ingredient is dissolved in the matrix as in the present case, i.e., $A \rightarrow C_p$

$$M_t = 2C_p(D_m t/\pi)^{1/2} \tag{10}$$

In the case of the active ingredient dispersed in the matrix i.e., $A \gg C_p$

$$M_t = [2D_m C_p(A - C_p)t]^{1/2} \tag{11}$$

This is same as eq. (6) except for the coefficient 0.5 for C_p which is of little significance in the limit $A \gg C_p$.

It is to be noted that for an active ingredient physically dispersed/dissolved in the matrix, either approach predicts that the release rate would be linear with respect to the square root of time since A, C_p and D_m are constant. Prior attempts to achieve zero order release from the matrix devices have therefore been focused on designing systems wherein the area across which the release takes place increases with time in a predetermined manner,[5] or the concentration profile of the active ingredient is nonuniform.[6] In the present case neither of these parameters could vary with the time of release. The only parameter which could possibly change with time in D_m. This possibility is explored further.

p-Nitro benzoic acid is released from the poly(HEMA-PNP) matrix by the hydrolysis of PNP to HEMA. This converts a hydrophobic component of the polymer to a hydrophilic one. As a result, equilibrium swelling of the matrix and hence the diffusivity of *p*-nitro benzoic acid through the matrix increases as the release proceeds with time. As a result the values of the release index tend to unity. This has already been shown to be the case for the release of theophylline through the swollen poly(HEMA-GMA) matrices into $0.05N$ H_2SO_4.[31]

The possibility of achieving zero order release of an active ingredient from the polymer matrix which would undergo chemical/physical change with time has been recently discussed.[9] It was proposed that these structural changes would lead to an increase in the diffusivity of the active ingredient with time. Although the form of the functional dependence of diffusivity with time has been debated,[10] it was argued that the concept did merit further investigation.[11] Lee[35] proposed the concept of time-dependent diffusivity, albeit in a slightly different context. The moving boundary problem describing the penetration of the medium into a glassy matrix accompanied by the diffusion of the active ingredient through the swollen polymer matrix was analyzed in terms of the time dependent diffusivity of the active ingredient. The dependence of diffusivity on time was expressed in the form

$$D(t) = D_i + (D_\infty - D_i)[1 - \exp(-Kt)] \tag{12}$$

where D_i and D_∞ denote the diffusivity of the active ingredient through the glassy and the swollen polymer and K^{-1} denotes the polymer relaxation time. It was shown that for the values of the Deborah number for release $1 \ll \mathrm{De}_r$ and $\mathrm{De}_r \gg 1$, the release follows the Higuchi relationship whereas for $\mathrm{De}_r \simeq 1.0$ and $(D_i/D_\infty) \ll 1$, the release index would tend to unity.

In the present case, *p*-nitro benzoic acid diffuses through the matrix only after the pendent chain is cleaved by hydrolysis. The time scales associated with diffusion and the structural change in the polymer (i.e., transformation of the hydrophobic polymer into the hydrophilic one) are comparable. Thus the Deborah number for release would be of the order of unity. The ratio (D_i/D_∞) in the present case would be the ratio of the diffusivity of the *p*-nitro benzoic acid through the various polymers I-A to I-E in swollen state to that in poly(HEMA) since the copolymer will be eventually converted to poly(HEMA) at the end of release. For the release of *p*-nitro benzoic acid from poly(HEMA-PNP) matrix I-C, the diffusivity of *p*-nitro benzoic acid has been experimentally found to be given by $D_i = 2.3 \times 10^{-8}$ cm^2/s, and $D_\infty = 2.94 \times 10^{-7}$ cm^2/s. The hydrolysis constant for the *p*-amino benzoic acid ester of HEMA has been estimated from the release kinetics to be 1.41×10^{-6} s^{-1}.[23] Although the corresponding rate constant for PNP cannot be determined since the release is not reaction controlled, it would be reasonable to assume that this would be about four to five times higher than that for *p*-amino benzoic acid ester of HEMA. This leads to $\mathrm{De}_r = 16$. Further, $D_i/D_\infty = 0.078$. The zero order release of *p*-nitro benzoic acid observed in these systems is thus in good qualitative agreement with the predictions [$\mathrm{De}_r = 10$, $(D_i/D_\infty) \to 0$] made by Lee.[35] The values (D_i/D_∞) summarized in Table I confirm that the ratio is sufficiently less than unity for all the systems investigated. We therefore con-

clude that the zero order release of *p*-nitro benzoic acid from the matrices I-C to I-E results from increasing diffusivity of *p*-nitro benzoic acid with time which compensates for the diffusion time if the diffusivity were to be constant.

