Swellable Hydrogel Matrices for the Release of the Pendent Chain-Linked Active Ingredients over Extended Time Periods*

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SYNOPSIS

Zero-order release of the physically dispersed active ingredients from the glassy hydrogels has been explained in the past on the basis of the case II transport of the penetrant medium into the matrix. This communication reports the zero-order release of the pendent chain-linked *p*-nitrobenzoic acid from glassy as well as swollen hydrogel matrices. This has been explained on the basis of the time-dependent diffusivity of *p*-nitrobenzoic acid resulting from the structural changes in the matrix accompanying the release. *p*-Nitrobenzoic acid would be released from these systems at a constant rate for periods of up to 5 months. Implants of this type in which the drug molecule is linked to the polymer backbone through the pendent chain are potentially promising systems for drug delivery at a constant rate for extended time periods.

INTRODUCTION

The importance of the controlled release delivery systems that release the drug at a constant rate is well recognized.[1] Although the matrix systems offer a major advantage in the ease of fabrication and manufacture on large scale, they suffer from the limitation that the release of the drug from the matrix device follows first-order kinetics.[2] Consequently, a number of innovative approaches have been proposed in the past to achieve zero-order release from the matrix systems.[3-7] The most notable among these is the swelling controlled delivery system, pioneered by Hopfenberg and Hsu[6] and Peppas and Franson.[7] These systems exploit the case II penetration of the surrounding medium into the glassy hydrogel polymer matrix. A number of criteria to predict zero-order release from such systems have been proposed in the past that essentially rely upon the manipulation of the time scales of the relaxation processes in the polymer and that for the diffusion of the active ingredient from the swollen matrix. In a recent study, Lee[8] explained the zero-order release of the active ingredient from glassy hydrogels in terms of time-dependent diffusion coefficient. The concept of the Deborah number for release De_r was proposed to elucidate the release characteristics of the active ingredient from the swollen hydrogel [$De_r = (D_\infty / Kl^2)$], where D_∞ denotes the diffusivity of the active ingredient from the swollen hydrogel, K^{-1} is the relaxation time, and l is the half thickness of the polymer specimen. The model predicted that the zero-order release of the active ingredient can be realized as the Deborah number for release approached unity and the ratio D_i / D_∞, where D_i denotes the diffusivity of the active ingredient in the glassy state, which was very small.

In earlier communications[9,10] it was shown by us that an active ingredient, whether physically dispersed or chemically linked to the polymer through the pendent chain, could be released at a constant rate even from the swollen hydrogel matrices. Thus the release of theophylline from the swollen poly(2-hydroxyethyl methacrylate-co-glycidyl methacrylate) hydrogel in water followed the conventional Higuchi relationship ($n = 0.5$), whereas in 0.05 N sulfuric acid, the release index approached values

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close to unity ($n = 0.9$). From the observed release profiles it was apparent that the total exhaustion would take place within 20 h.[9] Similarly the release of *p*-nitrobenzoic acid from poly(2-hydroxyethyl methacrylate-co-methacryloyl hydroxy ethyl *p*-nitrobenzoate), poly(HEMA-co-PNP), into 0.01 *N* sodium hydroxide solution followed zero-order kinetics. Depending on the polymer composition, the release could proceed up to 2 months.[10]

Clearly, there is a need to enhance the time scales for release if such systems are to have any pragmatic applications. This communication reports the release of *p*-nitrobenzoic acid from poly(HPMA-co-PNP) matrices, which could release the active ingredient up to 5 months. The mechanism of release of *p*-nitrobenzoic acid from glassy as well as from the swollen hydrogel matrices has been also elucidated.

