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Pilocarpine release from hydroxypropylcellulose–polyvinylpyrrolidone matrices

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Summary

Characteristics of pilocarpine release from cast plasticized hydroxypropylcellulose (HPC) and HPC–polyvinylpyrrolidone (PVP) matrices were studied using tritiated pilocarpine. Increased concentration of PVP and decreased molecular weight of HPC accelerated release of pilocarpine from the matrices. The aqueous solution penetrated rapidly into the matrices, which swelled rapidly to their equilibrium volumes. With increased molecular weight and concentration of HPC in the matrices, the rate of solvent penetration decreased and swollen volume of the matrix increased. Pilocarpine concentration also decreased in the ungelled cores of the matrices, indicating that the solvent had penetrated these cores. Solvent penetration alone did not control the rate of drug release, because penetration was at least twice as rapid as pilocarpine release. In the matrices without polymer dissolution, the best fits of the release data were obtained with diffusional square-root of time dependence, although relaxation of the polymers caused slight deviations from the Fickian diffusion. Thus the rate-limiting step of pilocarpine release was the diffusion of the drug from the matrix. The decreased rate of pilocarpine release with increased molecular weight and concentration of HPC was due to the decreased rate of drug diffusion from the matrix. Retardation of this diffusion was caused by the increased swelling of the matrix and decreased diffusivity of the drug. High initial concentration of PVP resulted in substantial deformation and attrition of the matrices.

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Pilocarpine release from these matrices was best fitted with the dissolutional cube-root and first-order equations.

Introduction

Hydrophilic polymer matrices are usually xerogels, which are penetrated by water when in contact with aqueous dissolution medium. Consequently, a gel layer is formed around the core, and the drug is dissolved in the penetrating fluid and diffused from the matrix. Traditionally, drug release from non-disintegrating polymer matrices has been described by the square-root of time approximation of Fickian diffusion (Buri and Doelker, 1980). Drug release from polymer matrices that are initially dry and glassy is, however, also affected by many factors other than drug diffusion. These include penetration of the aqueous solvent, swelling of the matrix, dissolution of the drug and polymers, and relaxation of the polymeric chains. Consequently, deviations from the square root of time dependence have been reported in release studies carried out using compressed (Gibaldi and Weintraub, 1968; Lapidus and Lordi, 1968; Touitou and Donbrow, 1982a) and cast hydrophilic polymer matrices (Korsmeyer and Peppas, 1981).

Ocular absorption of an antiglaucomatous agent, pilocarpine, is increased and duration of its ocular effects is prolonged when the drug is applied in soluble hydrophilic polymer matrices (Maichuk, 1975; Saettone et al., 1984; Urtti et al., 1985a). The characteristics of drug release from the polymer matrices affect both the absorption of pilocarpine into the eye (Saettone et al., 1984) and into the systemic circulation (Urtti et al., 1985b). Unmedicated HPC-matrices are used for treatment of keratitis sicca (Katz et al., 1978; Lacrisert, Merck, Sharp and Dohme) and they have been suggested as possible carriers of drugs as well (Harwood and Schwartz, 1982; Saettone et al., 1984; Urtti et al., 1985a-b).

The aim of this study was to describe the mechanism of release of a water-soluble model drug, pilocarpine, from HPC-matrices. The properties of the HPC-matrices were modified by adding another polymer, poly(vinylpyrrolidone) (PVP), to the matrices in varying proportions.

Materials and Methods

Materials

Free pilocarpine base (Pharmaceutical Manufacturer Star, Tampere, Finland) was used as a model drug in the matrices. [G-^{3}H]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%. HPC (Aldrich Chemicals, Milwaukee, WI, U.S.A.) with low (100,000; HPC-L) and medium (300,000; HPC-M) molecular weights and PVP K60 (MW 160,000; Fluka AG, Buchs SG, Switzerland) were used as matrix polymers. PVP was purchased and used as a 45% solution in water. Glycerin was added to matrices as a plasticizer.

