Effect of non-uniform initial drug concentration distribution on the kinetics of drug release from glassy hydrogel matrices

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The effect of non-uniform initial drug concentration distribution, on the kinetics of drug release from polymer matrices has been examined theoretically. The results indicate that a constant-rate of drug release can be achieved, via a specific sigmoidal drug concentration distribution without the need to have a saturated drug reservoir as in a membrane-reservoir system. To test this concept, a novel approach has been developed, which utilizes the non-Fickian swelling behaviour in glassy hydrogels to develop an inflection-point containing drug concentration profile, followed by a freeze-drying step to rapidly remove the swelling solvent and immobilize *in-situ* the desired sigmoidal drug concentration distribution. The drug release from such a system generally exhibits a characteristic time-lag and a constant-rate release region similar to that of a membrane-reservoir system. The applicability of the present concept and process has been demonstrated experimentally with the release of oxprenolol HCl from hydrogel beads; based on 2-hydroxyethyl methacrylate polymerized with a polymeric crosslinking agent.

(Keywords: glassy hydrogels; zero-order drug release; non-uniform concentration distribution; diffusion modelling; non-Fickian swelling kinetics; poly(2-hydroxyethyl methacrylate); oxprenol hydrochloride)

INTRODUCTION

Polymeric delivery systems based on a diffusion-controlled mechanism are becoming increasingly important in the area of controlled release of pharmaceuticals[1-4]. To effectively meet therapeutic requirements especially for drugs with short physiological half-lives, it is often desirable to have a constant-rate (or zero-order) of drug release[5]. Membrane-reservoir devices are generally employed for this purpose where the drug core is surrounded by a rate controlling polymeric membrane[6]. The presence of a saturated drug reservoir is essential in this case to maintain a constant chemical potential gradient across the membrane and therefore a constant rate of release.

However, matrix devices, where the drug is uniformly dissolved or dispersed in a polymer generally exhibit release rates continuously diminishing with time[6,7]. This is a consequence of the increasing diffusional distance and decreasing area at the penetrating diffusion front. In addition to the use of geometry factors[8], modification of matrix systems to approach a constant rate of drug release generally involves the introduction of either a constant rate of surface erosion much larger than the drug diffusion rate in the polymer matrix[9-11] or a constant rate of solvent front penetration (Case II swelling) much smaller than the drug diffusion rate in the swollen region[12,13]. The applicability of these systems may further be limited by the need to maintain a constant surface area at the erosion or penetrating solvent front.

An important area which has not been explored in the past involves the approach to constant-rate drug release from a glassy polymer matrix; via a non-uniform initial drug concentration distribution. It will become clear later that the desired constant-rate drug release can be achieved via stable, inflection point containing, sigmoidal concentration profile. Hydrogel polymers are particularly suitable for this application, because they are glassy in the dry state, capable of immobilizing any non-uniform drug distribution introduced prior to the dehydration step. Whereas in the presence of water, hydrogels can absorb a significant amount of water to form an elastic gel and, at the same time, release the dissolved drug by diffusion through the swollen region[14,15]. Furthermore, when a drug loaded hydrogel matrix, is partially penetrated by a swelling solvent, the non-Fickian diffusion behaviour enables the development of sigmoidal concentration profiles for both the drug and the solvent.

In this paper, we examine the effect of non-uniform initial drug concentration distribution on the kinetics of drug release from polymer matrices. Specific examples based on the release of oxprenolol HCl from glassy hydrogel beads will then be utilized to illustrate a process for the generation of non-uniform drug concentration distribution and the associated constant-rate drug release behaviour.

THEORY

The diffusion characteristics of matrix devices containing uniformly dissolved or dispersed drug are well known[6,11,16,17]. However the effect of non-uniform initial drug distribution on the release behaviour has not been reported in the literature. To examine this effect, we consider a spherical polymer bead with radius a and an

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initial drug concentration distribution $f(r)$ being in contact with a solvent maintained at zero drug concentration. For a system with constant diffusion coefficient D, the drug concentration distribution at any time $t>0$ and radial position r within the bead can be described by the following equation originally derived for a similar heat transfer problem[18]:

$$C(r,t)=\frac{2}{ar}\sum_{n=1}^{\infty} e^{-Dn^2\pi^2t/a^2}\sin\frac{n\pi r}{a}\int_0^a r'f(r')\sin\frac{n\pi r'}{a}\,dr' \quad (1)$$

