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Research Article

Effect of Polymeric Network Structure on Drug Release from Cross-Linked Poly(Vinyl Alcohol) Micromatrices

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Three types of poly(vinyl alcohol) were cross-linked by glutaraldehyde to form water-swellable materials possessing a three-dimensional, molecular network. Proxyphylline and theophylline were incorporated into the polymer networks during the cross-linking reaction. The firm hydrogels formed were dried and reduced to a particle size of 400–630 μm. The molecular structure of the gels was characterized by equilibrium swelling measurements which allowed the determination of the average distance between two cross-links and, hence, the macromolecular mesh size. The sulfate and glutaraldehyde residues contained in the purified and nonpurified cross-linked polymers were analyzed, and methods for their elimination and inactivation were developed. Drug release from the highly cross-linked gels could be controlled over more than 12 hr, as the diffusion process in these very dense macromolecular networks is rather slow. The extent of branching and entanglement of the polymeric chains appeared to have an important effect. In addition, the release rate was influenced greatly by the amount and, to a lesser extent, by the type of drug in the network.

KEY WORDS: cross-linked poly(vinyl alcohol); macromolecular network structure; swellable micromatrices; drug release; proxyphylline; theophylline.

INTRODUCTION

Prolonged-release micromatrices based on hydrophilic polymers are a potentially interesting dosage form. Such monolithic particles in the range of a few hundred micrometers are particularly attractive for pediatric and geriatric medication, where the swallowing of tablets or capsules may be a problem. However, these hydrogel-forming systems generally release a drug at a relatively high rate owing to their hydrophilicity and their large surface area (1).

One simple and effective way to prolong drug release from such systems is to modify the macromolecular structure of the polymeric material. This can be done by cross-linking the macromolecular chains in order to form a three-dimensional network. In such a network, the free space available for solute diffusion, the macromolecular mesh size, is reduced (diffusion-controlled system) (2). Several investigators have indeed noted a distinct dependence of the solute diffusion coefficient on the cross-linking density and its related characteristics such as the volume degree of swelling and the molecular weight between cross-links (3–9). The type of drug release from these systems is commonly termed Fickian transport.

A second approach for prolonging drug delivery from hydrophilic, particulate devices is to use a polymer which is in its glassy state at the temperature of the experiment (usually the body temperature) and undergoes a glassy-to-rubbery state transition upon water penetration (swelling-controlled system) (10–20). This thermodynamic transition can greatly modify the type and rate of the drug release. If the time for this macromolecular relaxation process is longer than the time for drug diffusion in the swollen phase, drug delivery is no longer exclusively diffusion controlled. This type of drug release is termed anomalous or non-Fickian transport.

In a recent publication (21), we presented results obtained with micromatrices based on cross-linked rubbery polymers, namely, poly(alkylene oxides). Structural characteristics of the network such as the interlinking degree and the distance between interlinking sites were shown to affect considerably the apparent drug diffusion coefficient in the hydrogel. Only a very dense network structure allowed control of the drug delivery rate from these microparticulate hydrogels because a diffusion coefficient of the order of 10^{-8} to 10^{-9} cm^2 sec^{-1} was required to prolong the release process over a period of several hours.

In this contribution we used the glassy polymer poly(vinyl alcohol) whose network structure was modified by cross-linking with glutaraldehyde. The aim of this study was to investigate methods of modification of drug release from micromatrices containing a reasonable amount of medicament.

MATERIALS AND METHODS

Chemicals. The two model drugs proxyphylline and

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theophylline were kindly supplied by Zyma, Nyon, Switzerland. Three types of poly(vinyl alcohol), henceforth referred to as PVA, were received from Du Pont de Nemours, Wilmington, Del. (Elvanol 71-30), and from Hoechst, Frankfurt, Federal Republic of Germany (Mowiol 40-88 and 66-100). Their characteristics as supplied by the manufacturers are shown in Table I. The term "degree of hydrolysis" indicates to what extent the starting polymer, poly(vinyl acetate), has been hydrolyzed in order to obtain PVA. In agreement with common chemical terminology, however, we prefer the term "degree of esterification" simply given by 100% − degree of hydrolysis; in this contribution, we therefore refer to nonesterified and partially esterified PVA. All other chemicals used were commercial reagent-grade products.