Methods

Preparation of the matrices. Matrices with different proportions of low or medium molecular weight HPC and PVP K60 were prepared. Pilocarpine (0.425 g), glycerin (0.300 g) and polymers (HPC + PVP 2.275 g) were dissolved in methanol. Tracer (10–30 nCi/l mg of pilocarpine) was added and the solution was poured onto teflon-coated petri dishes, which were covered with filter papers to prevent too rapid evaporation of the solvent. The solvent was allowed to evaporate overnight at room temperature. Circular matrices (diameter 13 mm) were cut from the resulting films with a cork borer. The thicknesses of the matrices (0.318–0.430 mm) were measured with an electronic digital micrometer (Digitrix NSK 901-101 ED-25, Japan Micrometer Mfg.).

Test procedures. The matrices were dried in a desiccator until their weights equilibrated. After that the matrices were carefully pressed onto glass microscope slides with silicone vacuum grease ensuring that all edges adhered and no lubricant touched the outer surface of the matrices. Slides were immersed in 200 ml of salt solution at 32°C which had been adjusted to pH 7.4. The salt solution was composed of 0.49% sodium chloride, 0.075% potassium chloride, 0.03% magnesium chloride, 0.048% calcium chloride, 0.39% sodium acetate, and 0.19% sodium citrate in water. The solution was stirred with a magnetic stirrer. Samples of 500 μl were pipetted from the solution into liquid scintillation vials. Scintillation liquid (ACS, Radiochemical Centre Amersham) was added and the samples were stored for at least 12 h in darkness before counting. Radioactivities of the samples were counted using a liquid scintillation counter (Rackbeta 1216, LKB Wallac, Turku, Finland).

Solvent penetration into the matrices and their swelling were studied in test conditions similar to those for release of pilocarpine from the matrix. Besides the dried preweighed matrices, steel slabs with known dimensions were attached onto the microscope slides with silicone vacuum grease. The slides were removed at fixed times from the stirred salt solution and the matrices and steel slabs were photographed instantly from both planar and curved sides using a magnification of 1.5 in a 200 mm Medical-Nikkor (Nippon, Kogaku, Japan) objective. The gel portion and core of the matrix were readily separated with a spatula and placed between dried and preweighed Whatman GF/B filters, which were then weighed and dried in a desiccator until their weight reached equilibrium. Water contents of the samples were obtained from their weight loss during storage in a desiccator. The dried samples were dissolved in 0.5 N sodium hydroxide and their radioactivities measured using liquid scintillation counting.

The negatives of the films were reflected with a Durst M301 negative magnifier. The thicknesses and diameters of the matrices were measured from the magnified reflections. In each picture a steel slab with known dimensions was used as a control scale.

Hydrophilicities of the matrices were tested by measuring their water vapor absorption. Dried and preweighed HPC and HPC-PVP matrices were placed at room temperature above a saturated solution of ammonium chloride in a relative air humidity of 79.3%. The matrices were weighed 36 h later and their water contents were calculated from their weight increases.

Analysis of the results. One-sided diffusion-controlled release of water-soluble drugs from a slab-shaped polymer matrix that is capable of swelling obeys Eqn. 1 (Lapidus and Lordi, 1968; Touitou and Donbrow, 1982b):

$$Q = 2A \cdot \left(\frac{S}{V}\right)\left(\frac{D't}{\pi}\right)^{0.5} \quad (1)$$

where Q and A are the amounts of drug released at time t and infinity, respectively; S is the exposed surface area of the matrix; V is the volume of the swollen matrix; D′ is the effective diffusion coefficient of pilocarpine in the hydrated matrix. The value of D′ is $D_0 \cdot \epsilon/\tau$, where D_0 is the diffusion coefficient of the drug in water, ϵ is the porosity and τ the tortuosity of the hydrogel matrix. For highly water-soluble drugs like pilocarpine, the square-root of time approximation of Fickian diffusion (Eqn. 1) applies accurately only when $Q < 0.6A$ (Kim et al., 1980; Hutchison et al., 1981). Thus Q vs $t^{0.5}$ plots should be linear up to drug release of 60% when S/V-ratio remains constant and the rate of drug release is controlled by diffusion of the drug. S/V-ratios of the polymer matrices during the time scale of the release studies were calculated from the magnifications of the film negatives.

The slopes of the log(Q) vs log(t) plots were calculated from the linear regression lines of the least-squares using data points at which S/V-ratio remained constant and Q was less than 0.6A. When the slope of the log–log plot is 0.5, drug release is governed only by diffusion of the drug. Slopes above 0.5 indicate deviations from the Fickian diffusion.