Integrating the flux at the surface with respect to time, one can obtain the fractional release:

$$\frac{M}{M_\infty}=1-\left[\sum_{n=1}^{\infty}\frac{(-1)^{n+1}}{n}I(n)e^{-n^2\pi^2\tau}\Big/\sum_{n=1}^{\infty}\frac{(-1)^{n+1}}{n}I(n)\right] \quad (2)$$

where M is the amount released at time t, M_∞ the total amount released, $\tau=Dt/a^2$ and

$$I(n)=\int_0^1 \xi f(\xi)\sin(n\pi\xi)\,d\xi \quad (3)$$

When the initial drug concentration distribution is of the sigmoidal type, e.g.:

$$f(r)=C_s\left\{1-\exp\left[-0.5\left(\frac{a-r}{a-r_i}\right)^2\right]\right\}\Big/\left\{1-\exp\left[-0.5\left(\frac{a}{a-r_i}\right)^2\right]\right\} \quad (4)$$

where C_s is the drug concentration in the core and r_i the initial position of the inflection point in the concentration profile, the corresponding cumulative release curves calculated from equations (2)–(4) for $r_i<a$ show typical zero-order release characteristics with apparent time-lags similar to that of membrane-reservoir devices (*Figure 1*). The linear release region and t_{50}, the time required to reach 50% of the total release, appear to be lengthened as the inflection point in the initial concentration profile moves closer to the core. It is important to note that the slope at the inflection point in the initial concentration distribution also affects the duration of the constant-rate release region in such systems.

In contrast, when the initial drug concentration distribution is of the parabolic type containing no inflection point, e.g.:

$$f(r)=\begin{cases}C_s & 0\leqslant r\leqslant r_c\\ C_s\left[1-\left(\dfrac{r-r_c}{a-r_c}\right)^2\right] & r_c\leqslant r\leqslant a\end{cases}$$

where r_c is the radius of the core with uniform drug distribution. The cumulative release curves predicted from equations (2), (3) and (5) for $r_c<a$ exhibit first-order release behaviour with progressively decreasing initial slope as r_c approaches 0 (*Figure 2*).

Although equations (1)–(5) describe the drug release from spherical matrices, similar results are expected for planar and cylindrical geometries. Since no satisfactory model appears to be capable of predicting the transient swelling behaviour as well as the solvent and drug concentration profiles within the swelling glassy polymer

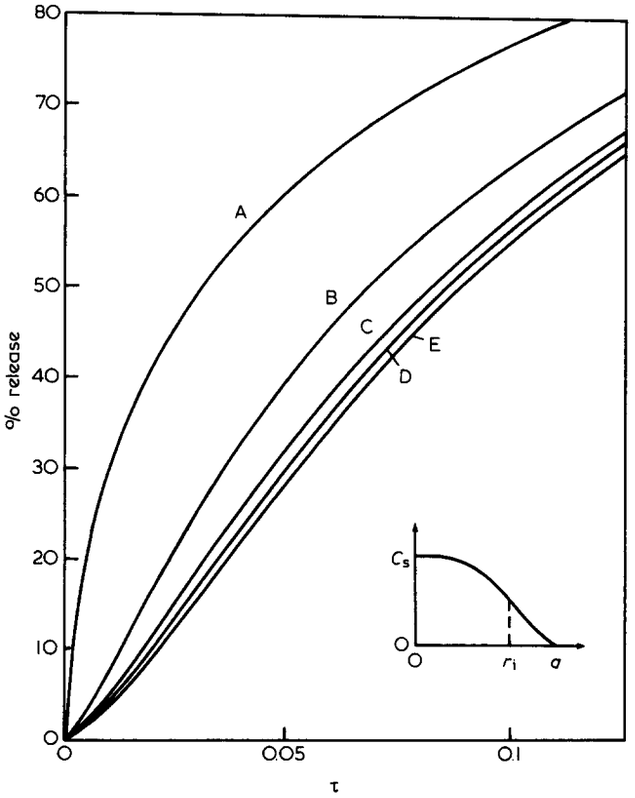


Figure 1 Effect of sigmoidal initial drug concentration distribution on the cumulative drug release from spherical matrices as predicted from equations (2)–(4): **A**, $r_i=a$; **B**, $r_i=0.8a$; **C**, $r_i=0.6a$; **D**, $r_i=0.4a$; **E**, $r_i=0$. Insert: Sigmoidal concentration profile described in equation (4)