Cross-Linking Procedure for PVA and Micromatrix Preparation. The cross-linking of PVA was accomplished by glutaraldehyde following the method described by Korsmeyer and Peppas (13). Typically, PVA powder was dissolved in hot water at 80–90°C and its concentration adjusted to 10%. After cooling to room temperature, 100 g of the 10% PVA solution was mixed with 20 g of a 50% aqueous solution of methanol (quencher for the reaction), 30 g of a 10% aqueous solution of acetic acid, and 10 g of a 1% aqueous solution of sulfuric acid (used as a catalyst). The drug was then dissolved in this mixture and a desirable amount of the cross-linking agent (25% aqueous glutaraldehyde solution, Merck, Darmstadt, Federal Republic of Germany) was added. This amount was dependent upon the desirable polymer cross-linking ratio, X, defined as the number of moles of cross-linking agent per mole of PVA repeating unit. The reactants were stirred thoroughly and the mixture was poured into petri dishes to obtain polymer disks about 3–4 mm in thickness. The petri dishes were sealed with plastic foil to prevent evaporation.

The samples with a cross-linking ratio higher than 0.1 were initially kept at room temperature for 12 hr and then heat treated at 60°C for 6 hr in order to promote cross-linking. The samples with a cross-linking ratio lower than 0.1 were directly heated at 60°C for 12 hr. Upon completion of the reaction, the cross-linked hydrogels were cut into small slabs and dried to constant weight under vacuum at a temperature of about 40–50°C. The polymer was finally ground, and the particle fraction of 400–630 μm was separated by sieving and used for the drug release experiments.

Polymer Characterization. The hydrogels produced were characterized by calculating the number average molecular weight between cross-links, $\bar{M}_c$, via swelling measurements at 37°C. In a typical swelling experiment, a thin slice of polymer was cut off the cross-linked material immediately after reaction, and its relaxed volume, V_r (volume at which cross-links were introduced) was determined by weighing it in air and in toluene (buoyancy effect). The specimen was then placed in distilled water at 37°C and swollen for about 3 weeks until thermodynamic equilibrium was reached. The equilibrium swollen volume of the specimen, V_s, was determined in a way analogous to V_r. Finally, the samples were dried and the weight of polymer, W_p, was measured. This procedure allowed the calculation of the volume fraction of polymer in the relaxed, $v_{2,r}$, and in the swollen state, $v_{2,s}$:

$$v_{2,r} = \frac{W_p}{\rho_p V_r} \tag{1}$$

$$v_{2,s} = \frac{W_p}{\rho_p V_s} \tag{2}$$

Here ρ_p is the polymer density (1.269 g cm^{-3} for PVA). The parameter $\bar{M}_c$ was determined by the equation developed by Bray and Merrill (22) for gels cross-linked in the presence of a solvent:

$$\frac{1}{\bar{M}_c} = \frac{2}{\bar{M}_n} - \frac{\bar{v}/V_1[\ln(1 - v_{2,s}) + v_{2,s} + \chi v_{2,s}^2]}{v_{2,r}[(v_{2,s}/v_{2,r})^{1/3} - \frac{1}{2}(v_{2,s}/v_{2,r})]} \tag{3}$$

Here, $\bar{M}_n$ is the number average molecular weight of the uncross-linked PVA (see Table I), $\bar{v}$ is the polymer specific volume (0.788 cm^3 g^{-1} for PVA), V_1 is the molar volume of the solvent (18 cm^3 mol^{-1} for water), and χ is the polymer–solvent interaction parameter. The latter parameter is a function of temperature and polymer volume fraction, $v_{2,s}$. At 37°C, χ varies between 0.484 for $v_{2,s} = 0.04$ and 0.504 for $v_{2,s} = 0.12$ (23). For polymer volume fractions higher than 0.20, a limiting value of $\chi = 0.51$ was extrapolated from Peppas' data and adopted for our calculations.

Other cross-linking parameters can also be calculated, such as the equilibrium volume swelling ratio, Q, and the average mesh size expressed by the root mean square end-to-end distance between two cross-links in the swollen state, $(\bar{r}^2)^{1/2}$:

$$Q = \frac{1}{v_{2,s}} \tag{4}$$

$$(\bar{r}^2)^{1/2} = l\, n^{1/2} \left[\frac{1 - \cos\theta}{1 + \cos\theta}\right]^{1/2} Q^{1/3} \tag{5}$$

Here, l is the C–C bond length (1.54 Å), n is the number of C–C bonds of each chain between two cross-links, and θ is the angle formed by a C–C bond (109.5°). Lacking precise indications about the rotation angle in a PVA chain, Eq. (5) for freely rotating chains was applied.

