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Effects of the method of drug incorporation and the size of the monolith on drug release from cross-linked polymers

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Summary

Poly(vinyl alcohol) was cross-linked by glutaraldehyde to form a water-swellable polymer possessing a three-dimensional molecular network. The glassy polymeric material was loaded with proxyphylline, used as a model drug, and shaped into two geometrically different types of monolithic devices, i.e. micromatrices and monolithic slabs. In the case of the micromatrices, the drug was incorporated either during the cross-linking reaction by dissolving it in the reaction solution or after cross-linking by a soaking technique. For the slabs, drug loading was performed only by the soaking method. The polymer network structure was characterized by equilibrium swelling measurement which allowed the determination of the average distance between cross-links. Drug release from the micromatrices loaded during cross-linking could be controlled over more than 8 h if the cross-linking density of the polymeric substrate was high. In these dense networks, the type of release appeared to be diffusion-controlled. In addition to the cross-linking density, the particle size greatly influenced the delivery rate. In contrast, the micromatrices loaded by the soaking method released the drug in less than 20 min. The monolithic slabs, drug-loaded by the soaking method, showed the most interesting release behaviour. After 8 h, only 40–60% of proxyphylline was released although the slabs contained up to 51% of this highly water-soluble compound. Moreover, drug release was found to be controlled not only by the solute diffusion but also by the polymer swelling process.

Introduction

Homogeneous, water-swellable matrices have become a realistic alternative to the classical, heterogeneous tablets as prolonged drug delivery system for oral application. Among the various polymeric substrates which have been investigated for this purpose, poly(vinyl alcohol), PVAL, has particularly interesting characteristics. At the temperature of experimentation (usually the body temperature), dry PVAL is in its glassy state. In contact with an aqueous release medium, a glassy-to-rubbery state transition occurs which can greatly modify the type and rate of drug release (Korsmeyer and Peppas, 1981a). Moreover, PVAL can be cross-linked to form a three-dimensional network. This is generally done by glutaraldehyde which allows to obtain highly cross-linked, polymeric structures. In these dense networks the free space for diffusion is greatly reduced and the drug delivery therefore prolonged (Korsmeyer and Peppas, 1981a; Gander, 1986; Gander et al., 1989).

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In comparison with other carriers, cross-linked PVAL matrices have been rarely studied (Peppas, 1987). The main contributions stem from Peppas and coworkers who reported on PVAL-based controlled release devices (Kosmeyer and Peppas, 1981a,b). Recently, we have shown (Beltrami et al., 1988; Gander et al., 1989) the importance of the macromolecular network structure and the type and amount of drug in the matrices on polymer swelling and release behaviour.

The object of this study was to evaluate (i) the effect of the method of drug incorporation into the polymeric material and (ii) the importance of the size of the monolithic device on drug release. Particular emphasis was put on using a very water-soluble drug and fairly high loadings, both being most challenging parameters to attain prolonged release.

Materials and Methods

Materials

The highly water-soluble (higher than 600 mg/ml at 37°C) drug proxyphylline was kindly supplied by Zyma S.A., Nyon, Switzerland. The two types of PVAL used in these experiments were Elvanol®71-30 (Du Pont de Nemours, Wilmington, DE), with number and weight average molecular weights of 52800 and 113000, respectively, and Mowiol®66-100 (Hoechst, Frankfurt, F.R.G.), with a weight average molecular weight of 224400. Both samples are fully hydrolyzed and contain less than 0.5% residual acetyl group. Glutaraldehyde (25% aqueous solution, Merck, Darmstadt, F.R.G.) was employed as the cross-linking agent. All other chemicals used were commercial, reagent-grade products.

Cross-linking procedure

Cross-linking of PVAL was accomplished by glutaraldehyde following the method described by Korsmeyer and Peppas (1981a). Typically, 10 g of PVAL powder was dissolved in 90 g of hot water at 80–90°C. After cooling to room temperature, this 10% w/w polymer solution was mixed with 20 g of 50% w/w methanol solution, 10 g of 1% w/w sulphuric acid solution and 30 g of 10% w/w acetic acid solution. Then, an adequate amount of cross-linking agent was added to give the desired cross-linking ratio, X, expressed in mol glutaraldehyde per mol PVAL repeating unit. Reaction conditions and method of matrix preparation were varied and will be specified hereafter.