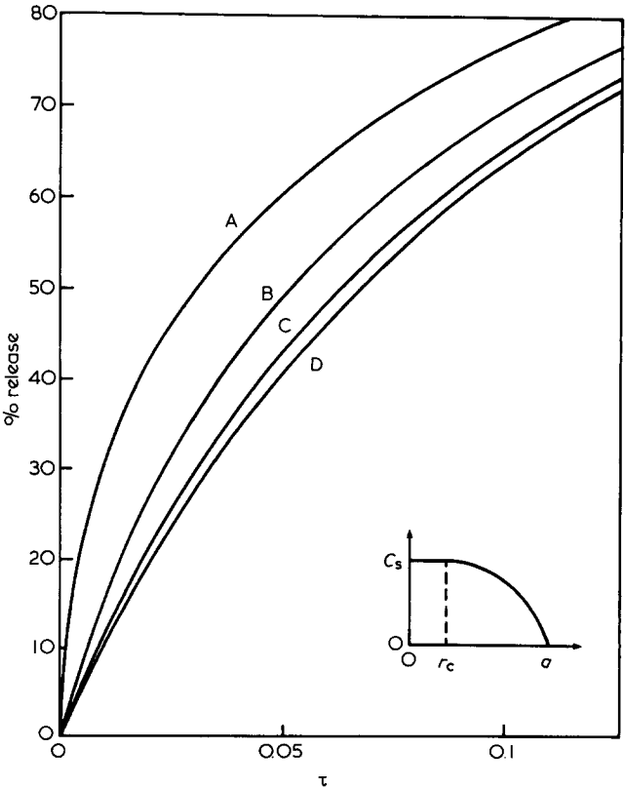


Figure 2 Effect of parabolic initial drug concentration distribution on the cumulative drug release from spherical matrices as predicted from equations (2), (3) and (5); **A**, $r_c=1$;, **B**, $r_c=0.8a$; **C**, $r_c=0.6a$; **D**, $r_c=0$. Insert: Parabolic concentration profile described by equation (5)

during the simultaneous solvent swelling and drug release, only idealized initial drug concentration profiles [equations (4) and (5)] are utilized here to illustrate the concept. Similar difficulties also lead to the use of a constant diffusion coefficient in the present analysis without taking into account the moving boundary conditions due to solvent penetration and swelling. A constant diffusion coefficient may not rigorously characterize the entire course of the diffusional release especially for the initial swelling period of a glassy polymer. However, since the time scale for the solvent penetration is generally much shorter than that for drug release and the role of the solvent is to facilitate Fickian diffusion in the hydrogel matrix, the results obtained here are expected to describe (at least qualitatively), a major portion of the drug release from glassy hydrogels with non-uniform initial drug concentration distribution.

EXPERIMENTAL

The hydrogel beads used in this study were prepared by free-radical suspension polymerization of a monomer mixture containing 70–80% of 2-hydroxyethyl methacrylate (HEMA) and 20–30% of a polymeric cross-linking agent (PX)[24], which was derived from poly-n-butyleneoxide ($MW=2000$) by end capping with isophoronediisocyanate followed by reaction with excess HEMA (*Table 1*). After the completion of suspension polymerization in a saturated salt solution, these beads were filtered and extracted in a Soxhlet with ethanol for 24 h before being dried and fractionated. For the present study, the fraction of beads with an average dry diameter of 0.115 cm and an average water-swollen diameter of 0.130 cm was used. Both hydrogel compositions utilized here exhibit major glass transition temperatures at about 110°C as determined by d.s.c. Their equilibrium water and ethanol swellings are included in *Table 1*.

Oxprenolol HCl, a β-blocker with very high water solubility (about 77% at room temperature), was used as a model drug. The drug loading was achieved by equilibrating the hydrogel beads in an excess amount (>5 to 1) of a 50% oxprenolol HCl solution prepared in a 60:40, ethanol:water mixture. After filtering and very brief rinsing, the swollen loaded beads were dried at 50°C in a vacuum oven to yield a uniform 34.4% oxprenolol HCl loading. These dry, loaded beads were then divided into several portions and subjected to a controlled-extraction process in an excess volume of water under vigorous stirring at 23°C for periods of 5, 15, 20 and 30 min, respectively. The extraction process was controlled in such a way that the extraction time was shorter than the time required for the penetrating solvent fronts to meet at the centre. In other words, the extraction process was carried out to the extent that there would always be an outer swollen, partially extracted region and an inner glassy core. Immediately after separating the extracting solvent, the controlled-extracted beads were freeze-dried under high degree of vacuum (0.025 mm Hg) for 15 h to rapidly remove the swelling solvent and to immobilize a sigmoidal drug concentration distribution in a decreasing fashion from the core to the surface.

Table 1 Hydrogel composition and swelling properties

	Composition (%)		Equilibrium swelling (%)	
Hydrogel	HEMA	PX	Water	Ethanol
1	70	30	25	49
2	80	20	30	52

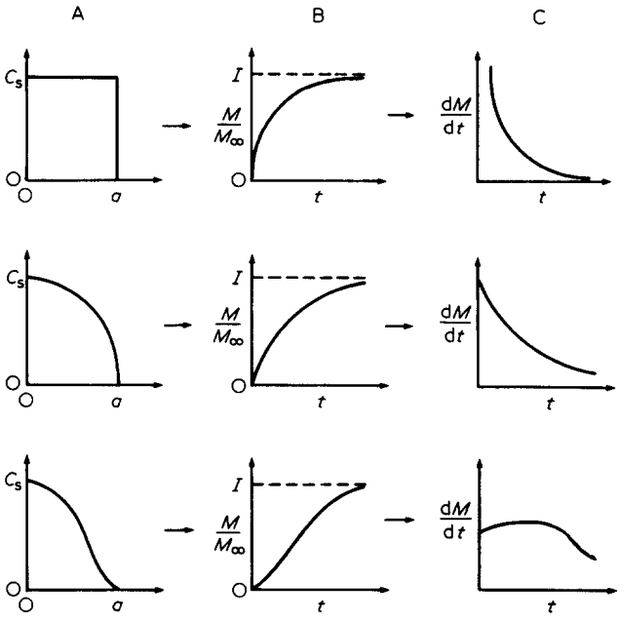


Figure 3 Theoretical profiles illustrating the effect of initial drug concentration distribution on the characteristics of drug release from spherical matrices