Residue Content. Sulfuric acid and glutaraldehyde content in the cross-linked polymer was determined for thoroughly washed and unwashed samples. The extraction process took place with 1 g of cross-linked material placed in 20.0 ml of water at 6°C for 7 days. At this temperature polymer swelling is increased, which allows a rapid and complete release of the residues. The sulfate was assayed by high-performance ionic chromatography (mobile phase, phthalate buffer of pH 4) using conductimetric detection (Wescan

Table I. Characteristics of PVA Samples Used

PVA grade	Degree of hydrolysis (%)	Molecular weight	
		$\bar{M}_n$[a]	$\bar{M}_w$[b]
Elvanol 71-30	99.0–99.8	52,800	113,000
Mowiol 40-88	86.7–88.7	—	127,400
Mowiol 66-100	99.3–99.9	—	224,400

[a] Number-average molecular weight.
[b] Weight-average molecular weight.

Table II. Macromolecular Network Characteristics of the Cross-Linked PVA Samples and Drug Loading in the Micromatrices

PVA grade	X (mol/mol)	$\overline{M}_c$[a]	Q (cm³/cm³)	$(\bar{r}^2)^{1/2}$ (Å)	Fractional drug loading, w_m	
					Calculated[b]	Experimental
		Cross-linking in the absence of drug				
Elvanol 71-30	0.01	5770 ± 160	18.76	95.4		
	0.05	1030 ± 40	6.04	27.6		
	0.10	770 ± 60	5.11	22.6		
	0.15	620 ± 50	4.61	19.6		
	0.20	480 ± 60	4.06	18.2		
Mowiol 40-88	0.20	220 ± 50	2.85	4.9		
Mowiol 66-100	0.20	240 ± 20	3.00	5.5		
		Cross-linking in the presence of proxyphylline				
Elvanol 71-30	0.01	4410 ± 360	16.85	80.6	0.363	0.333
	0.01	4470 ± 120	18.52	83.8	0.777	0.750
	0.20	260 ± 10	3.14	5.8	0.059	0.076
Mowiol 40-88	0.20	220 ± 50	3.00	4.9	0.108	0.132
	0.20	300 ± 10	3.42	6.8	0.282	0.280
Mowiol 66-100	0.20	300 ± 40	3.32	6.7	0.062	0.077
	0.20	310 ± 90	3.36	7.0	0.116	0.144
	0.20	500 ± 80	4.14	11.3	0.324	0.313
		Cross-linking in the presence of theophylline				
Elvanol 71-30	0.05	500 ± 30	4.15	11.3	0.048	0.053
	0.10	220 ± 40	2.95	5.0	0.030	0.040
	0.15	250 ± 20	3.12	5.7	0.031	0.039
	0.20	240 ± 40	3.00	5.5	0.014	0.023

[a] ±Standard deviation; $N = 4$.
[b] See Eq. (6).

Model 213, Santa Clara, Calif.). The glutaraldehyde was assayed colorimetrically as 2,4-dinitrophenylhydrazone (method B of Ref. 23).

Drug Release. A flow-through cell dissolution apparatus (Dissotest, Sotax, Basel, Switzerland), with a laminar flow rate of 20 ml min^{-1}, was used for the drug release experiments. All experiments were carried out in a pH 6.8 phosphate buffer (Ph. Helv. VI) at 37 ± 0.2°C. Cumulative drug release curves were obtained using an automatic flow-through UV spectrophotometer (Beckman, Model 35-7, Berkley, Calif.) and following the absorbance of proxyphylline at 273 nm and of theophylline at 271 nm.

RESULTS

Matrix Preparation. Polymer cross-linking using glutaraldehyde was performed in the presence of the drugs. A preliminary compatibility test between the two xanthine compounds and the glutaraldehyde under cross-linking conditions did not give evidence for any interactions. The proxyphylline content in the reaction mixture remained constant as assayed spectrophotometrically (accuracy within 0.4%). Furthermore, no by-products could be detected by thin-layer chromatography using silica gel 60 F_{254} (Merck) as stationary phase and the mixture chloroform–ethanol–acetic

Table III. Amounts of Sulfate and Glutaraldehyde Residues in Purified and Nonpurified Cross-Linked PVA Samples