The release data were fitted to the dissolutional cube-root (Hixson and Crowell, 1931; Eqn. 2) and first-order equations (Wagner, 1959; Eqn. 3) and to the diffusional square-root of time dependence (Eqn. 4; Touitou and Donbrow, 1982b).

$$\sqrt[3]{100} - \sqrt[3]{m} = bt + a \quad (2)$$

$$\ln(m) = -bt + a \quad (3)$$

$$100 - m = b\sqrt{t} + a \quad (4)$$

In these equations m designates percentage of undissolved pilocarpine; t is time; a is the intercept of the y-axis; and b is the slope. Eqns. 2–4 were fitted to the release data of the first 60% of pilocarpine release after equilibration of the S/V-ratio. After the values of a and b were calculated, the fits were compared according to the method of Bamba et al. (1979). The goodness of the fits was evaluated by their deviations from data points (Bennett and Franklin, 1954). The fitted values and actual data points were compared using Eqns. 5, 6 and 7 (Bamba et al., 1979).

$$m = \left(\sqrt[3]{100} - bt - a\right)^3 \quad (5)$$

$$m = e^a e^{-bt} \quad (6)$$

$$m = 100 - b\sqrt{t} - a \quad (7)$$

The sums of the squares of the deviations between the data points and the fit were calculated. Variance estimates were obtained by dividing the sums of the squares by the degrees of freedom, i.e. n − 2. Statistical significance of the differences between the accuracies of the fits for each formulation was tested with a one-sided *F*-test using the ratios of the variances (Armitage, 1971).

Results and Discussion

With an increased concentration of PVP in the matrices, release of pilocarpine from HPC and HPC-PVP matrices was accelerated (Fig. 1). The decreased molecular weight of HPC also increased the rate of pilocarpine release (Fig. 1). In most cases, pilocarpine was released from the matrices linearly with the square-root of time (Fig. 1). Substantial positive deviations from the square-root of the time relationship occurred when the fraction of PVP of the total polymer content was at least 40% in HPC-L and at least 60% in HPC-M matrices. We analyzed the influence of different stages of drug release on the aforementioned trends.

Swelling of the matrices

Hydrophilic polymer matrices swell in contact with water (Buri and Doelker, 1980). This feature restricts the applicability of the square-root of time approximation of the Fickian diffusion to the formulations and time intervals with constant S/V ratio (Eqn. 1; Touitou and Donbrow, 1982b).

In our study the dimensions of HPC and HPC-PVP matrices increased relatively

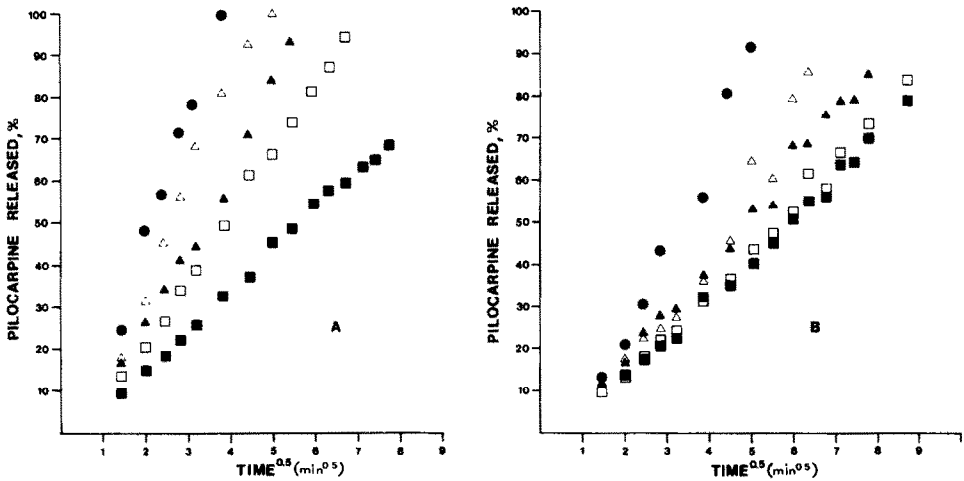

Fig. 1. Release of pilocarpine from polymer matrices prepared from mixtures containing HPC of low (A) and medium (B) molecular weight and PVP K60. The initial pilocarpine concentration of the matrix was 14.2% (w/w). Ratios of the amounts of HPC and PVP were: (●) 20/80; (△) 40/60; (▲) 60/40; (□) 80/20; and (■) 100/0. Means of 5 determinations are shown. For the sake of clarity error bars were omitted.

