International Journal of Pharmaceutics, 26 (1985) 45–55
Elsevier

IJP 00868

Pilocarpine release from matrices of alkyl half-esters of poly(vinyl methyl ether/maleic anhydride)

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(Received February 27th, 1985)
(Modified version received March 27th, 1985)
(Accepted April 19th, 1985)

Key words: pilocarpine – half-esters of PVM/MA – drug release – polymer matrices – poly(vinyl methyl ether/maleic anhydride)

Summary

Alkyl half-esters of poly(vinyl methyl ether/maleic anhydride) (PVM/MA) have been suggested as possible matrix polymers for the erosion-controlled delivery of highly water-soluble drugs. Ethyl, propyl and butyl half-esters of PVM/MA were synthetized and solvent cast with and without a water-soluble drug, pilocarpine hydrochloride. Dissolution of the polymers and release of pilocarpine from the matrices were studied in 1.3 mM and in 66.7 mM phosphate buffers with initial pH of 7.4. Pilocarpine release and polymer dissolution were faster from matrices of ethyl half-esters than from propyl and butyl half-esters of PVM/MA, which were in this respect similar. The only exception was that pilocarpine was released faster from propyl than from butyl half-ester of PVM/MA in 1.3 mM phosphate buffer. The half-esters were dissolved from the matrices at a slower proportional rate than pilocarpine was. This caused a decrease in the drug concentration of the undissolved matrix portion. Pilocarpine was released at a constant rate from butyl half-ester matrices; but from ethyl and propyl half-esters, pilocarpine was released at decreasing rates. In drug release from half-ester matrices, diffusional leaching was significantly increased with increasing hydrophilicity of the matrix and decreasing size of the alkyl ester group. The constant rate of drug release from butyl half-ester matrices was probably due to Case II transport, i.e. drug release was controlled by the constant rate of solvent-induced polymer relaxations in the matrices. The rates of pilocarpine release and polymer dissolution were decreased by diminishing the

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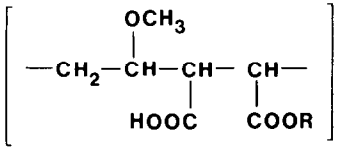
concentration of phosphate buffer. At the same time diffusional leaching was increased.

Introduction

Alkyl half-esters of poly(vinyl methyl ether/maleic anhydride) (PVM/MA) have been used in pharmaceutics for film-coating of tablets (Lappas and McKeehan, 1965 and 1967) and in compressed and cast polymer matrices (Woodruff et al., 1972; Heller et al., 1978). These polymers contain two essential components: a solubilizing carboxylic group and a hydrophobic ester group. The chemical structure of the alkyl half-esters of PVM/MA is shown below (R = alkyl group).



Half-esters of PVM/MA become water-soluble when a large enough fraction of the carboxylic groups of the polymer surface is in ionized form, while the hydrophobic ester group retards penetration of water into the polymeric material (Heller et al., 1978). The ionized fraction of carboxylic groups needed in dissolution of the polymer depends on the size of the neighbouring ester group; the larger the ester group, the larger is the needed fraction (Heller et al., 1978). As the pK_a-value of the polyacid in water is 6.0 (Heller et al., 1978), each alkyl ester has a characteristic pH of dissolution above which it is soluble. The pH of dissolution is increased and the rate of polymer dissolution decreased with increased length of the alkyl ester (Lappas and McKeehan, 1965; Woodruff et al., 1972; Heller et al., 1978). When the alkyl ester group is smaller than $C_{10}H_{21}$, the polymers are water-soluble at pH 7.4; and thus they can be used in fabrication of bioerodible polymer matrices.