The change in oxprenolol HCl concentration during the drug release under perfect sink diffusion conditions at 37.5°C were followed as a function of time on a Beckman ACTA C-III u.v.-visible spectrophotometer at 272 nm using a flow-through cell. Similar to a previous study[15], the transient solvent front penetration was recorded on photographs using an optical microscope. The storage stability tests were carried out in capped vials either under room conditions or at 45°C.

RESULTS AND DISCUSSION

The characteristics of drug release from spherical matrices as a function of the initial drug distribution are summarized in *Figure 3*. These theoretical curves clearly demonstrate that both the uniform and parabolic initial concentration distributions produce an initially high rate of release; followed by a rapid decline (with the latter distribution exhibiting a reduced initial rate of release compared to that of the former). In contrast, an initial sigmoidal drug distribution is shown to be capable of introducing a characteristic inflection point and therefore the cumulative release curve becomes increasingly linear. As a result, a prolonged constant-rate of drug release similar to a membrane-reservoir system is obtained.

A convex concentration distribution containing no inflection point (similar to the parabolic profile described above) is generally characteristic of Fickian diffusion in rubbery polymers having concentration independent diffusion coefficient[25,26]. But a sigmoidal concentration distiribution is characteristic of glassy polymers partially penetrated by a swelling solvent undergoing non-Fickian diffusion. During the water (or other swelling solvent) penetration of a glassy hydrogel matrix having uniform

drug loading, a sharp penetrating solvent front separating an outer rubbery, swollen region from an unpenetrated glassy core is usually observed[15]. In terms of drug distribution, the moving front separates the undissolved core from a partially extracted region; with the dissolved drug diffusing through the swollen rubbery phase into the external releasing medium. Such penetration and swelling generally do not follow a Fickian diffusion mechanism. The existence of some molecular relaxation process in addition to diffusion is believed to be responsible for the observed non-Fickian behaviour[12,20-23]. In this case, the role of the solvent can be considered to facilitate Fickian diffusion in the hydrogel matrix in a time dependent manner[19]. As a result, an inflection point is introduced into both the concentration profile of the penetrating solvent and the corresponding drug distribution in a partially penetrated hydrogel as shown in *Figure 4*. Similar solvent profiles have been reported for the partial penetration of organic swelling solvents in glassy polymers[23,27,28]. The physical situation depicted in *Figure 4* is believed to reflect the solvent and drug distribution generated by the controlled-extraction process described in the Experimental section. The subsequent vacuum freeze-drying step is intended to reduce the polymer segmental mobility, by lowering the temperature via evaporative cooling and, at the same time, rapidly removing the swelling solvent to immobilize a sigmoidal drug distribution in the hydrogel matrix.

As shown in *Figures 5a* and *5b*, *SEM* X-ray microprobe chlorine scans for oxprenolol HCl across the cross-sections of hydrogel 1 confirm that the combination of controlled-extraction and freeze-drying steps has immobilized a sigmoidal drug concentration profile in the 20-min extracted sample as compared to the uniform concentration distribution in the unextracted control. The corresponding *in vitro* percentage release of oxprenolol HCl from the controlled extracted beads as a function of release time was measured by u.v. spectro-