Preparation of micromatrices with drug incorporation during cross-linking

Proxyphylline was directly dissolved in the reaction mixture and cross-linking took place in the presence of the drug. A preliminary compatibility test between proxyphylline and glutaraldehyde under the cross-linking conditions used had shown that this drug does not interfere with the cross-linking reaction. The reaction mixture was poured into Petri dishes to obtain polymer disks of about 3–4 mm thickness and covered with plastic cling film. The samples were initially kept at room temperature for 12 h and then heat-treated at 60°C for 6 h to promote cross-linking. Upon completion of the reaction, the cross-linked hydrogels were cut into small slabs of approximatively 8 × 8 mm and dried to constant weight under vacuum at 40–50°C. The brittle polymer was finally ground, and the particle size fractions of 160–315, 400–500 and 800–1000 μm were separated by sieving.

Preparation of micromatrices with drug incorporation after cross-linking

Cross-linking was performed as described before, but in the absence of the drug. After reaction, the cross-linked hydrogel was cut into small slabs and washed thoroughly over 3 days. The purified material was loaded by soaking the samples in 2–12% w/w aqueous solutions of proxyphylline during 3 days at room temperature. Finally, the drug-loaded hydrogels were dried and ground as described before.

Preparation of cylindrical monoliths with drug incorporation after cross-linking

Cross-linking was performed as described before, but in the absence of the drug. Here, the acetic acid was omitted because we have found that its presence did not influence the extent of cross-linking. The reaction solution was poured

into glass tubes of 16.3 mm diameter, and cross-linking occured at room temperature during 42 h. After the reaction, the firm cylinders were cut into monoliths of 10 mm length, washed for 3 days and finally dried at room temperature. The dimensions of the dry cylindrical monoliths were 7 mm in diameter and 6.5 mm in length. The monoliths were loaded by soaking in aqueous proxyphylline solution (30% w/w) during 4 days and dried to constant weight.

Polymer characterization

The hydrogels produced were characterized immediately after cross-linking by means of equilibrium swelling measurements in water at 37 °C as described elsewhere (Gander et al., 1989). These measurements allowed calculation of the volume fraction of polymer in the swollen state, $v_{2,s}$, the equilibrium volume swelling ratio, q_v $(= v_{2,s}^{-1})$, and the number average molecular weight between cross-links, $\overline{M}_c$. The latter parameter was determined by the equation developed by Bray and Merrill (1973) for gels cross-linked in a solvent.

Drug release

Drug release from the micromatrices was performed in a pH 6.8 phosphate buffer (Ph.Helv. VI) at 37 °C using a flow-through cell dissolution apparatus (Dissotest CE6, Sotax, Basle, Switzerland) with a laminar flow rate of 20 ml/min. Drug release from the cylindrical monoliths was measured in distilled water at 37 °C using the rotating paddle method (50 rpm) with a stationary basket containing the device (USP XXI, apparatus 1). The amount of drug released, M_t, was determined spectrophotometrically at 273 nm.

Results and Discussion

Network characteristics

Experimental values of the polymeric network parameters and drug loading in the matrices are reported in Table 1. The amount of proxyphylline contained in the dry material depends on the drug concentration in the cross-linking reaction solution or the soaking solution and on the polymer swelling ratio. The values of the molecular weight between cross-links indicate that these hydrogels possess rather dense networks with very moderate equilibrium swelling ratios. The $\overline{M}_c$ values differ depending on the actual preparation method. Cross-linked at room temperature, the monolithic slabs logically have slightly looser networks than the micromatrices. It is also noteworthy that the equilibrium swelling measurements of the samples cross-linked at ratios of 0.1 and 0.2 did not reveal significant differences in their network density. More precise information about the effects of the cross-linking ratio, the type of PVAL, and the

TABLE 1

Macromolecular network characteristics of the cross-linked PVAL samples and drug loadings in the final matrices