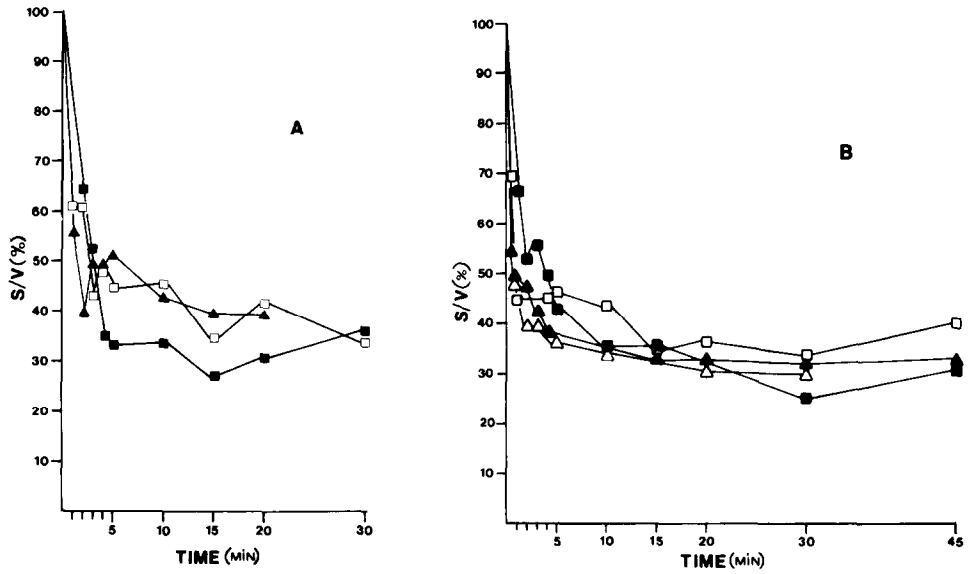

Fig. 2. Exposed surface area to volume ratio (S/V) of pilocarpine matrices containing HPC of low (A) and medium (B) molecular weight and PVP K60. S/V is expressed as percentages of the original S/V ratio. Ratios of the amounts of HPC and PVP were: (△) 40/60; (▲) 60/40; (□) 80/20; and (■) 100/0. The values are means of 2 determinations.

more in the thickness axis than in the radial axis. Consequently, the volumes of the matrices increased relatively more than did their surface areas, thus leading to decreased S/V-ratios (Fig. 2). Initially the matrices swelled rapidly, but swelling became substantially slower or ceased entirely after 1–10 min (Fig. 2, Table 1). After that, the S/V ratios of the matrices shown in Fig. 2 remained fairly constant until 60% of the drug had been released (Figs. 1 and 2, Table 1), and the S/V-ratio could be treated as a constant parameter in Eqn. 1 after the initial period of rapid swelling (Table 1; Touitou and Donbrow, 1982b). Some matrices with high concentrations of PVP, however, underwent substantial attrition which made the determination of S/V-ratios impossible. HPC-L matrices with a 60% content of PVP and HPC-M matrices with an 80% content of PVP swelled only slightly and deformed substantially after 5 min. Owing to the rapid and extensive attrition of the HPC-L matrices containing 80% PVP, their S/V-ratios could not be measured at all.

The volume of equilibrium swelling of the matrices (V_{sw}) was affected both by the molecular weight of the HPC and the initial concentration of PVP in the matrix (Table 1). HPC-M matrices swelled more than HPC-L matrices, and PVP decreased the swollen equilibrium volume. Correspondingly, the equilibrium level of S/V decreased with increasing molecular weight and concentration of HPC.