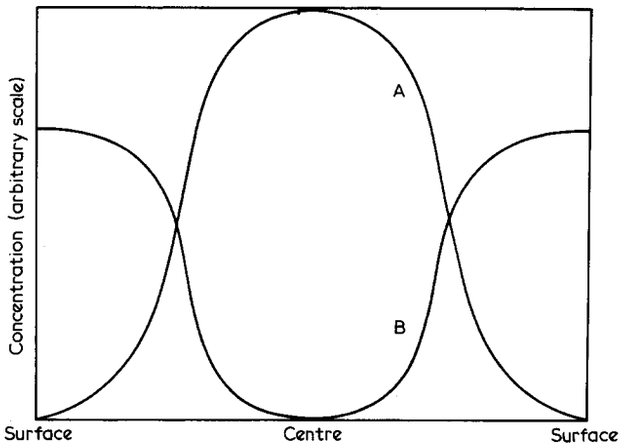
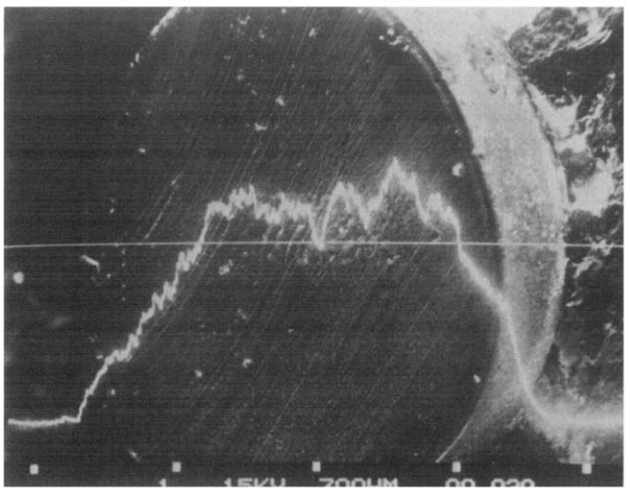
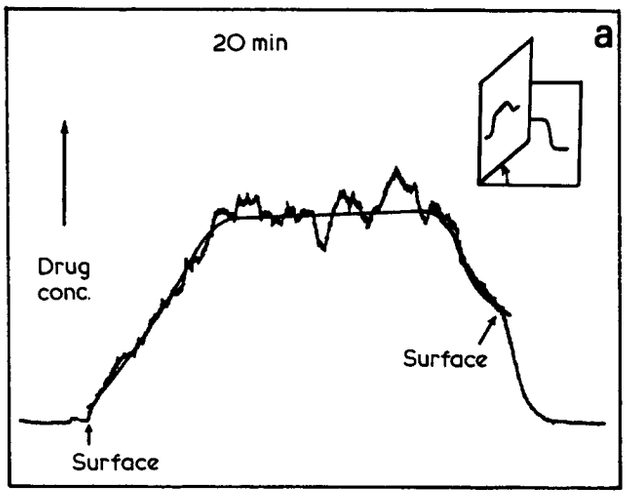
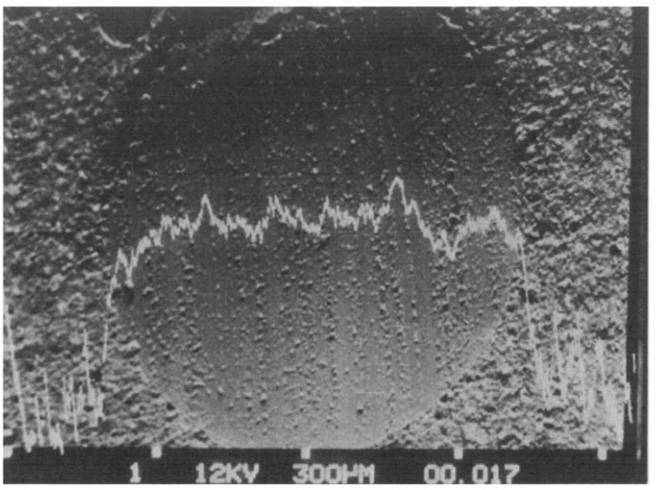


Figure 4 Idealized concentration profiles in a drug loaded glassy hydrogen matrix during the penetration of a swelling solvent: **A**, drug; **B**, solvent







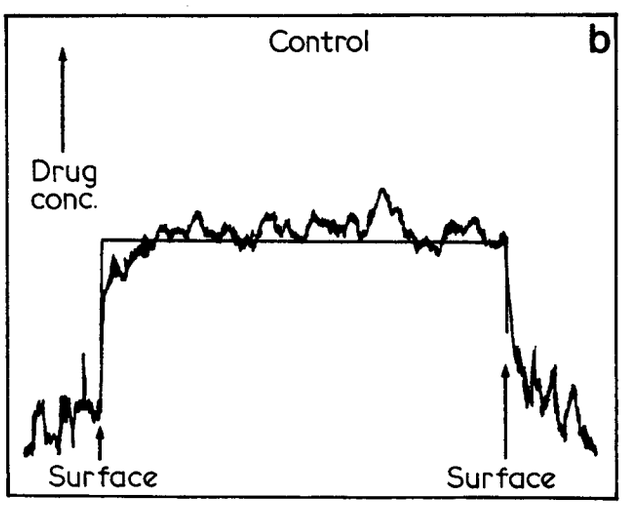


Figure 5 *SEM* X-ray microprobe chlorine scans for oxprenolol HCl on the cross-sections of hydrogel 1 beads. (a) controlled-extracted in water for 20 min. (b) unextracted control