EXPERIMENTAL

The monomer 2-methacyloyl ethyl *p*-nitrobenzoate (PNP) was prepared by condensing 2 hydroxy ethyl methacrylate (HEMA) with *p*-nitrobenzoyl chloride. The monomer PNP was then copolymerized with 2 hydroxy propyl methacrylate (HPMA) in various proportions as listed in Table I. The details of synthesis and characterization of monomer PNP as well as copolymer poly(HPMA-co-PNP) are described elsewhere.[11]

The polymer disks of 1.6 cm diameter and 1.0 to 1.2 mm thickness were used for the release of *p*-nitrobenzoic acid from glassy hydrogels. For the release of *p*-nitrobenzoic acid from swollen hydrogels, the polymer disks were swollen in deionized water to equilibrium swelling as confirmed by weight gain method before commencing the release study. The monomer composition, penetration velocities and the indices for release from the glassy hydrogels are summarized in Table I. The equilibrium swelling values and the indices for release from the equilibrium swollen hydrogels are summarized in Table II. *p*-Nitrobenzoic acid released during this step was negligible, as was confirmed by the spectroscopic analysis of water in which the disks were swollen. The release experiments were carried out in 0.01 *N* sodium hydroxide solution at 37°C. The kinetics of release was followed by monitoring the *p*-nitrobenzoic acid released, on a UV spectrophotometer ($\lambda_{max} \simeq 274$ nm).

Table I Kinetics of Release of *p*-Nitrobenzoic Acid from Glassy Poly(HPMA–PNP) Hydrogels

Polymer	HPMA Weight %	Penetration velocity v (cm/s) $\times 10^7$ By Weight Gain Method	Penetration velocity v (cm/s) $\times 10^7$ From Release Experiments	Release Index (n)
A	90.90	5.67	—	0.85
B	76.90	3.37	0.190	0.96
C	66.66	2.70	0.074	1.05

Table II Kinetics of Release of *p*-Nitrobenzoic Acid from Swollen Poly(HMPA–PNP) Hydrogels

Polymer	Q^*	Release Index (n)
B	11.26	1.03
C	7.70	1.05

Q^* = Equilibrium degree of swelling at the start of the experiment.

RESULTS AND DISCUSSION

The release of an active ingredient physically dispersed in the glassy hydrogel involves the penetration of the surrounding medium into the polymer, accompanied by swelling and the transition of the polymer from a glassy to a rubbery phase. The active ingredient is practically immobilized in the glassy matrix ($D = 10^{-11}$ cm^2/s). However, it can diffuse through the swollen hydrogel since the diffusivity is enhanced severalfolds ($D = 10^{-6}$–10^{-7} cm^2/s). It was demonstrated by Peppas and Franson[7] that if the penetration of the surrounding medium follows case II transport characterized by the penetration velocity v, and if the diffusivity of the active ingredient through the swollen polymer (D_∞) be such that the equilibrium swelling interface number (SW_e), is far less than unity, swelling controlled zero-order release of the active ingredient can result. Here SW_e is defined as

$$SW_e = v\delta/D_\infty \quad (1)$$

where δ denotes the thickness of the equilibrium swollen disk.

When the active ingredient such as a substituted benzoic acid is chemically linked to the pendent chain of the hydrogel matrix, an additional step, viz.,

hydrolysis of the ester linkage, is involved in the release kinetics. If the rate of this step is fast enough and the diffusivity of the released molecule through the swollen hydrogel is high enough, the release of the active ingredient could be expected to follow zero-order kinetics. In a prior communication the release of *p*-nitrobenzoic acid from poly(HEMA-co-PNP) was shown to follow zero-order release kinetics.[11] The release rate calculated from the penetration velocity agreed well with the release rate experimentally observed, which further confirmed that the release was indeed controlled by the velocity of penetration of the surrounding medium. *p*-Nitrobenzoic acid was released at a constant rate from the glassy hydrogel in 14 h.[11]