Type of monolith	Type of PVAL	X	Drug loading (% w/w)	q_v	$\overline{M}_c$ [a]
Micromatrices drug-loaded during cross-linking	Elvanol®71-30	0.20	7.6	3.1	260 ± 10
	Elvanol®71-30	0.20	14.2	3.2	270 ± 60
	Mowiol®66-100	0.10	13.6	3.7	320 ± 10
	Mowiol®66-100	0.20	15.4	3.6	340 ± 40
Micromatrices drug-loaded by soaking	Elvanol®71-30	0.10	20.7	4.1	390 ± 30
	Elvanol®71-30	0.20	8.3	4.1	460 ± 100
	Mowiol®66-100	0.20	17.6	3.0	240 ± 20
Cylinders drug-loaded by soaking	Elvanol®71-30	0.05	50.5	6.5	949 ± 100
	Elvanol®71-30	0.10	27.1	4.9	613 ± 100
	Elvanol®71-30	0.20	7.8	5.0	714 ± 50

[a] Each value is the mean ± S.D. of 4 sample determinations.

presence and amount of drug in the reaction solution on PVAL cross-linking can be found in a recent publication (Gander et al., 1989).

Analyzing the macromolecular structure of such a glassy material is an important step in order to understand the drug release process from these polymers. In a cross-linked, glassy polymer, the solvent (aqueous release medium) penetration into the monolith and the drug diffusion through the network both may indeed contribute to the control of the drug release process. It is evident that with increasing cross-linking density the drug diffusion considerably slows down and, hence, becomes the rate-limiting process in the drug delivery.

Drug release

On the basis of our recently published results about prolonged drug delivery from micromatrices loaded during the cross-linking reaction (Gander et al., 1989), we aimed to investigate the influence of the particle size on release rate. Fig. 1 illustrates the proxyphylline release profiles from the three different particle size fractions 160–315, 400–500 and 800–1000 μm with cross-linking ratios of 0.1 and 0.2. It appears that the reduction of the particle size leads to higher delivery rates, most probably as a consequence of the increased surface

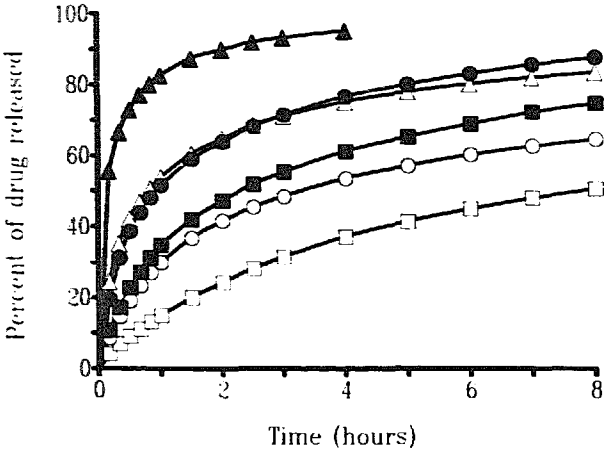

Fig. 1. Drug release from PVAL (Mowiol®66-100) micromatrices of various sizes, cross-linked at ratios of $X = 0.1$ (closed symbols) and $X = 0.2$ (open symbols), and loaded during cross-linking with 13.6 and 15.4% w/w drug, respectively. Size fractions: 160–315 μm (▲, △); 400–500 μm (●; ○); 800–1000 μm (■, □).

area of the micromatrices and the shorter diffusional distance for the drug. On the other hand, Enscore et al. (1977) and Robert et al. (1985) have shown that the equilibrium swelling ratio of cross-linked polymeric microspheres is increased in smaller particles. This means that the smaller particles have a comparatively higher network expansion leading to increased solute transport through the polymeric substrate. Robert (1987) has also reported decreasing water penetration rates into cross-linked PHEMA microspheres for increasing particle sizes (from 235 to 1000 μm in diameter). Therefore, solvent penetration rate, equilibrium swelling ratio and drug diffusional distance all may contribute to the overall reduction in proxyphylline delivery rate from the larger micromatrices.