Dissolution of the polymers

Dissolution of water-soluble polymers from polymer matrices may increase the rate of drug release (Donbrow and Friedman, 1975). Both HPC and PVP dissolve in

TABLE 1

RELATIVE SWOLLEN VOLUMES (V_{sw}) AND ABSOLUTE (S/V) AND RELATIVE $(S/V)_{rel}$ SURFACE AREA/VOLUME RATIOS OF THE MATRICES AFTER THE INITIAL HYDRATION PERIOD. MEANS ± S.E. OF n DATA POINTS ARE PRESENTED. EACH DATA POINT IS THE MEAN OF 2 DETERMINATIONS

Polymer composition (%)		Initial swelling period (min)	S/V (cm^{-1})	S/V^a_{rel} (%)	V_{sw} (%)	n
HPC-L	*PVP*					
100	0	4	1.37 ± 0.07	32.9 ± 1.4	401 ± 12	6
80	20	3	1.66 ± 0.08	41.5 ± 2.1	267 ± 15	7
60	40	2	1.91 ± 0.10	44.3 ± 2.1	248 ± 13	7
40	60	0.5	3.92 ± 0.26	81.3 ± 4.6	135 ± 8	6
HPC-M	*PVP*					
100	0	10	1.28 ± 0.14	32.2 ± 3.3	438 ± 57	4
80	20	4	1.66 ± 0.10	40.1 ± 2.0	309 ± 20	7
60	40	4	1.42 ± 0.17	32.7 ± 2.4	362 ± 27	6
40	60	2	1.64 ± 0.10	34.4 ± 1.5	327 ± 20	7
20	80	1	2.54 ± 0.11	48.1 ± 1.7	233 ± 9	5

[a] Percentage of the S/V-ratio of the unhydrated matrix.

water, PVP being more water-soluble than HPC (Takai et al., 1984). Thus, increased drug release with high PVP concentrations might be due to leaching of PVP from the matrices and to the consequent decrease in diffusional resistance.

Total dissolution of the polymers and the plasticizer during solvent penetration was studied gravimetrically. The amount of released pilocarpine was subtracted from the loss in dry weight during storage in a desiccator. The amount of glycerin in our matrices was 4–5 mg. As a highly water-soluble small molecule, it probably leaches from the matrices faster than PVP does. The significant losses of dry weight (above the amount of glycerin) were observed only when PVP made up at least 40% of the total polymer concentration in HPC-L matrices and at least 60% in HPC-M matrices. The dry weight losses became significant at the following times (weight loss in parentheses as milligrams): HPC-L matrices with a 40% content of PVP at 20 min (10.4) and containing 60% PVP at 10 min (10.2), HPC-M matrices with a 60% content of PVP at 30 min (8.9) and with an 80% content of PVP at 5 min (5.0). Similarly, in the study of Borodkin and Tucker (1974) HPC-L did not dissolve during drug release from cast matrices. Dissolution of PVP from polymer matrices during pilocarpine release is also supported by the results of earlier studies (Gibaldi and Weintraub, 1968; Lapidus and Lordi, 1968).

In most cases, the dissolution rate of PVP was insignificant compared to that of pilocarpine. This is not surprising, because the dissolution rate is affected by both the solubility and the diffusivity of the molecules (Touitou and Donbrow, 1982a). Because in water, and especially in gel networks, macromolecules diffuse much more slowly than small molecules do (Touitou and Donbrow, 1982a), dissolved PVP is diffused much more slowly from the gelled matrix than pilocarpine is. In addition, the diffusional distance in the hydrated matrix is decreased with increasing con-

TABLE 2

PILOCARPINE RELEASE FROM AND WATER PENETRATION INTO HPC AND HPC–PVP MATRICES. INITIAL PILOCARPINE CONTENT OF THE MATRICES WAS 14.2% AND GLYCERINE CONTENT WAS 10%

Polymer content (%)		Uptake of water vapor (%)	Rate of drug release [a]	Penetration of gel layer [b]			Total water penetration [b]		
				r^2	rate [a]	n	r^2	rate [a]	n
HPC-L	*PVP*								
100	0	10.3	9.4 ± 0.4 [c]	0.73	15.6	8	0.91	33.1	7
80	20	11.7	13.4 ± 0.3	0.99	17.0	8	0.97	34.2	8
60	40	15.1	14.5 ± 0.7	0.94	17.8	9	0.94	34.7	9
40	60	17.0	18.9 ± 0.6	0.95	18.5	6	0.99	50.1	6
20	80	17.2	19.8 ± 1.8	–	–	–	–	–	–
HPC-M	*PVP*								
100	0		8.0 ± 0.4	0.93	9.5	10	0.97	24.7	10
80	20		8.2 ± 0.5	0.94	10.4	6	0.98	27.2	6
60	40		10.5 ± 0.5	0.69	12.3	6	0.93	36.5	6
40	60		10.1 ± 0.3	0.69	11.1	5	0.91	37.5	6
20	80		15.1 ± 0.7	0.97	24.4	8	0.97	55.6	7

[a] Percentage in $min^{0.5}$.