The equilibrium swelling of the hydrogel I-B is lower than that of I-A. This results in a very sharp fall in the value of the diffusivity of *p*-nitro benzoic acid from the swollen matrix as compared to the decrease in the velocity of the penetrating front. The diffusion of *p*-nitro benzoic acid, therefore, lags behind the velocity of the penetrating front. The release kinetics in systems I-B to I-E, therefore, is expected to be diffusion controlled, i.e., $n = 0.5$. The zero order release of *p*-nitro benzoic acid from the matrices I-C to I-E has already been explained on the basis of increase in the diffusivity of *p*-nitro benzoic acid as a result of increase in the swelling due to the hydrolysis of PNP. However, increase in the equilibrium swelling of the matrix I-B is not as significant as in the case of matrices I-C to I-E. The increase in the diffusivity of *p*-nitro benzoic acid during the course of release is, therefore, inadequate to compensate for the increase in diffusion time. The release of *p*-nitro benzoic acid from the matrix I-B, therefore, follows anomalous kinetics ($n = 0.88$).

Thus as can be seen from Table I, the polymer composition significantly affects the ratio (D_i/D_∞). This ratio decreases as the degree of hydrophobicity increases. The value for the polymer I-B is 0.119 whereas for the polymer matrix I-C and I-D it is 0.078 and 0.024, respectively. The values are in good agreement with the model predicted by Lee[35] [see Fig. 3 (inset)]. Although this ratio is as high as 0.9 for the matrix I-A, zero order release is observed. However, this is not a consequence of increase in the diffusivity with time but is swelling controlled. It is also for this reason that in the case polymer matrix I-A, the release from the swollen hydrogel does not follows zero order kinetics, whereas for the matrices I-C and I-D it does.

Poly(HEMA–DNP): The difference in the release characteristics of the active ingredient from glassy and swollen hydrogels and further evidence of the zero order release brought about by an increase in the diffusivity as a function of time is presented in Figures 5 and 6. The release of 2,4 dinitro benzoic acid from poly(HEMA–DNP) follows the same mechanism as that for the release of *p*-nitro benzoic acid from poly(HEMA–PNP). However, since 2,4 dinitro benzoic acid is a bulkier molecule as compared to *p*-nitro benzoic acid, the release of 2,4 dinitro benzoic acid is controlled by the diffusion through the swollen matrix. As a result the release follows Higuchi relationship ($n = 0.55$) (see Fig. 5), while the release of *p*-nitro benzoic acid from the polymer I-A follows swelling controlled zero order kinetics (Fig. 3). In the case of the glassy polymers II-B and II-C, the release of 2,4 dinitro benzoic acid follows zero order release. Once again the values of the penetration velocities estimated from the release rate are lower than the experimentally determined ones indicating that the release is not swelling controlled. The release of 2,4 dinitro benzoic acid from the swollen polymers also follows the zero order kinetics (see Fig. 6, II-B, and II-C). These findings can be explained on the same lines as the release of *p*-nitro benzoic acid from the glassy and the swollen hydrogel matrices. It is interesting to note that in the case of polymers matrix II-C the release rates from the glassy and the swollen polymers matrices are identical. This is because the time required for the equilibrium swelling to be reached (20 h) is small as compared to the time required for the total release of 2,4-dinitro benzoic acid