Local ophthalmic drug treatment is one area of therapeutics in which bioerodible matrices can be utilized. For example, the poor ocular absorption of a topically applied anti-glaucoma drug, pilocarpine, has been increased by administering the drug in soluble hydrophilic polymer matrices instead of eye drops (Saettone et al., 1984; Urtti et al., 1984). Highly water-soluble pilocarpine, however, is rapidly diffused from hydrophilic matrices (Harwood and Schwartz, 1982; Urtti et al., 1985a). Consequently, the drug is delivered into the eye as prolonged pulse-entry (i.e. peak concentrations of the drug and dose-related side-effects are increased) (Urtti et al., 1984). By using delivery systems that release pilocarpine at a slow constant rate, the unnecessary high peak concentrations of the drug can be avoided in the eye (Sendelbeck et al., 1975) and in the general circulation as well (Urtti et al., 1985b). The diffusional release of drugs from water-soluble polymer matrices can be retarded, e.g., by increasing the molecular weight or the cross-linking density of the polymer (Korsmeyer and Peppas, 1981; Harwood and Schwartz, 1982; Urtti et al., 1985a). At the same time, however, water solubility of the polymer decreases and a

"ghost matrix" without drug remains in the conjunctival fornix for a long time after the drug has been released. Matrices from which drug and polymer dissolve at slow constant rates, would seem to be potentially promising bioerodible systems of drug delivery for ophthalmic use.

In the study of Heller et al. (1978) hydrocortisone was released from the matrices of alkyl half-esters of PVM/MA at a constant rate, which was controlled only by the dissolution rate of the polymer, i.e. hydrocortisone and polymer dissolved at the same rate. They dissolved only from the matrix surface and hydrocortisone did not diffuse from the undissolved portion of the matrix. Release by slow dissolution of polymer surface is an interesting approach, especially for delivery of highly water-soluble drugs, because they are rapidly leached from matrices of hydrophilic water-soluble polymers.

Previously our group reported a zero-order release of highly water-soluble pilocarpine hydrochloride from matrices of *n*-butyl half-ester of PVM/MA (Urtti et al., 1985b). Release characteristics of highly water-soluble drugs from matrices of alkyl half-esters of PVM/MA have still not been studied in detail. The aim of this study was to characterize the release kinetics of pilocarpine hydrochloride from matrices of ethyl, propyl and butyl half-esters of PVM/MA.

Materials and Methods

Materials

Pilocarpine hydrochloride (Pharmaceutical Manufacturers Star, Tampere, Finland) was used as a water-soluble model drug in the matrices. [^{3}H]G-Pilocarpine in ethanol solvent (spec. act. > 1 Ci/mmol) was obtained commercially (Radiochemical Centre, Amersham, U.K.). The radiochemical purity of the tracer was 98%. The molecular weight of PVM/MA (Aldrich Chemicals, Milwaukee, WI, U.S.A.) was about 360,000. Molecular weight was calculated from the relative viscosity (1.75) of 1% PVM/MA solution in methyl ethyl ketone (Woodruff et al., 1972). Ethanol (Oy Alko Ab, Finland), *n*-propanol (E. Merck, Darmstadt, F.R.G.) and *n*-butanol (E. Merck, Darmstadt, F.R.G.) were all of reagent grade.

Methods

Half-esterification of PVM/MA. About 10 g PVM/MA was placed in an excess (300 ml) of *n*-alkanol. The mixture was heated at the reflux temperature of each *n*-alkanol used. The reaction times needed for half-esterification were investigated in preliminary tests using infra-red spectroscopy (Heilman, 1974; Heller et al., 1978). The decrease of the anhydride peak (1780 cm^{-1}) and the increase of the ester peak (1725 cm^{-1}) were followed until they no longer changed. In an excess of *n*-alkanol the reaction continues until the anhydride is half-esterified. More than 50% esterification is obtained only with the help of a mineral acid catalyzer (Heller et al., 1978). The reaction times were 3 h for ethyl, 5 h for propyl and 5.5 h for butyl half-ester formation. After the reaction, the solution was cooled and precipitated by pouring it into cold petroleum ether. The precipitate was washed 3 times in boiling *n*-hexane, dried, and pulverized.

Degree of esterification was assessed quantitatively by titrating the product in an ethanol solution with 0.1 N NaOH until the phenolphthalein end-point (Lappas and McKeehan, 1965; Woodruff et al., 1972). The degree of esterification was 42.8% for ethyl, 47.1% for propyl and 49.1% for butyl ester.