The same figure also shows the pronounced effect of the cross-linking ratio on drug release. This contrasts with the results from the equilibrium swelling measurements which did not show a significant difference between the network characteristics of these two samples. As the swelling measurements were made immediately after cross-linking but before drying the gels, cross-linking most likely continued during the drying process owing to the presence of residual glutaraldehyde which could not be eliminated from these drug-containing samples. The final network of the directly loaded micromatrices might therefore be much denser than indicated by the values given in Table 1. In a recent investigation, we have studied this phenomenon of continuing cross-linking due to residual or incompletely reacted (only one of the two aldehyde functions has formed an acetal bond with PVAL) glutaraldehyde (Beltrami et al., 1989). The results showed that the elimination and inactivation of free aldehyde groups result in looser networks for a given cross-linking ratio.

The irregular shape and ill-defined size distribution of the micromatrices produced, as shown in Fig. 2, do not allow a proper analysis of the type of drug delivery (Fickian or non-Fickian). Ritger and Peppas (1987) have recently demonstrated that these two morphological parameters greatly affect this type of analysis. We observed, however, that water penetration into the micro-

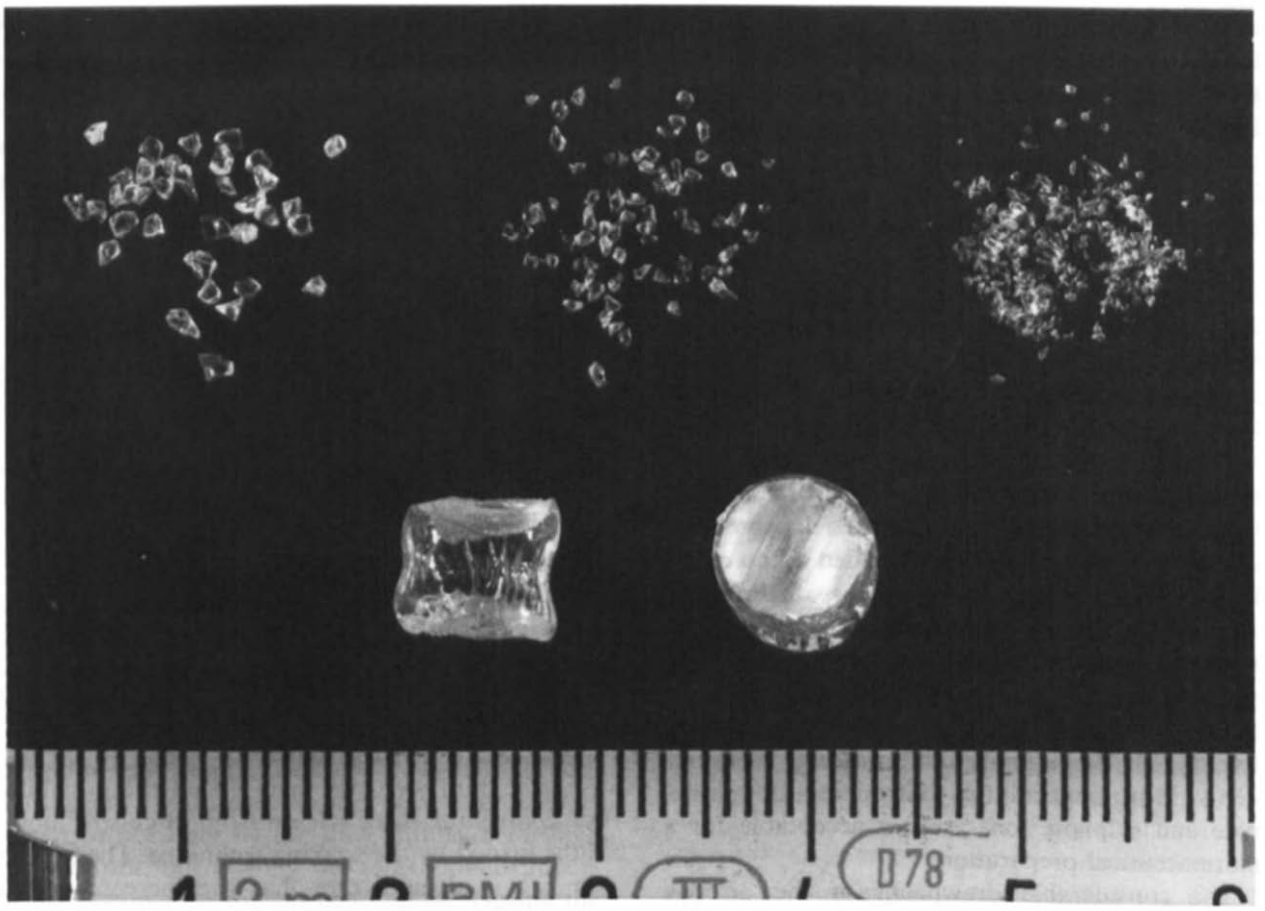

Fig. 2. Photograph of the micromatrices (the three particle size fractions used) and the cylindrical monoliths.

matrices and the related rubbery-to-glassy state transition of the PVAL were relatively fast processes (of the order of 20–40 min) compared to the drug delivery (over 12 h). We can therefore reasonably assume that drug release from these densely cross-linked systems is essentially diffusion-controlled. Hence, the apparent drug diffusion coefficient in the hydrogel, D_i, was determined using the simplified diffusion equation for drug release from spherical matrices containing dissolved drug (Baker and Lonsdale, 1974):

$$\frac{M_t}{M_\infty} = \left[\frac{36 D_i t}{\pi r^2}\right]^{1/2} - \frac{3 D_i t}{r^2} \qquad (1)$$

The fractional release, M_t/M_∞, from 0 to 0.4 was

TABLE 2

Apparent diffusion coefficient and time parameters of proxyphylline released from cross-linked PVAL (Mowiol®66-100) micromatrices of various sizes

Size range (μm)	X	Drug loading (% w/w)	$D_i \times 10^9$ [a] ($cm^2 \cdot s^{-1}$)	Time parameters (min)	