Peppas and Franson[7] proposed the following relationship for the velocity of the penetrating front:

$$v_{max} = k[C(x^*, t) - C^*]^m \qquad (2)$$

where v_{max} denotes the maximum velocity of the penetrating medium, $C(x^*, t)$ denotes the penetrant concentration in the polymer at the equilibrium degree of swelling, C^* denotes the threshold concentration of the penetrant in the polymer at which the glass transition temperature of the polymer is lowered to the experimental temperature, and k and m are the kinetic constant and the exponent of the swelling kinetics, respectively. If it is assumed that for a given family of polymers k and m would be the same, it follows that the penetration velocity would decrease as the term $[C(x^*, t) - C^*]$ decreases. C^* would depend on the glass transition temperature of the polymer and the ability of the penetrating medium to plasticize it. However, since the variation in $C_{max}(x^*, t)$ would be more significant than that of C^*, it is logical to expect that the penetration velocity would decrease with the equilibrium swelling of the polymer. Since poly(2-hydroxypropyl methacrylate) (PHPMA, T_g = 75°C and Q = 21%) has lower equilibrium swelling (Q) than that of poly(2-hydroxyethyl methacrylate), (PHEMA, T_g = 86°C and Q = 40%). HPMA was chosen as the polymer matrix in the anticipation that the choice of this matrix would lead to a decrease in the penetration velocity of the medium, which would enhance the release period. The kinetics of release of *p*-nitrobenzoic acid from glassy poly(HPMA-co-PNP) hydrogel matrices are presented in Figure 1, and the relevant data are summarized in Table I. It follows that the release of *p*-nitrobenzoic acid from the polymers B and C follows zero-order release kinetics whereas in the case of polymer A there is a slight deviation from the zero-order release. The penetration velocities are also summarized in Table I. It is seen that the equilibrium swelling content as well as the penetration velocity values decrease with decreasing HPMA content of the copolymer. It could, therefore, be concluded that the zero-order release of *p*-nitrobenzoic acid is indeed swelling controlled and that the release rate decreases with decrease in the degree of hydration as a result of the

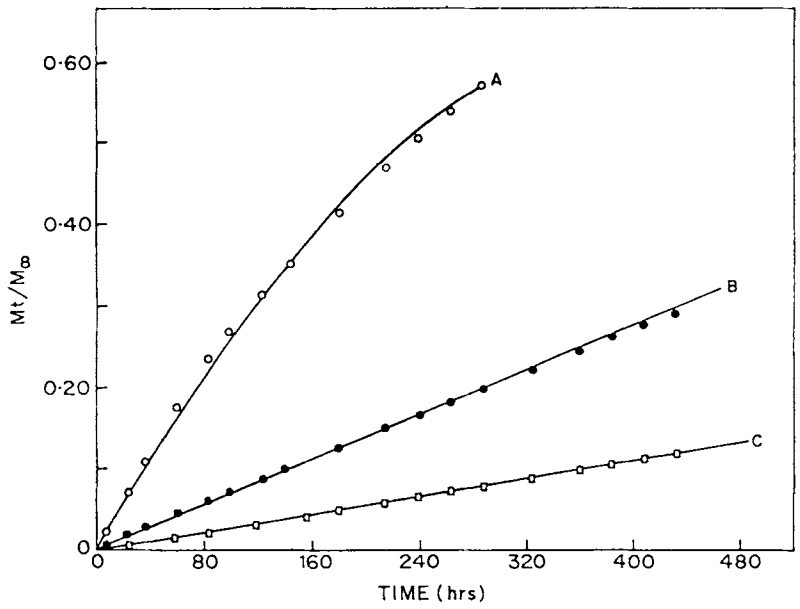

Figure 1 Kinetics of release of *p*-nitrobenzoic acid from glassy poly(HPMA-co-PNP) hydrogel matrices.

decrease in the velocity of the penetration of the surrounding medium.

A closer look at the release data (Table I) reveals some intriguing features. When the kinetics of release of an active ingredient is swelling controlled, the penetration velocity could also be calculated from the release data. Hopfenberg and Hsu[6] showed that the values of penetration velocity so calculated agree very well with the values of penetration velocity calculated from the dynamic swelling measurements as well as from the examination of the photomicrographs of the cross section of the film undergoing swelling as a function of time. However, in the present case the penetration velocities calculated from the dynamic swelling measurements are substantially greater than the values obtained from the release rate. This implies that the release of *p*-nitrobenzoic acid in this case continues even after the penetrating fronts have met, i.e., even from the swollen rubbery hydrogels.