Preparation of the films. The drug–polymer films were prepared by the solvent casting method. With this method 2.5 g of the half-ester, 0.5 g of pilocarpine hydrochloride and [^{3}H]pilocarpine tracer (10–50 nCi/mg of pilocarpine hydrochloride) were dissolved in acetone : methanol (1 : 1) mixture and poured on teflon-coated petri dishes. The solvent was allowed to evaporate overnight, and circular matrices (diameter 13 mm) were cut from the remaining films with a cork borer. Unmedicated matrices of half-esters of PVM/MA were cast similarly, except that 3 g of the polymer was used.

Test procedures. The matrices were stored in a desiccator until their weights had equilibrated. After that, the matrices were mounted on a glass microscope slide with silicone vacuum grease. The release of pilocarpine hydrochloride to 1.3 mM and 66.7 mM phosphate buffers (pH 7.4) was studied using the methods described in a previous publication (Urtti et al., 1985a). The pH of the release medium during drug release was measured with a digital pH meter.

Dissolution of unmedicated matrices of half-esters of PVM/MA was studied using a test procedure similar to that used in the release studies. Instead of 500 μl, however, samples of 3 ml were withdrawn. The polymer concentration of the samples was measured with a double beam spectrophotometer (Hitachi 220, Tokyo, Japan) at a wavelength of 216 nm.

Concentrations of water and pilocarpine in the undissolved portions of the matrices during drug release were studied in a separate test but using a test arrangement similar to that used in the study of pilocarpine release from the matrices. The matrices were removed from the release medium at fixed times and placed between dried and preweighed Whatman GF/B filters, which were then weighed and dried in a desiccator until their weights equilibrated. Water contents of the samples were obtained from their weight losses during storage in a desiccator. Pilocarpine concentrations of the dried samples were analyzed by first dissolving the dried samples in 0.5 N NaOH. Samples of 500 μl were withdrawn from the solution, and 4.5 ml of scintillation liquid (Lumagel, Lumac, Schaesberg, The Netherlands) which contained 10% 1 N hydrochloric acid, was added. Radioactivity was measured with a liquid scintillation counter (Rackbeta 1216, LKB Wallac, Turku, Finland).

Analysis of the results. Drug release from polymer matrices can be described by plotting the logarithm for the amount of released drug against the logarithm of time (Schwartz et al., 1968; Korsmeyer and Peppas, 1981). The slope of the log–log plot (k) is a parameter that characterizes the mechanism of solute release from a matrix. The values of k and t_{50} (time required for 50% of the drug to be released) were solved from log–log plots using linear regression lines of the least squares. The t_{50}-values were used to compare the rates of pilocarpine release from different matrices.

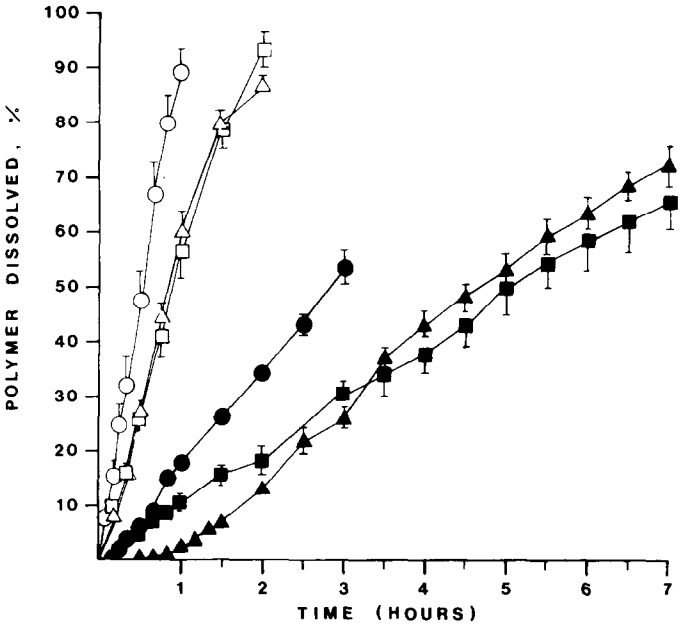


Fig. 1. Dissolution of the polymers from unmedicated matrices of ethyl (circles), propyl (squares) and butyl (triangles) half-esters of PVM/MA in 1.3 mM (closed symbols) and in 66.7 mM (open symbols) phosphate buffer solutions with initial pH of 7.4. Means ± S.E. are presented.