				$t_{50\%}$	$t_{75\%}$
160– 315	0.1	13.6	10.8 ± 0.7 [b]	470	> 720
400– 500			11.3 ± 0.3	200	> 720
800–1000			12.9 ± 0.7	50	240
160– 315	0.2	15.4	1.7 ± 0.1	140	490
400– 500			2.7 ± 0.1	55	220
800–1000			1.7 ± 0.1	9	39

[a] From Eqn. 1.
[b] Confidence limits for $P > 0.95$.

taken into account. For the three particle fractions 160–315 μm, 400–500 μm and 800–1000 μm, we assumed mean radii of the swollen particles of 200 μm, 250 μm and 500 μm, respectively.

The values of the apparent drug diffusion coefficient, D_i, reported in Table 2, are rather low and typical for highly cross-linked networks. As expected for a diffusional process, the D_i values are very similar for the three particle size ranges but differ considerably for the two cross-linking ratios, X. The $t_{50\%}$ and $t_{75\%}$ values give more evidence of the prolongation of drug release from the larger particles.

The micromatrices loaded during cross-linking exhibit a very interesting drug release behaviour. They have, however, the inherent disadvantage that they are unable to be purified after cross-linking without the concomitant loss of drug. Because of the residual cross-linking reagents in the polymer, the reaction continues during the drying process or storing. Therefore, the exact cross-linking density of the final polymer cannot be determined by equilibrium swelling measurements. More importantly, the residual glutaraldehyde and sulphate ions are not acceptable for a pharmaceutical preparation.

The considerable drawbacks of the directly loaded polymers directed our investigation to the preparation of matrices which were purified after cross-linking and drug loaded by soaking in an appropriate aqueous drug solution. Fig. 3 illustrates that the micromatrices (400–500 μm in diameter) prepared by the soaking method release the drug very quickly compared to the samples obtained by direct drug loading. Similar results have been observed with theophylline, incorporated into the same type of hydrogels at loadings varying between 2.3 and 4.0% (Gander, 1986). Two hypotheses can be put forward. In the directly loaded matrices, the residual glutaraldehyde continues cross-linking during the drying process and a much denser network is formed. The drug molecules are therefore tightly entrapped in the dense macromolecular structure and diffusion through the network occurs only slowly. In the soaking method, on the other hand, the drug molecules might concentrate in zones of lower cross-linking density, i.e. in the larger macro-