In order to verify that the zero-order release could also be realized from the swollen rubbery hydrogels, the polymers B and C were swollen to the equilibrium swelling in water and then exposed to 0.01 *N* sodium hydroxide solution. The release indeed followed zero-order kinetics (see Fig. 2). Thus zero-order release of *p*-nitrobenzoic acid from the glassy poly(HPMA-co-PNP) is not controlled by the case II transport of the penetrant medium into the glassy polymer.

We propose the following mechanism to explain our results. The swollen matrices *B* and *C* containing 16.66 and 33.3% PNP monomer by weight, respectively, are quite hydrophobic as compared to poly(HEMA). As the PNP is hydrolyzed and *p*-nitrobenzoic acid is released into the alkaline medium, the hydrophilicity of the polymer increases, reaching eventually the same value as that of poly(HPMA-co-HEMA) since PNP is converted to HEMA on hydrolysis. The hydrolysis takes place over the same span of time as release. Thus, the release of *p*-nitrobenzoic acid is accompanied by an increase in the hydrophilicity of the polymer. It has been well established that the diffusivity of a solute in the hydrogel increases with the degree of hydration.[12] Thus the diffusivity of *p*-nitrobenzoic acid through the polymer increases with time as the hydrolysis proceeds.

The equation for the diffusion of a solute through a parallel slab was solved by Lee[8] assuming a time-dependent diffusion coefficient of the form

$$D(t) = D_i + (D_\infty - D_i)[1 - \exp(-Kt)] \quad (3)$$

where D_i denotes the diffusivity of the active ingredient through the polymer in the glassy phase, D_∞ the diffusivity of the active ingredient through the swollen polymer, and K^{-1} denotes relaxation time associated with the transformation. The analysis predicts that the zero-order release can be realized

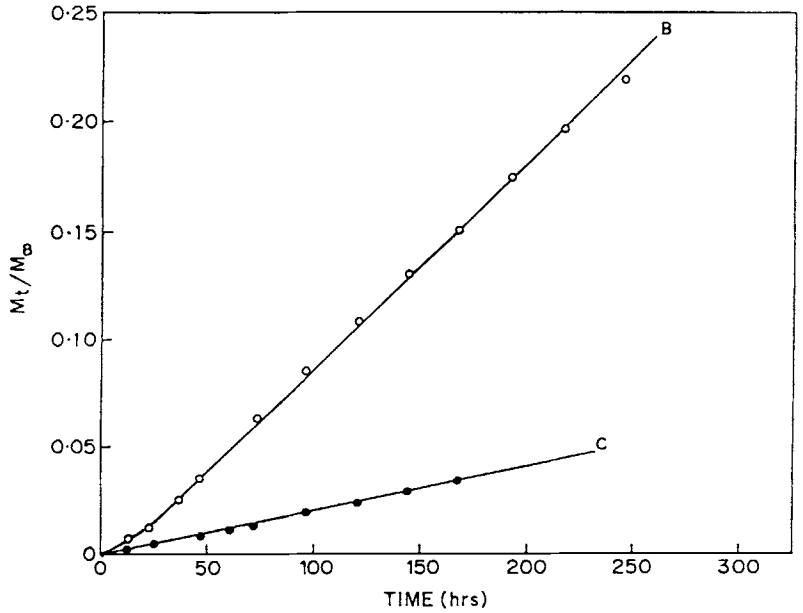

Figure 2 Kinetics of release of *p*-nitrobenzoic acid from swollen poly(HPMA-co-PNP) hydrogel matrices.

for the value $(D_\infty/Kl^2) \simeq 1.0$ and $(D_i/D_\infty) \ll 1$. Although the concept of time-dependent diffusivity was proposed to explain the zero-order release of a drug from a glassy polymer undergoing penetration-induced swelling, the concept and the solution of the diffusion equation would be applicable to any polymer matrix in which the diffusivity of the active ingredient would increase with time as a result of the structural transformation during release. In the present case the increase in the diffusivity results from the hydrolysis of PNP, which converts a hydrophobic polymer into a hydrophilic one. The constant K in the present case would then represent the rate constant for hydrolysis. And D_i and D_∞ are the diffusivity of the active ingredient through the swollen matrix before the onset and after the completion of the hydrolysis.