photometry as described in the Experimental section. The results are compared with that of the unextracted control (see *Figure 6* for hydrogel 1 and see *Figure 7* for hydrogel 2). A marked similarity is observed between the experimental release curves of *Figures 6* and *7* and that predicted in *Figure 1*. It is evident that a release time lag and a constant-rate release region similar to that of membrane-reservoir devices are introduced by the present process. By selecting a more hydrophilic polymer such as hydrogel 2, the constant-rate release region is extended up to 70% of the total release. With the increase in controlled-extraction time, the constant-rate release region can also be extended and the release t_{50} lengthened (more than doubled). The constant release region shows a progressively decreasing slope with an increasing controlled-extraction time. Inevitably, a certain amount of drug will be lost during the controlled-extraction process. However, as shown in *Figure 8*, where the oxprenolol HCl loading, is plotted as a function of controlled-extraction time in water, a maximum of 10–12% of the drug loading is removed at an extraction time as long as 30 min. In *Figure 8* it is also shown that hydrogel 2 generally exhibits higher loading levels than hydrogel 1 under identical loading and controlled extraction conditions. This is apparently due to the larger drug partition coefficient in hydrogel 2 as a result of the higher equilibrium water and ethanol swellings.

The effect of controlled-extraction on the solvent front penetration behaviour during oxprenolol HCl release is shown in *Figure 9a* for hydrogel 1 and *Figure 9b* for hydrogel 2. The solvent front penetration in these glassy hydrogel beads is seen to range from amomalous

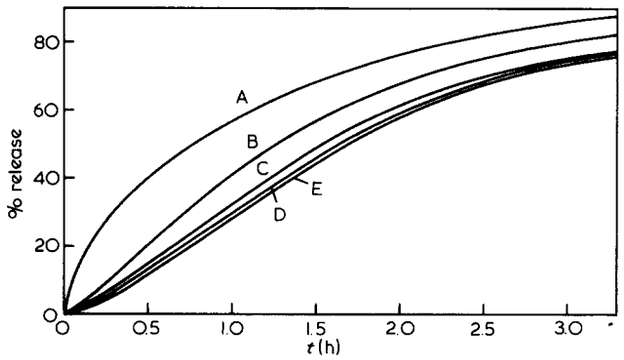


Figure 6 Effect of controlled-extraction time in water on the *in vitro* release of exprenolol HCl from hydrogen 1 beads; **A**, 0 min; **B**, 5 min; **C**, 15 min; **D**, 20 min; **E**, 30 min

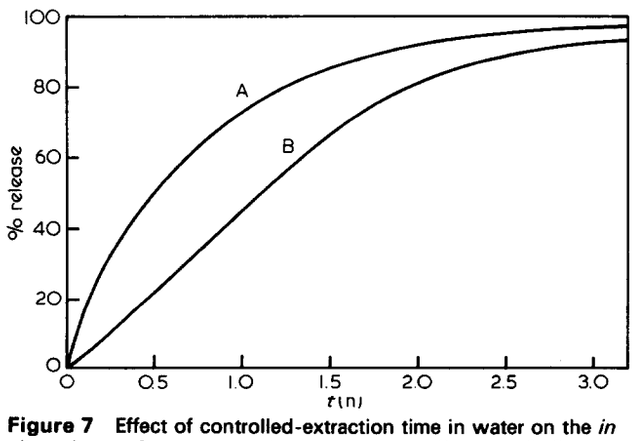


Figure 7 Effect of controlled-extraction time in water on the *in vitro* release of oxprenolol HCl from hydrogel 2 beads: **A**, 0 min; **B**, 20 min

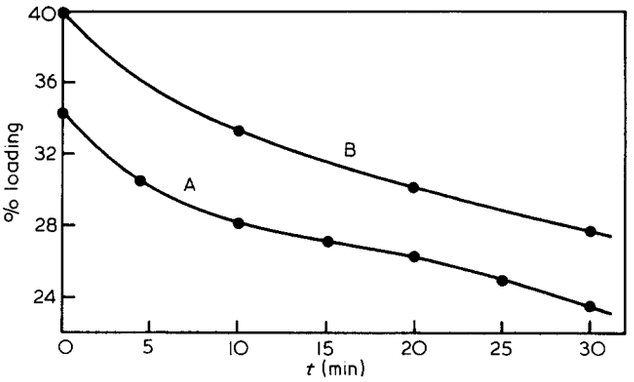


Figure 8 Effect of controlled-extraction time in water on the oxprenolol HCl loading: **A**, hydrogel 1; **B**, hydrogel 2