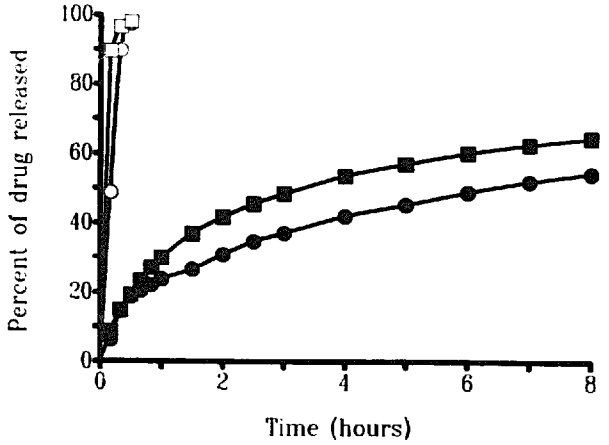

Fig. 3. Drug release from PVAL micromatrices of 400–630 μm drug loaded during (closed symbols) and after (open symbols) cross-linking ($X = 0.2$). Elvanol®71-30, drug loading = 8.3% (●); Mowiol®66-100, drug loading = 17.6% (■). Elvanol®71-30, drug loading = 7.6% (○); Mowiol®66-100, drug loading = 15.4% (□).

molecular meshes. It is, however, unknown to us to what extent the individual mesh size can vary within a cross-linked network.

In a third step, we investigated the possibility of controlling drug release from large-size monoliths loaded by the soaking technique. The profiles in Fig. 4 demonstrate that the increased diffusional distance in these cylindrical devices brings

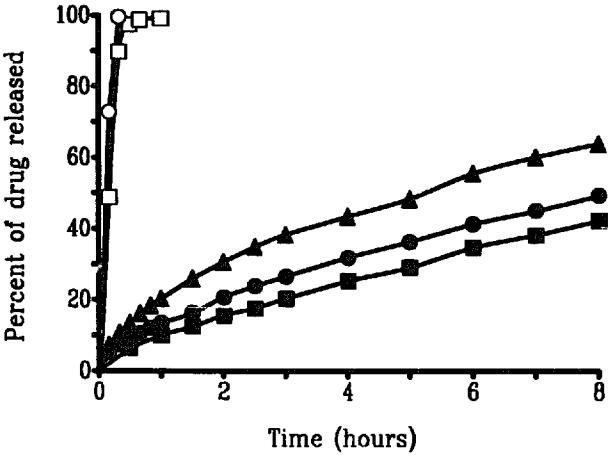

Fig. 4. Drug release from PVAL (Elvanol®71-30) micromatrices of 400–630 μm (open symbols) and cylindrical monoliths (closed symbols) drug loaded after cross-linking. $X = 0.1$, drug loading = 20.7% (○); $X = 0.2$, drug loading = 8.3% (□); $X = 0.05$, drug loading = 50.5% (▲); $X = 0.1$, drug loading = 27.1% (●); $X = 0.2$, drug loading = 7.8% (■).

TABLE 3

Water penetration time and proxyphylline release parameters obtained with the cylindrical monoliths prepared from cross-linked PVAL (Elvanol®71-30)

X	Drug loading (% w/w)	Water penetration time, θ_D (h)	M_t/M_∞ at $t = \theta_D$	$t_{50\%}$ (min)	Exponent [a] n
0.05	50.5	10	0.72	330	0.56
0.10	27.1	16	0.67	600	0.60
0.20	7.8	44	0.87	840	0.69

[a] From Eqn. 2.

about a considerable prolonging effect on drug delivery compared to the micromatrix system. The difference in the respective release times is too big to be explained solely by the longer diffusional distance for the drug in the monolith. It is also very interesting to note that the highly loaded samples (containing 27 and 51% w/w of proxyphylline) retain the drug for a rather prolonged period of time despite their low cross-linking ratio. This again indicates that the release process is governed not only by the drug diffusion through the network, but also by the relaxational process of the polymer on solvent penetration. During the release experiments we could indeed observe that the solvent diffusion time θ_D, necessary for the water penetration into the cylinders, i.e. when the penetration fronts met, was of the order of 10, 16 and 44 h for the samples cross-linked at ratios of 0.05, 0.10, and 0.20, respectively. At time θ_D, only 67–87% of the drug was already delivered from the devices (Table 3). This again gives strong evidence for the importance of the solvent penetration process for the drug delivery from these cylindrical monoliths.