Results and Discussion

Dissolution of polymers

In both 1.3 mM and 66.7 mM phosphate buffers, the ethyl half-ester of PVM/MA was dissolved faster than the propyl and butyl half-esters were (Fig. 1). Propyl and butyl half-esters of PVM/MA were dissolved at about the same rate; but in a 1.3 mM buffer solution, dissolution of butyl half-ester started only after a lag time of about 50 min (Fig. 1). Ethyl half-ester was dissolved faster than propyl and butyl esters because its dissolution pH and the fraction of ionized carboxylic groups needed for polymer dissolution are lower than those for the propyl and butyl half-esters of PVM/MA (Woodruff et al., 1972; Heller et al., 1978). For ethyl, propyl and butyl half-esters of PVM/MA the dissolution pH is 4.3, 4.9 and 5.0, respectively (Woodruff et al., 1972).

All half-esters of PVM/MA were dissolved faster in 66.7 mM than in 1.3 mM phosphate buffer (Fig. 1). In 1.3 mM but not in 66.7 mM phosphate buffer the pH of the solution decreased during dissolution of polymers and pilocarpine hydrochloride in the release study. During whole dissolution period, the pH of the 1.3 mM buffer solution was decreased 0.8 units by ethyl, 1.1 units by propyl and 0.9 units by butyl half-esters of PVM/MA and pilocarpine hydrochloride. Dissolution times were 3 h for ethyl and 7 h for propyl and butyl half-ester matrices. The amount of released pilocarpine decreased the pH by less than 0.1 units. Thus the decreased pH can be considered to be due to dissolution of the polymers.

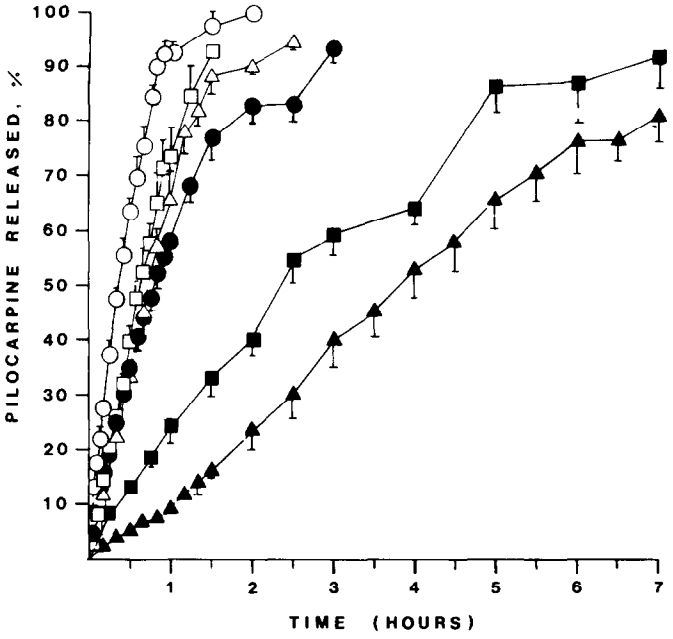


Fig. 2. Pilocarpine release (%) from matrices of alkyl half-esters of PVM/MA in phosphate buffer solutions. Means ± S.E. are presented. For symbols see legend to Fig. 1.

Decreased pH was not the main reason for the large difference in rates of polymer dissolution (Fig. 1) and pilocarpine release (Fig. 2) between two buffer solutions. If it had been, the half-ester polymers would initially have dissolved at the same rate in 1.3 mM and in 66.7 mM phosphate buffers, and the dissolution rate would then have decreased in 1.3 mM buffer with decreasing pH. The dissolution rates, however, were already different at the beginning of dissolution and did not decrease significantly during the experiment (Fig. 1).