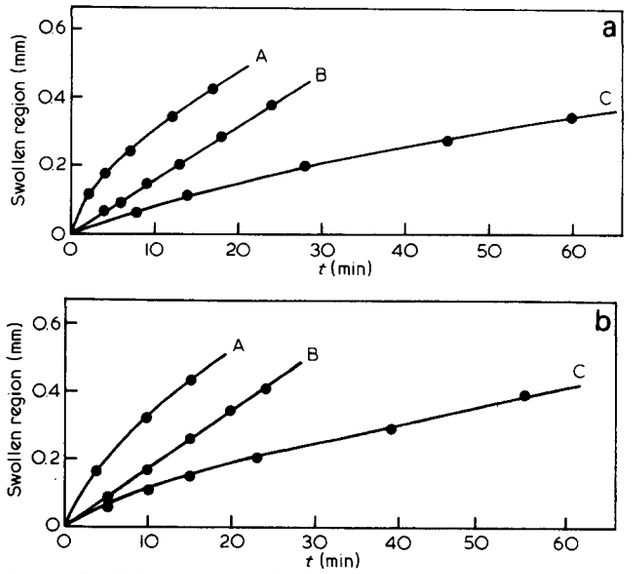


Figure 9 Solvent (water) front penetration in oxprenolol HCl loaded hydrogel beads at 25°C. (a) hydrogel 1. (b) hydrogel 2: **A**, loaded control; **B**, controlled-extracted in water for 20 min: **C**, unloaded control

behaviour (with $t^{0.78}$ and $t^{0.80}$ dependencies for hydrogel 1 and 2, respectively) in the unloaded control to that closer to Fickian diffusion (with $t^{0.56}$ and $t^{0.70}$ dependencies for hydrogel 1 and 2, respectively) in the oxprenolol HCl loaded system. Interestingly, in addition to the increase in solvent penetration rate in the loaded beads comparing to the unloaded control, the solvent penetration in the controlled-extracted and freeze-dried beads coincidentally exhibits linear dependence on t for both hydrogel compositions. As previously shown[15], the swelling kinetics during the release of dissolved or dispersed drum from a glassy hydrogel matrix are more complex than for a single penetrant transport in glassy polymers. The presence of an additional component (the water soluble drug), alters both the swelling osmotic pressure and the associated viscous response of the hydrogel network, during the simultaneous absorption of water and desorption of drug. The rate of solvent penetration is therefore very sensitive to the local drug concentration in the hydrogel. As a result of the non-uniform drug concentration distribution, immobilized in the hydrogel bead, the solvent penetration will initially be slow near the surface region where the drug concentration is low. Despite the fact that the solvent penetration rate will increase as the solvent front moves into regions of higher drug concentration, the increasing diffusional distance

tends to offset this acceleration. This gives rise to an apparent penetration behaviour which approaches linear time dependence as seen in *Figures 9a* and *9b*.

In the absence of moisture, the sigmoidal drug concentration distribution generated by the present process can be preserved indefinitely in the glassy hydrogel matrix. The release of the entrapped drug should not occur until the hydrogel matrix is swollen (at the time of use). This is illustrated by a comparison of oxprenolol HCl release rates from both the unextracted control and controlled-extracted beads of hydrogel 1, at 0 and 59 day storage as shown in *Figures 10a* and *10b*. In addition to the specific feature of prolonged constant-rate release from controlled-extracted samples (as compared to the rapid decay of release rate in the unextracted control), one also observes very little change in the release rates after almost two months of storage under room conditions. Further storage stability tests also show that under 45°C storage, the characteristic time lag in the release curves is well preserved for at least two weeks and a considerably constant release region is still retained even after 50 days storage.

We have experimental evidence indicating that when the extraction process is carried out on drug loaded beads in the fully swollen state instead of the dry glassy state or when the drying is done at elevated temperature instead of the freeze-drying conditions utilized here, no inflection point or constant-release region will be observed in the cumulative drug release profiles. Apparently, a convex drug concentration distribution characteristic of Fickian diffusion in the rubbery state is produced which does not lead to a constant-rate of release (see *Figures 1–3*). Other parameters such as hydrogel composition and extracting solvent also play important roles in determining the resulting release characteristics. These will be examined in a subsequent publication.

In summary, we have described a novel approach to constant-rate drug release from glassy hydrogel beads via an immobilized sigmoidal drug distribution. The combination of controlled-extraction and freeze-drying processes is critical for the *in-situ* immobilization of such a non-uniform concentration distribution. The concept and process described here have several distinct advantages in addition to the constant-rate release characteristics: (a) Simple and economical, since no coating or chemical modification is required; (b) No geometry limitation, since it is applicable to glassy hydrogels of any geometry including granules, beads and sheets; (c) The burst-effect generally associated with membrane-reservoir devices is eliminated; and (d) A saturated reservoir of active ingredient as in the membrane-reservoir device is not required because the constant release is achieved by a non-uniform concentration distribution instead of the constant activity in a reservoir. This is particularly suitable for drugs with high water solubility.