To analyze further the release behaviour of these devices, we expressed the drug fraction released, M_t/M_∞, as a function of time, t, by the general equation:

$$M_t/M_\infty = kt^n \tag{2}$$

Here, k is a kinetic constant and n is the exponent indicating the type of transport process. For a given transport mechanism (diffusional or swelling-controlled), the value of n, for $M_t/M_\infty < 0.6$, depends on the geometry of the device (Ritger and Peppas,1987). As the cylindrical monoliths studied here have a geometry similar to a sphere (Fig. 2), we correspondingly consider n values of 0.43 and 0.85 for Fickian and Case-II transport, respectively. The intermediate values $0.43 < n < 0.85$ denote anomalous (non-Fickian) transport.

The calculated n values, given in Table 3, are typical for an anomalous release behaviour. It is noteworthy that even the sample containing 51% of this very hydrophilic drug gives a non-Fickian release, although the value of n is relatively low. On the other hand, the time parameter $t_{50\%}$ demonstrates the high potential of these devices for prolonged drug delivery in oral applications.

In order to calculate the apparent drug diffusion coefficient in the hydrogel, the final portion of the profiles, $0.6 < M_t/M_\infty < 1.0$, was analyzed. For this portion, drug release is a pure diffusional transport through the fully swollen hydrogel. The simplified diffusion equation (Baker and Lonsdale, 1974) applicable for spherical matrices containing dissolved drug was therefore used:

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2} \exp - \left[\frac{\pi^2 D_i t}{r^2}\right] \tag{3}$$

The average diffusional distance, r, corresponding to half the diameter of the fully swollen cylindrical device, is given in Table 4. The reader should note that the calculated D_i values are slightly underestimated as the actual diffusional distance varies

TABLE 4

Analysis of the release mechanism of proxyphylline from cross-linked cylindrical monoliths

X	$v \times 10^6$ (cm/s)	$D_i \times 10^7$ [a] (cm^2/s)	δ_{max} (cm)	Sw_e	Exponent n [b]
0.05	9.3	10.0	0.50	5	0.56
0.10	6.9	8.4	0.47	4	0.60
0.20	4.6	1.7	0.40	10	0.69

[a] from Eqn. 3.
[b] from Eqn. 2.

between r and $1.4 \cdot r$ depending on the direction of drug diffusion in theses cylindrical monoliths.

The calculated D_i values, reported in Table 4, depend on the cross-linking ratio. Diffusion in highly cross-linked networks is greatly reduced and one can notice that a 4-fold increase in X results in a 5-fold decrease in D_i. When we compare these values with the ones obtained with the micromatrices, in Table 2, we observe that the apparent diffusion coefficient in the cylindrical monoliths is about 100 times higher for X values of 0.1 and 0.2. This difference is consistent with the much looser network of the cylindrical slabs as found by the equilibrium swelling measurements (Table 1) and related to the different preparation conditions.

The knowledge of the apparent drug diffusion coefficient in the swollen hydrogel and of the water penetration rate into the monolith allows the calculation of the equilibrium swelling interface number, Sw_e (Peppas and Franson, 1983):

$$Sw_e = \frac{v\delta_{max}}{D_i} \quad (4)$$

Here, v is the average penetration velocity of the aqueous release medium and δ_{max} is the maximum half-thickness of the swollen hydrogel. This dimensionless number compares the velocity of the penetrating solvent front with the diffusional drug transport in the hydrated material. When the rate of solute transport through the swollen gel, D_i/δ_{max}, is faster than the rate at which the dissolution medium penetrates, Sw_e is smaller than 1 and, hence, drug release is supposed to be controlled by the swelling process of the polymer rather than by drug diffusion. For Sw_e values of about 1 both mechanisms control the drug delivery and an anomalous, non-Fickian release is observed. If Sw_e is greater than 1, drug diffusion should be the rate limiting process and Fickian-type release occurs.