The different rates of polymer dissolution in 1.3 mM and 66.7 mM phosphate buffers were due rather to different capacities of the buffer solutions to transfer hydrogen ions (H^+) from the polymer surface to bulk solution. During polymer dissolution, hydrogen ions, if not transferred away, accumulate in the polymer surface and block further ionization of the polymer when the dissolution pH of the polymer is reached at the surface of the matrix (Heller et al., 1978). In addition to their normal diffusion, H^+-ions are coupled with the buffer and carried to the bulk solution, where they are released. Thus increased buffer concentration accelerates transfer of the hydrogen ions from the polymer surface to the bulk solution. At the same time, the ionization rate of the polymer surface and the diffusion of polymer anions (P^-) to the bulk solution are increased, because polymer anions are diffused from the polymer surface to the bulk solution by the requirement of charge neutrality (Heller et al., 1978). The significance of buffer concentration on polymer dissolution has already been demonstrated by Heller et al. (1978). In phosphate buffer concentrations of 0.008 M and 0.1 M with a pH of 7.0, the observed

TABLE 1

RELEASE OF PILOCARPINE FROM MATRICES OF ALKYL HALF-ESTERS OF PVM/MA IN 66.7 mM (A) AND 1.3 mM PHOSPHATE BUFFERS (B)

Slopes of log (pilocarpine released) vs log (time) plots (k), times for 50% release (t_{50}), and number of experiments (n) are presented. Values are means ± S.E. of n determinations.

Ester	Release medium	Pilocarpine		
		k	t_{50}	n
ethyl	A	0.798 ± 0.016	22.9 ± 1.2	10
	B	0.724 ± 0.033	51.1 ± 2.9	5
propyl	A	0.932 ± 0.017	41.5 ± 3.1	10
	B	0.766 ± 0.032	163.2 ± 14.1	5
butyl	A	0.985 ± 0.050	44.9 ± 3.0	5
	B	1.047 ± 0.026	254.9 ± 23.8	5

difference in dissolution rates of *n*-butyl half-ester of PVM/MA was about 5-fold, while increasing of the solution pH from 6.5 to 7.4 increased the rate of polymer dissolution only slightly.

Pilocarpine release

The rate of pilocarpine release decreased with increasing length of the alkyl ester and with decreasing buffer concentration, except that the rates of pilocarpine release from propyl and butyl half-esters in 66.7 mM phosphate buffer were about the same (Fig. 2, Table 1).

If pilocarpine release were controlled only by the surface erosion of the matrix, as the release of hydrocortisone from half-esters of PVM/MA is (Heller et al., 1978), the concentration of pilocarpine per dry weight of the remaining matrix should not change. Release of pilocarpine from half-esters of PVM/MA does not seem to be controlled only by erosion of the matrix surface, as indicated by the decrease of pilocarpine concentration in the undissolved matrix portion (Fig. 3). This decrease was retarded by increased length of the alkyl ester group (Fig. 3). Correspondingly, water contents of the undissolved matrices were decreased with increasing length of the alkyl ester (Fig. 4). These results reflect the increased hydrophobicity of the polymers with increased length of the alkyl ester chain. During drug release, leaching of pilocarpine from the undissolved matrix portion apparently is increased by the increased hydrophilicity of the matrix.

A drug is released at a constant rate from the polymer matrix, when the release from a slab-shaped matrix is controlled only by the polymer dissolution of the matrix surface without dissolution in the bulk matrix (Hopfenberg, 1976). Nevertheless, a constant rate of drug release from polymer matrices and consequently slopes of log–log plots of unity ($k = 1.0$) are also achieved when the relaxations of the glassy polymer, which are a prerequisite for drug release, occur at constant rate that is much slower than the rate of drug diffusion (Hopfenberg and Hsu, 1978; Frisch, 1980). This kind of constant release kinetics is called Case II transport. If the rate of