PVA grade	Condition of preparation	Cross-linking degree, X (mol/mol)	Sulfate content (ppm)	Glutaraldehyde content (ppm)
Elvanol 71-30	Purified	0.05	55	<5
	Purified	0.20	146	12
Elvanol 71-30	Nonpurified	0.20	988	1512
Mowiol 66-100	Nonpurified	0.20	1050	1924

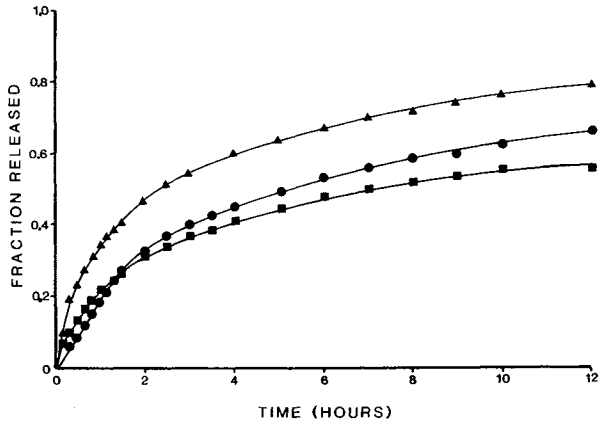

Fig. 1. Effect of the type of PVA on the release of proxyphylline from micromatrices cross-linked at a ratio, X, of 0.20 and loaded with 14% drug. Type of PVA: Elvanol 71-30 (▲); Mowiol 40-88 (■); Mowiol 66-100 (●).

acid (88 + 10 + 2) as mobile phase; a single spot corresponding to proxyphylline was detected by UV absorption at 254 nm and by iodine vapor (1).

The amount of drug which can be loaded into the polymeric material depends on three parameters, namely, the drug solubility in the initial cross-linking solution, the solvent volume fraction of the cross-linked hydrogel, $1-v_{2,r}$, and the drug partition coefficient between the polymer and the solution. The two latter parameters become important only if the cross-linking density is relatively high such that the network can not accommodate the entire volume of reaction liquid. This phenomenon of expelling solvent from a gel caused by contraction is known as syneresis. In our experimental systems, syneresis was observed for cross-linking ratios, X, equal to or higher than 0.05. For these samples, the drug content (weight fraction) in the final dried material, w_m, was calculated as

$$w_m = \frac{w_{sol}(1 - v_{2,r})}{v_{2,r} + w_{sol}(1 - v_{2,r})} \quad (6)$$

where w_{sol} is the weight fraction of the drug in the cross-linking solution. Equation (6) gives only an estimate of the actual drug content in the final polymer, as it assumes that the solute is distributed mainly in the solvent phase of the cross-linked material. Moreover, $v_{2,r}$, was determined for drug-loaded PVA samples, and hence its values are slightly higher than without drug. Nevertheless, Eq. (6) provides a rather meaningful tool for calculating drug loadings in the dried, cross-linked polymers (Table II).

Network Characteristics. Experimental values of the network parameters are reported in Table II. For the samples of Mowiol, the number average molecular weight, $\overline{M}_n$, was not known; it was estimated from the weight average molecular weight values, $\overline{M}_w$, (see Table I) assuming a polydispersity index of 2.14, identical to the one reported for Elvanol 71-30.

It can be noted that with increasing amount of cross-linking agent (expressed by the cross-linking ratio, X) the polymer becomes effectively more cross-linked as evidenced by the values of $\overline{M}_c$ and Q. In the absence of drug during the cross-linking reaction, a slightly less swellable material is obtained from the high molecular weight and acetyl group-containing polymers. This result does not, however, necessarily reflect a higher proportion of cross-linking sites in the Mowiol 40-88 and Mowiol 66-100 samples. The network characteristics as determined by swelling measurements depend not only on the number of cross-links but also on the entanglement of the macromolecular chains and the PVA–water interaction parameter, χ (2). Chain entanglement is generally enhanced with increased molecular weight of the uncross-linked PVA, resulting in a decreased network expansion. On the other hand, the interaction parameter, χ, is not known for the partially esterified PVA; in our studies, the value of the acetyl free polymer was adopted. In reality, Mowiol 40-88 is supposed to have a higher χ value, which would result in an increased molecular weight between cross-links, $\overline{M}_c$, as shown in Eq. (3).

The equilibrium volume swelling ratio, Q, varies from about 3 to 19, indicating that the swollen samples contain between 65 and 95% water. In the latter case, the hydrogels are extremely fragile.