The calculated values of Sw_e, as shown in Table 4, are clearly greater than unity indicating that the rate of solvent penetration is higher than that of drug release through the swollen layer. This does not mean however that the drug delivery process is mainly diffusion controlled. The n values show that both mechanisms, i.e. drug diffusion and solvent penetration, govern the overall delivery behaviour. In a recent paper, Davidson and Peppas (1986) calculated an n value of 0.749 and a Sw_e of 11.4 for theophylline-loaded (HEMA-*co*-MMA)-copolymer films. The authors conclude that the type of release cannot be predicted solely on the basis of the Sw_e value. They demonstrate that a second dimensionless quantity, the diffusional Deborah number, is necessary for a complete analysis of the release process from this type of material.

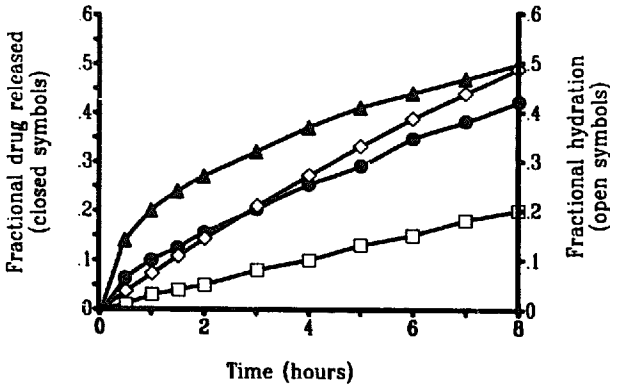

Fig. 5. Experimental drug release (●) compared to theoretical, pure diffusion-controlled release (▲) and position of the solvent penetration front expressed as one-dimensional penetration depth (□) and hydrated volume (◇).

Fig. 5 visualizes that the actual release process is initially controlled by the solvent penetration. Up to 4 h, the experimental release profile coincides with the one representing the fraction of solvent-penetrated (hydrated) volume of the monolith. This fractional volume was calculated from the penetration depth of the solvent front. For comparison we plotted the theoretical profile for purely diffusion-controlled drug release. Some important aspects can be pointed out. The solvent penetration rate is rather low for such a hydrophilic polymeric system indicating that the macromolecular chains undergo a relaxational process which is not instantaneous. Only when the polymer has changed from its glassy to its rubbery state, the drug molecules can start to diffuse outwards. As a consequence, the actual drug delivery is clearly slower than the pure diffusional process. This confirms that this particular polymeric sys-

tem releases the drug, at least at an initial stage, by an essentially swelling- or relaxation-controlled mechanism. At a later stage, i.e. after approx. 5 h, the actual drug delivery appears to be controlled by both polymer swelling and solute diffusion.

Conclusions

Chemically cross-linked PVAL was shown to be a suitable material to control the release of a highly water-soluble and very hydrophilic drug over a period of 24 h or longer. In the case of micromatrices, this control can be accomplished with very dense networks where drug diffusion is greatly reduced. This again requires that the drug has to be loaded into the polymer during cross-linking. Such a directly loaded system is, however, not acceptable as a pharmaceutical dosage form as it cannot be purified without the concomitant loss of drug. More promising results were obtained with larger, cylindrical monoliths. Here, a less dense network is needed and, hence, the drug can be loaded into the device by soaking the cross-linked and purified polymer in an appropriate drug solution. With these larger devices, drug release is not essentially controlled by the solute diffusion but by the relaxational process of the glassy polymer on water penetration. This glassy-to-rubbery state transition of the macromolecular chains is a relatively slow process and controls the drug release at least at the initial stage of delivery. This type of cylindrical monolithic device appears to be a realistic dosage form for prolonged release and oral application. Indeed, drug loadings as high as 50% or more can be obtained and the release period can be controlled over 12 or even 24 h.

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