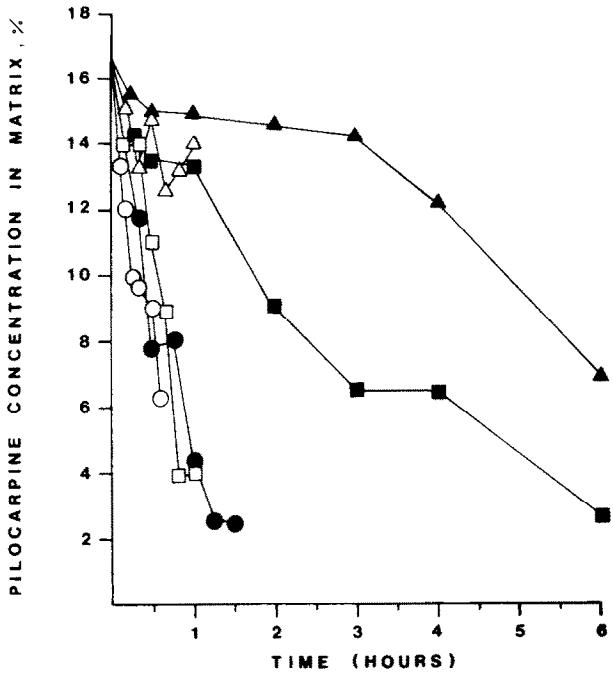


Fig. 3. Pilocarpine concentrations (percents of the matrix dry weight) of undissolved portions of polymer matrices during drug release. For symbols see legend to Fig. 1.

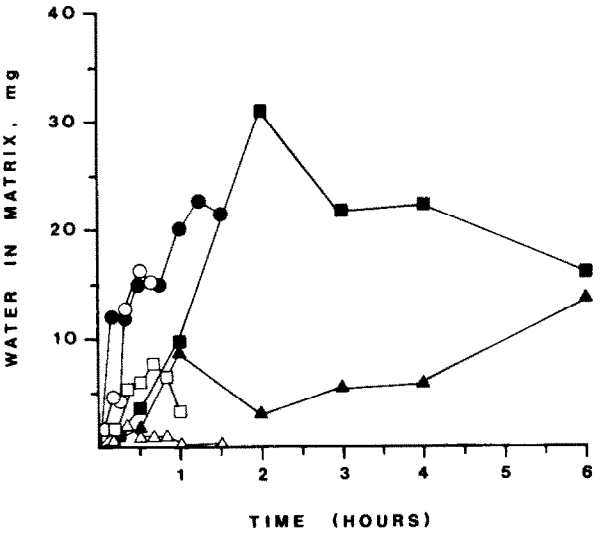


Fig. 4. Water contents (mg) of the undissolved portions of polymer matrices during drug release. For symbols see legend to Fig. 1.

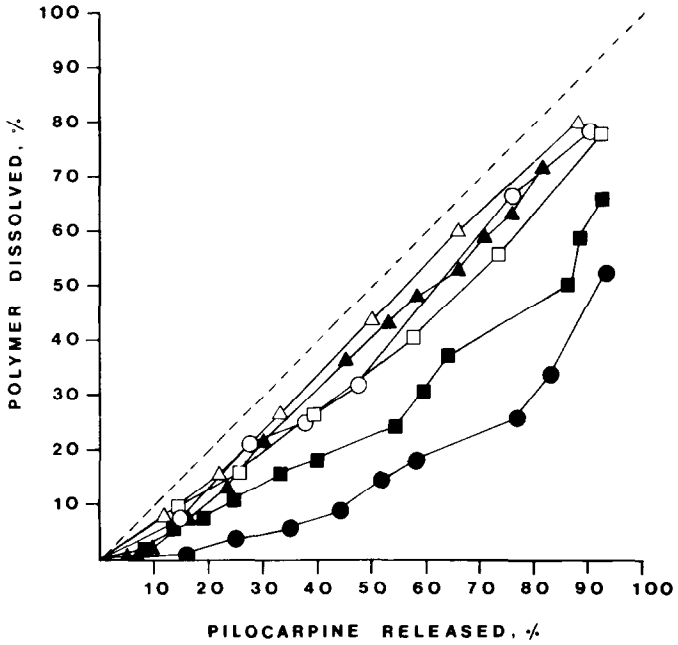


Fig. 5. Pilocarpine release vs dissolution of the half-ester polymers from unmedicated matrices. The dotted line represents the erosion-controlled drug release. For symbols see legend to Fig. 1.

drug diffusion is comparable to that of polymer relaxations, anomalous release behaviour with values of k between 0.5 and 1.0 are obtained (Frisch, 1980). Drug release by Fickian diffusion results in a k-value of 0.5.