[b] Calculated using n data points, each of which was the mean of two determinations.

[c] Mean ± S.E. of five determinations.

centration of PVP (Table 1). In matrices with low concentrations of PVP, the dissolution rate of PVP was insignificant; but in the matrices with high concentration of PVP its relative and absolute rates of dissolution increased substantially both in the study of Gibaldi and Weintraub (1968) and in our study. These findings are consistent with the theory of Higuchi (1965) on dissolution rates in polyphase mixtures.

Differences in the equilibrium volumes of swollen matrices (Table 1) are not due to leaching of PVP, however, because the matrices usually swell to their equilibrium volumes in 1–4 min (Fig. 2, Table 1); and polymers dissolve later or do not dissolve during the drug release. Because the extent of matrix swelling was proportional to the HPC-concentration of the matrix and inversely proportional to the concentration of PVP (Table 1), the extent of matrix swelling apparently is governed by the concentration of HPC.

Polymer dissolution was accompanied by significant deviations of pilocarpine release from the square-root of the time relationship (Fig. 1). Without polymer dissolution, no substantial upward shifts from the linearity of the Q vs $t^{0.5}$ plots were observed (Fig. 1). On the basis of our film negatives, it was evident that substantial attrition of the matrix and consequent changes in S/V-ratio accompanied the dissolution of PVP. Increased diffusivity (D′) of the drug in the gel may also account for accelerated drug release by polymer dissolution.

Dissolution of the polymers cannot be the main reason for differences in the rates of drug release in Fig. 1, however, because pilocarpine is also released from the matrices without polymer dissolution at different rates. Polymer dissolution increases the rate of pilocarpine release only in the few aforementioned cases and sometimes only during a limited time interval (Fig. 1).

Solvent penetration into the matrices

Diffusion of small molecules in dry polymer is very slow ($D \sim 10^{-12}$ cm^2/s) compared to their diffusion in hydrogels ($D \sim 10^{-6}$ cm^2/s) (Lapidus and Lordi, 1968; Korsmeyer and Peppas, 1981). Consequently, the drug diffusion in the unwetted portion of a hydrophilic polymer is generally considered to be insignificant during drug release. Because the penetration of water into the matrices thus initiates drug release, the differences in rate of pilocarpine release could be due to differences in the rates of solvent penetration into the matrices.

According to Fatt and Goldstick (1966), the mass of water absorbed by the swelling membrane should be a function of the square-root of time. We plotted both the fraction of gelled polymer (%) and the released amount of pilocarpine (%) against the square-root of time. The release rates and gelling rates were calculated as the slopes of the plots. The gelling rates were higher than or equal to the corresponding rates for drug release (Table 2). The gelling rate of the matrices was accelerated with increasing concentration of PVP (Table 2), indicating that the penetration of aqueous solvent is accelerated by PVP. The differences in the rates of solvent penetration into the matrices could be due, for example to different hydrophilicities of the matrices or to dissolution of a water-soluble constituent (Donbrow and Friedman, 1975). Sorption of water vapor from air by the polymers can be used as a

measure of matrix hydrophilicity (Lappas and McKeehan, 1965; Borodkin and Tucker, 1974). PVP increased the absorption of water vapor by the plasticized matrices, indicating that PVP is more hydrophilic than HPC (Table 2; Urtti et al., 1985a). The increased hydrophilicity is probably one reason for the increased permeation of water with increased concentration of PVP.

In addition the increased molecular weight of HPC decreased both the penetration rate of the gel-core boundary and the rate of drug release (Table 2). In this case, the decrease in the rate of solvent penetration is probably due to increased entanglement of the macromolecules, which would lead to increased swelling and decreased rate of solvent penetration (Ueberreiter, 1968).