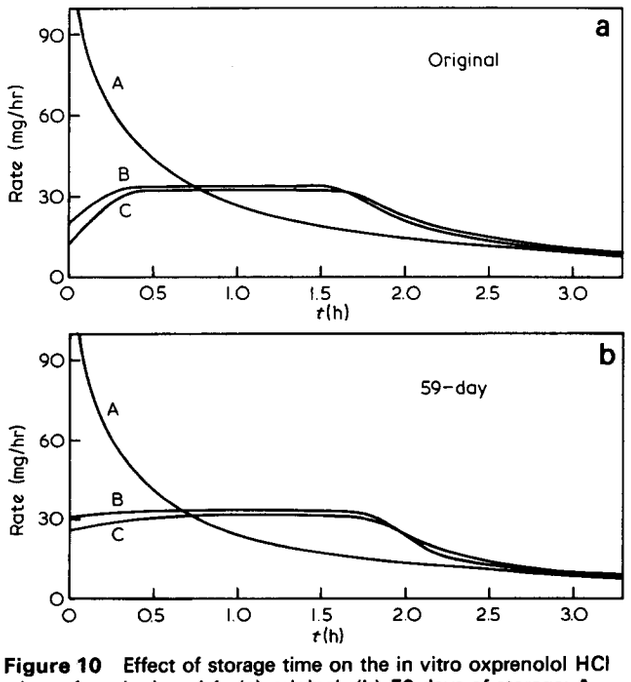


Figure 10 Effect of storage time on the in vitro oxprenolol HCl release from hydrogel 1. (a) original. (b) 59 days of storage: **A**, loaded control; **B**, controlled-extracted in water for 20 min; **C**, controlled-extracted in water for 30 min

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REFERENCES

1 Roseman, T. J. and Mansdorf, S. Z., Eds 'Controlled Release Delivery Systems', Marcel Dekker, New York, 1983
2 Juniper, R., Ed 'Pharmaceutical Applications of Polymers', Rubber and Plastic Research Association of Great Britian, Shawbury, UK, 1981
3 Langer, R. S. and Peppas, N. A. *Biomaterials* 1981, **2**, 201
4 Kydonieus, A. F., Ed 'Controlled Release Technologies: Methods, Theory, and Applications', Vol. I and II, CRC Press, Boca Raton, Florida, 1980
5 Rogers, J. D. and Kwan, K. C. in 'Controlled-Release Pharmaceuticals', (Ed J. Urquhart), American Pharmaceutical Association, Washington, D.C., 1981, p. 95
6 Baker, R. W. and Lonsdale, H. K. in 'Controlled Release of Biologically Active Agents', (Eds A. C. Taquary and R. E. Lacy), Vol. 47 of Advances in Experimental Medicine and Biology, Plenum Press, NY, 1974, p 15
7 Roseman, T. J. and Higuchi, W. I. *J. Pharm. Sci.* 1970, **59**, 353
8 Hsieh, D. S. T., Rhine, W. D. and Langer, R. *J. Pharm. Sci.* 1983, **72**, 17
9 Heller, *J. Biomaterials* 1980, **1**, 51
10 Lee, P. I. in 'Controlled Release of Pesticide and Pharmaceuticals', (Ed D. H. Lewis), Plenum Press, NY, 1981, p 39
11 Lee, P. I. *J. Membrane Sci.* 1980, **7**, 255
12 Korsmeyer, R. W. and Peppas, N. A. in 'Controlled Release Delivery Systems', (Eds T. J. Roseman and S. Z. Mansdorf), Marcel Dekker, NY, 1983, p 77
13 Hopfenberg, H. B. and Hsu, K. C. *Polym. Eng. Sci.* 1981, **18**, 1186
14 Good, W. R. in 'Polymeric Delivery Systems', (Ed R. Kastelnik), Gordon and Breach, NY, 1976, p 139
15 Lee, P. I. *Polymer* 1983, **24** (*Commun.*), 45
16 Higuchi, T. *J. Pharm. Sci.* 1961, **50**, 874
17 Higuchi, T. *J. Pharm. Sci.* 1963, **52**, 1145
18 Carslaw, H. S. and Jaeger, J. C. 'Conduction of Heat in Solids', end ed., Clarendon Press, Oxford, 1959, p 233
19 Lee, P. I. in '9th International Symposium on Controlled Release of Bioactive Materials', Ft. Lauderdale, FL, Controlled Release Society, 1982, p 54
20 Thomas, N. L. and Windle, A. H. *Polymer* 1982, **23**, 529
21 Thomas, N. L. and Windle, A. H. *Polymer* 1978, **19**, 255
22 Thomas, N. L. and Windle, A. H. *Polymer* 1977, **18**, 1195
23 Ware, R. A. and Cohen, C. *J. Appl. Polym. Sci.* 1980, **25**, 717
24 Mueller, K. F., Heiber, S. and Plankl, W., U.S. Pat. 4,224,427 (1978)
25 Crank, J. 'Mathematics of Diffusion', 2nd ed., Clarendon Press, Oxford, 1975
26 Crank, J. and Park, G. S., Eds 'Diffusion in Polymers', Academic Press, London, 1968
27 Rudolph, F. B. *J. Polym. Sci. Polym. Phys. Edn.* 1980, **18**, 2323
28 Zachmann, H. G. *Faserforsch. Text.* 1967, **18**, 95