The values for $(\bar{r}^2)^{1/2}$ give an approximate indication of the average distance between two cross-links and, consequently, of the average macromolecular mesh size in the swollen hydrogel. However, the exact mesh size can vary significantly in the same network, and the chains between two cross-linking sites oscillate around a mean position. Therefore, the free space available for any solute transport can greatly change from one mesh to another in the network or during time.

Residues. Among the reactive agents used for cross-linking, sulfuric acid and glutaraldehyde are not desirable in pharmaceutical dosage forms. Due to the preparation method used, their elimination is not possible without the concomitant loss of drug. In the nonpurified polymers, a

Table IV. Apparent Diffusion Coefficient and Time Parameters of Proxyphylline Released from PVA Micromatrices with a Cross-Linking Ratio, X, of 0.2 mol/mol

PVA grade	Drug loading (wt%)	$D_i \times 10^{9a}$ (cm^2 sec^{-1})	Time parameter (min)	
			$t_{50\%}$	$t_{75\%}$
Elvanol 71-30	14.2	5.53 ± 0.33[b]	145	570
Mowiol 40-88	13.2	2.19 ± 0.13	420	>720
Mowiol 66-100	14.4	1.49 ± 0.03	310	>720

[a] From Eq. (7).
[b] Confidence limits for $P = 0.95$.

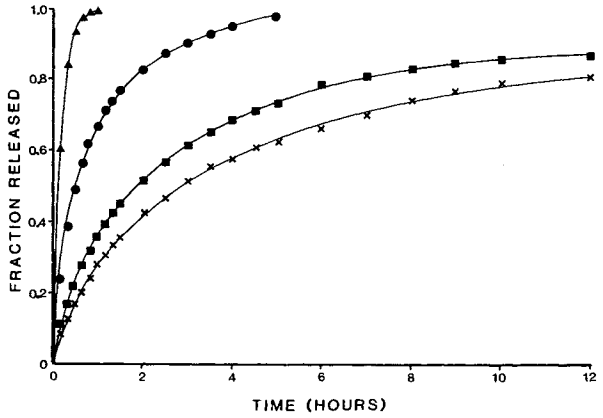

Fig. 2. Effect of the cross-linking ratio on the release of theophylline from micromatrices produced from Elvanol 71-30 and loaded with 4% drug. Cross-linking ratio, X: 0.05 (▲); 0.10 (●); 0.15 (■); 0.20 (x).

relatively substantial amount of sulfate and glutaraldehyde is present as shown in Table III; this may not be acceptable for a drug delivery system. The sulfate content is about 50% of the value expected according to Eq. (6). Hence, a certain portion of the acid is apparently eliminated during the drying process.

The residual glutaraldehyde content represents only about 0.5–0.7% of the initial amount in the reaction mixture. Therefore, most of the cross-linking agent has reacted with the polymer and virtually no alteration of the network structure by aging is likely to occur.

For comparison, some unloaded gels were thoroughly washed for 3 days immediately after cross-linking and assayed for the aforementioned reactive agents. Glutaraldehyde was almost completely eliminated as shown in Table III, whereas a considerable amount of sulfate could still be found in the gels. Thus, it appears that in the highly cross-linked hydrogels, diffusion is very slow, and it would require a longer washing process in order to eliminate entirely any sulfate ions.

Drug Release from the Micromatrices. Among the various parameters that could affect drug delivery, the type of PVA, the cross-linking ratio X, and the amount and type of drug contained in the matrices were studied here.

Due to the irregular shape and the ill-defined size distribution of the particles, we renounced to determine whether drug delivery was a Fickian or non-Fickian process. Ritger and Peppas (25,26) have recently shown that these two geometric parameters considerably affect this type of analysis. However, based on the observation that the time for water penetration into the micromatrices and the related rubbery-to-glassy state transition of the PVA was short (of the order of 20 to 40 min) compared to the time required for drug delivery (over 12 hr), we can reasonably assume that drug release from the matrices is essentially diffusion controlled. Therefore, we determined the apparent drug diffusion coefficient in the hydrogel, D_i, using the simplified diffusion equation for drug release from spherical matrices (27):

$$\frac{M_t}{M_\infty} = 6\left[\frac{D_i t}{\pi r^2}\right]^{1/2} - \frac{3D_i t}{r^2} \qquad (7)$$

The fractional release, M_t/M_∞, between 0 and 0.4 was considered, and an average mean radius, r, of the swollen particles of 250 μm was assumed. The reader should notice that, due to the irregular shape of the particles, the determined D_i values are estimates.