In this study increased deviations from the constant rate of drug release were associated with increased matrix hydrophilicity and pilocarpine leaching. This was reflected as values of k below 1.0 (Table 1). Pilocarpine was released according to zero-order kinetics only from the matrices of butyl half-ester of PVM/MA (Table 1), but even in butyl half-ester matrices the pilocarpine concentration per dry weight of matrix was decreased (Fig. 3). There still seems to be a trend towards erosion-controlled zero-order release kinetics when the hydrophobicity of the matrix is increased (Table 1, Fig. 5). Apparently, in ethyl and propyl half-esters of PVM/MA neither Case II transport nor erosion-controlled release is obtained (Table 1, Fig. 5). In these cases pilocarpine release is a combination of drug diffusion, dissolution of the drug and polymer, and polymer chain relaxations induced by solvent penetration. In butyl half-ester matrices zero-order drug release was achieved and was probably due to release kinetics of the Case II transport type (Table 1, Fig. 5). In butyl half-esters solvent penetration was slower, and surface erosion of the matrices was relatively rapid in relation to solvent penetration, when compared to ethyl and propyl half-esters (Fig. 5). Compared to polymer relaxations, this accelerated the drug diffusion.

Release of pilocarpine from half-esters of PVM/MA deviated more from the erosion-controlled kinetics in 1.3 mM than in 66.7 mM phosphate buffer (Table 1,

Fig. 5). Also higher water contents of the undissolved matrices were obtained with 1.3 mM than with 66.7 mM buffer (Fig. 4). During the period of drug release the mean percentual concentrations ($\pm$S.E.) of water in undissolved matrices were for ethyl, propyl and butyl half-esters 11.4 ± 2.5, 5.7 ± 1.7 and 0.9 ± 0.2, respectively, in 66.7 mM and 17.6 ± 2.4, 20.2 ± 4.3, and 8.3 ± 1.8, respectively, in 1.3 mM buffer. Solvent penetration into the matrices apparently did not decrease with decreased buffer concentration in the same proportion as dissolution of the polymer surface did (Figs. 1 and 4). This caused the increased leaching of pilocarpine from the matrices. The buffer concentration of the dissolution medium seems to have a great effect on both the rate and mechanism of solute release from matrices of half-esters of PVM/MA.

The mechanism of pilocarpine release from matrices of half-esters of PVM/MA differed from that of hydrocortisone (Heller et al., 1978). The aqueous solvent also penetrated into the matrices of Heller et al. (1978), but the dispersed, poorly water-soluble hydrocortisone probably did not dissolve in the water in the matrices. Thus leaching of the drug was negligible, and drug release was erosion-controlled. In addition, the paper of Heller et al. (1978) reports constant erosion-controlled release of hydrocortisone from half-esters of PVM/MA only with *n*-butyl and longer alkyl ester groups. Whether erosion-controlled constant release of hydrocortisone is achieved with the ethyl or propyl half-esters or with alkyl half-esters in weak buffer solutions remains unclear.

Although the rates of pilocarpine release and dissolution of the half-esters from the matrices were comparable in vitro, "ghost" matrices remained after the drug had been released (Fig. 5). Larger "ghost" matrices remain after pilocarpine release in 1.3 mM than in 66.7 mM phosphate buffer (Fig. 5). Because the buffering capacity of tear fluid is low (Carney and Hill, 1979), the in vitro results with 1.3 mM buffer correspond better to the in vivo situation than do results with 66.7 mM buffer (Urtti et al., 1985b). Consequently, the erosion-controlled zero-order release of pilocarpine from half-esters of PVM/MA into the tear fluid is improbable. Case II transport, however, also seems possible in vivo and in that case the problem of "ghost" matrices is also smaller than with conventional cross-linked hydrophilic polymer matrices.

Acknowledgements

This study was supported by the Academy of Finland. I thank Ms. Lea Pirskanen for her skillful technical assistance, Ms. Rauni Laurila for her help during a preliminary experiment, and Professor Markku Juslin for helpful discussion during the study.

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