It has been shown by us earlier that for the release of *p*-nitrobenzoic acid from poly(HEMA-co-PNP) containing 33.3% PNP, $D_i = 2.3 \times 10^{-8}$ cm^2/s, and $D_\infty = 2.94 \times 10^{-7}$ cm^2/s. The hydrolysis constant for the *p*-aminobenzoic acid ester of HEMA has been estimated from the release kinetics to be 1.41×10^{-6} s^{-1}. 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*-aminobenzoic acid ester of HEMA. This leads to $De_r = 16$. Further, $(D_i/D_\infty) = 0.078$.[13] The zero-order release of *p*-nitrobenzoic acid observed in these systems is thus in good agreement with the predictions made by Lee,[8] viz., $De_r = 10$, $(D_i/D_\infty) \rightarrow 0$. The zero-order release of *p*-nitrobenzoic acid from the swollen poly(HPMA-co-PNP) can similarly be explained on the basis of the increase in the diffusivity of *p*-nitrobenzoic acid with time as a result of hydrolysis of PNP and consequent increase in the hydration of the polymer.

Hopfenberg and Hsu[6] have demonstrated the zero-order release of Sudan Red IV as a result of the phase erosion in which the glassy phase is eroded at a constant velocity as a result of the case II transport of the penetrant. Heller et al.[14] have demonstrated the zero-order release of hydrocortisone as a result of the mass erosion of the matrix from the surface. Zero-order release in both cases results from surface erosion. This communication demonstrates for the first time the zero-order release of an active ingredient from a polymer matrix undergoing bulk erosion. It also shows that it is indeed possible to design polymer matrices that change chemically and physically with time, which would result in time-dependent diffusivity and hence the zero-order release.[15]

In the case of release from the glassy hydrogels deployed in this work, the penetration of the surrounding medium into the glassy polymer follows case II transport kinetics. However, the release rate is not controlled by the velocity of the penetrating front as is evident from the fact that the values of the penetration velocity estimated from the release data lag substantially behind the values experimentally observed. It then appears that although during the release from a glassy hydrogel matrix the penetration of the surrounding medium transformed a glassy hydrogel into a swollen rubbery matrix, the release kinetics is still governed by the time-dependent diffusivity of the active ingredient through the matrix as a result of the hydrolysis. If this were to be so, the release rate from the glassy hydrogel matrix would be expected to be the same as that from a swollen hydrogel. This is indeed so in the case of polymer C, which contains 33.3% PNP. It is evident from the values of the penetration velocity that the time required for the equilibrium swelling of the polymer is only 4 days as against the time of release, which is 158 days. Most of the release, therefore, takes place after the hydrogel has reached equilibrium swelling.

CONCLUSIONS

In conclusion, this work reports an interesting approach to achieve the zero-order release of *p*-nitrobenzoic acid from glassy as well as swollen poly(HPMA-co-PNP) hydrogel matrices. It has been shown that in both the cases the release kinetics is governed by the time-dependent diffusivity of *p*-nitrobenzoic acid as a result of the hydrolysis of PNP monomer. *p*-Nitrobenzoic acid would be released from such devices up to 5 months. The life of such devices could be further extended by increasing the loading of PNP in the copolymer. Replacing *p*-nitrobenzoic acid by a suitable drug molecule can lead to controlled release delivery system of pragmatic importance that would release the drug at constant rate over extended time periods.

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