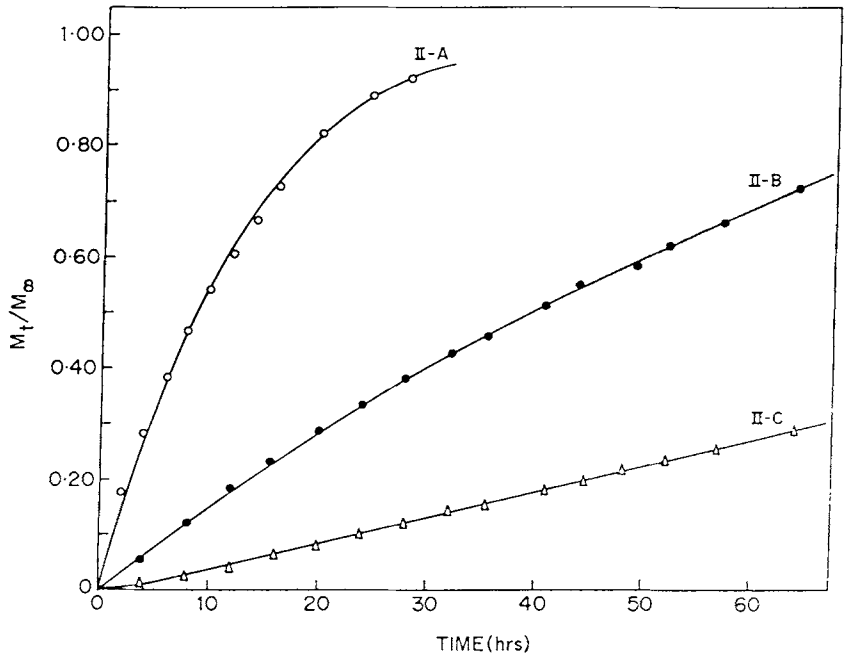


Fig. 5. Kinetics of release of 2,4 dinitro benzoic acid from glassy poly(HEMA–DNP) hydrogel matrices.

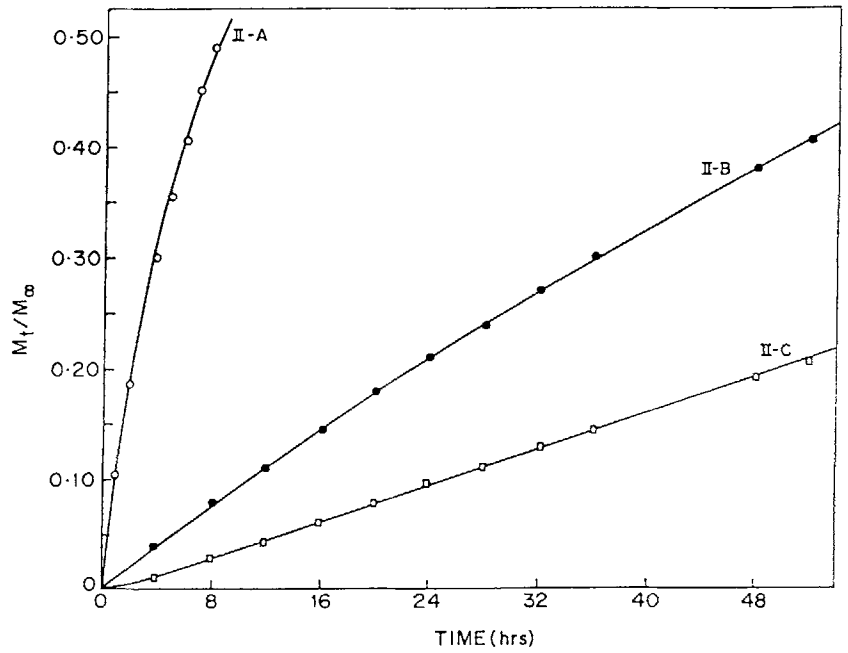


Fig. 6. Kinetics of release of 2,4 dinitro benzoic acid from swollen poly(HEMA–DNP) hydrogel matrices.

(225 h). Most of the release from the initially glassy hydrogels, therefore, proceeds when the hydrogel is already transformed into the swollen phase.

CONCLUSIONS

The release of *p*-nitro benzoic acid from the glassy poly(HEMA–PNP) containing more than 90% HEMA follows swelling-controlled zero order release. The release of 2,4 dinitro benzoic acid from the glassy poly(HEMA–DNP) is controlled by the diffusion of 2,4 dinitro benzoic acid through the swollen matrix. However, the release of the *p*-nitro benzoic acid as well as 2,4 dinitro benzoic acid from glassy as well as swollen hydrogels containing less than 90% HEMA follows zero order release as a result of the time-dependent diffusivity of the active ingredient resulting from the increased degree of swelling as the hydrolysis proceeds. This work further demonstrates that the concept of time-dependent diffusivity can successfully explain the zero order release of the active ingredient from the glassy and the swollen polymer matrices irrespective of whether the increase in diffusivity is brought about as a result of the physical or chemical change in the polymer matrix. In the past, the zero-order release of Sudan Red IV from polystyrene matrix into *n*-hexane medium was ascribed to the phase erosion of the matrix as a result of the case II transport of *n*-hexane. Heller[36] reported the release of hydrocortisone from poly(methyl vinyl ether–maleic anhydride) matrix as a result of mass erosion due to the dissolution of the matrix. Erosion in both these cases is a surface phenomenon. This paper reports for the first time the zero-order release of an active ingredient from the polymer matrix as a result of bulk erosion. The matrix, however, is not bioerodible. Development of such polymer matrices could be an interesting area for further research.

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