As mentioned earlier, solute transport through cross-linked polymer essentially depends on the network structure. This can be described by various parameters such as chain entanglement, degree of branching (side groups), and degree of cross-linking. In Fig. 1, we observe a prolonging effect on drug release of an increased molecular weight and the presence of acetyl side groups. This can be explained by the lower equilibrium swelling of these two samples compared to the Elvanol 71-30 hydrogel. Beside this swelling effect, the residual acetyl groups in the Mowiol 40-88 sample might sterically hinder drug diffusion, resulting in the particularly low release rate.

The values of the apparent diffusion coefficient reported in Table IV are particularly low and typical for highly cross-linked networks. The $t_{50\%}$ and $t_{75\%}$ values give more evidence of the prolongation of drug delivery from the high molecular weight and partially esterified PVA samples.

The effect of the cross-linking degree, X, on drug release is shown in Fig. 2. Evidently, an increasing X results in lower release rates. This contrasts with the findings from the equilibrium swelling measurements, which did not reveal any significant difference among the samples cross-linked at X ratios of 0.1, 0.15, and 0.2. This, however, is not especially surprising, as the residual glutaraldehyde most probably continues cross-linking during the drying process. On the

Table V. Apparent Diffusion Coefficient and Time Parameters of Theophylline Released from PVA Micromatrices Prepared from Elvanol 71-30

Cross-linking ratio, X (mol/mol)	Drug loading (wt%)	$D_i \times 10^{9a}$ (cm^2 sec^{-1})	Time parameter (min)	
			$t_{50\%}$	$t_{75\%}$
0.05	5.3	—[b]	6	15
0.10	4.0	—[b]	30	84
0.15	2.9	1.12 ± 0.07[c]	110	330
0.20	4.0	0.64 ± 0.05	175	520

[a] From Eq. (7).
[b] Could not be determined because of fast drug release.
[c] Confidence limits for $P = 0.95$.

other hand, the equilibrium swelling measurements were made before drying the gels, and therefore, they do not account for any further cross-linking during drying.

Table V shows the release parameters of theophylline from the cross-linked Elvanol 71-30 micromatrices. The apparent diffusion coefficient of theophylline in the sample cross-linked at $X = 0.2$ is about five times lower than that of proxyphylline in the same material, despite the similar molecular weights of these two drugs (see Table IV). This difference must be due to the different drug loading in the matrices. The $t_{50\%}$ and $t_{75\%}$ indicate that only the highly cross-linked samples ($X = 0.15$ and 0.2) give reasonably prolonged drug release in view of oral medication.

Figure 3 demonstrates the importance of the amount of drug contained in the micromatrices. From a practical point of view, this aspect is of great importance, as prolonged drug delivery systems often contain high doses of medicament. At loadings of 30 and 40%, drug delivery becomes very fast and the polymeric network structure can not act as an efficient diffusional barrier anymore.

For comparison, the effect of theophylline loading in the monoliths was also studied. Due to its relatively moderate solubility in the reaction mixture, a maximum theophylline content of 5.7% was attained in the matrices. As for proxyphylline, theophylline was released at a faster rate as the loading increased as seen in Table VI. The diffusion coefficient at a loading of 5.7% is very close to the value obtained for proxyphylline at a loading of 7.6% in the same hydrogel, which was 1.53×10^{-9} cm^2 sec^{-1} (1).

DISCUSSION

Various comments have to be made on the relationship between polymeric network characteristics and drug release from cross-linked PVA micromatrices. Network parameters such as $\bar{M}_c$, Q, and $(\bar{r}^2)^{1/2}$ were determined by swelling measurements; this is a simple though time-consuming method. It may indeed take several weeks until swelling is at equilibrium and, again, several weeks until the samples are completely dry. This second process is particularly slow in highly cross-linked polymers where the free space for water diffusion is reduced. Toward the final stage of drying, the temperature must be increased from approximately 40 to 75°C in order to maintain the polymer in its rubbery state (T_g for anhydrous PVA is about 80°C) and, hence, to facilitate solvent diffusion.

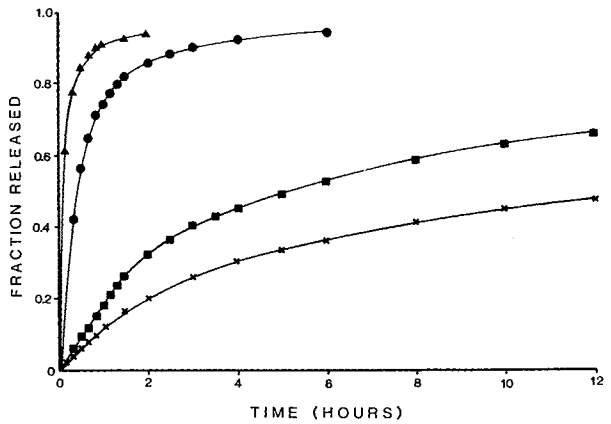

Fig. 3. Effect of drug loading on the release of proxyphylline from micromatrices prepared from Mowiol 66-100 cross-linked at a ratio, X, of 0.2. Drug loading: 7.7% (▲); 14.2% (●); 31.3% (■); 43.8% (x).

Table VI. Apparent Diffusion Coefficient and Time Parameters of Theophylline Released from PVA Micromatrices Prepared from Elvanol 71-30 Cross-Linked at a Ratio, X, of 0.2 mol/mol

Drug loading (wt%)	$D_i \times 10^{9a}$ (cm^2 sec^{-1})	Time parameter (min)	
		$t_{50\%}$	$t_{75\%}$
2.3	1.87 ± 0.08[b]	250	>720
4.0	1.70 ± 0.03	175	520
5.7	1.59 ± 0.05	130	430

[a] From Eq. (7).
[b] Confidence limits for $P = 0.95$.

The reader should note that two major assumptions have to be made in order to calculate $\bar{M}_c$ (2). The first concerns the additivity of volumes of water and polymer in the swollen hydrogel as expressed by Eqs. (1) and (2). The second is that the chains between cross-links are long enough ($\bar{M}_c > 4400$) for Gaussian chain distribution analysis to be applied, as assumed by Eq. (3). For most of the samples these two assumptions are not quite correct. In this work, however, the knowledge of exact $\bar{M}_c$ values is of lesser importance.

A moderate concentration of drug in the reaction mixture (lower than 6%, corresponding to w_m values lower than 0.15) does not appear to hinder the polymer cross-linking. In the case of Elvanol 71-30, $\bar{M}_c$ is even lower if the reaction takes place with proxyphylline or theophylline present. In contrast, higher drug concentrations (higher than 10%, corresponding to w_m values higher than 0.2) seem to have a slight hindering effect on cross-linking, except for the samples where no syneresis occurs (Elvanol 71-30 with $X = 0.01$). The present results do not provide enough evidence to explain the relatively minor influence of the drug presence on network formation. Nonetheless, swelling studies in aqueous solutions of theophylline and proxyphylline showed that a salting-out effect of these two drugs on the polymer can be excluded.

Swelling measurements are a relatively simple means to characterize cross-linked polymer networks and can be helpful in the interpretation of diffusional transport processes through the macromolecular material.

The presence of residual reactive agents in the micromatrices is certainly the major drawback of the directly loaded system which can not be purified. However, subsequent experiments have also shown that acetic acid can be omitted and the sulfuric acid concentration in the reaction mixture decreased from 0.07 to 0.03% without modifying the extent of reaction. For the cross-linking agent, its aldehyde function could be chemically reduced and inactivated completely by bisulfites.

From the release data we observe that cross-linking a linear polymer is undoubtedly a most effective way to reduce the transport rate of solutes in the macromolecular material. The higher the degree of cross-linking is, the smaller the mesh size of the three-dimensional network and hence the

free space for diffusion becomes (28). We have previously shown (8) that large solutes can permeate through swollen networks only if the mesh size is above a certain threshold value. For smaller solutes, such as those used in this work, a cutoff effect of cross-linked polymers has not been reported yet.

From a practical point of view, the amount of drug contained in a prolonged drug delivery system is an important aspect. Several investigators have shown that an increased drug content increases the rate and modifies the mechanism of drug release (10,11,16,17,29). This observation has been confirmed by this study, where loadings higher than 20% are shown to have a particularly marked effect.

In conclusion, drug release from swellable micromatrices can be controlled only if the polymeric substrate is highly cross-linked and drug loading is relatively low. In such dense networks, drug delivery is mainly diffusion controlled.

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