On the basis of the permeation rate of the gel-core interface in many cases dissolution and diffusion of pilocarpine apparently retards the rate of drug release only slightly. The gelling rate does not, however, describe the total penetration of solvent into a polymer matrix. The rubbery hydrogel layer is only one of the watery layers in the polymer during solvent penetration (Ueberreiter, 1968; Park, 1968). The solid core inside the gel normally contains two layers of penetrating solvent. Next to the rubbery gel is a plasticized layer of swollen polymer, which is still in a glassy state, and next to the dry core is the infiltration layer where solvent molecules have penetrated into the voids with molecular dimensions, but the polymer has not yet swollen (Ueberreiter, 1968). In our study the 'unwetted' cores also contained water, indicating the presence of infiltration layer and solid swollen layer. In PVP–HPC-L matrices, water contents of the cores (means $\pm$ S.E.s) varied depending on matrix formulation from $6.3 \pm 3.0\%$ to $16.6 \pm 1.2\%$ and in PVP–HPC-M matrices from $16.5 \pm 2.7\%$ to $22.3 \pm 4.5\%$. Drug diffusion in the core of the matrix contributed to drug release, as indicated by the decrease in the pilocarpine concentrations of the cores (Fig. 3). PVP accelerated the decrease of pilocarpine concentration in the core (Fig. 3). Consequently, the difference between the rates of total penetration of the

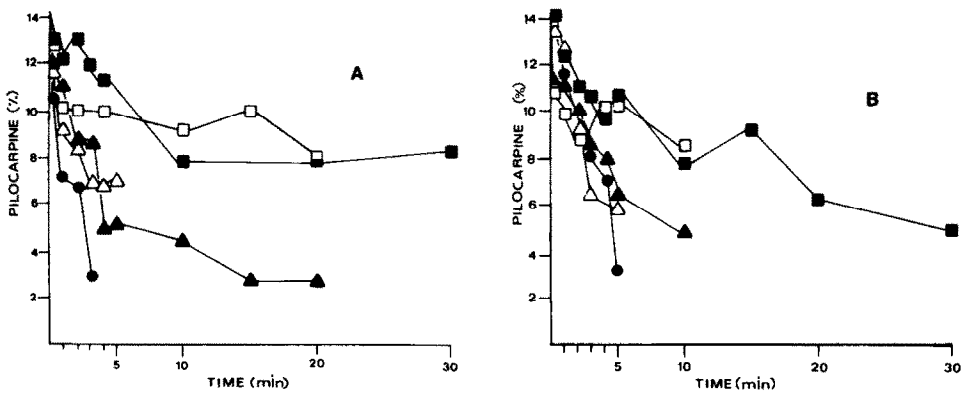

Fig. 3. Decrease in pilocarpine concentration (%) in the ungelled core of polymer matrices containing HPC of low (A) and medium (B) molecular weight and PVP K60. Ratios of the amounts of HPC and PVP were: (●) 20/80; (△) 40/60; (▲) 60/40; (□) 80/20; and (■) 100/0. The values are means of 2 determinations.

TABLE 4

EFFECTIVE DIFFUSION COEFFICIENTS (D') OF PILOCARPINE IN HPC AND HPC-PVP MATRICES

Polymer content (%)		D' (10^{-6} cm^2/s)
HPC-L	*PVP*	
100	0	1.1
80	20	2.1
60	40	1.5
HPC-M	*PVP*	
100	0	0.9
80	20	0.6
60	40	1.3
40	60	1.0

solvent and the rate of drug release is larger than indicated by the difference between rates of the gel-core boundary and drug release (Table 2). In our calculations the fraction of pilocarpine left in the core represented the portion of the matrix that has not been reached by the solvent. The calculated rate of total penetration of solvent is an underestimate, because some of the drug had been reached by the solvent, but had not yet diffused from the core to the gel. In spite of that, the calculated total penetration of water in the matrix far exceeded the rate of drug release (Table 2). Consequently, the penetration of water into the matrix initiates drug release, but does not determine the rate of drug release.

Dissolution and diffusion of pilocarpine

The vast differences between rates of pilocarpine release and total penetration of solvent are due to dissolution or diffusion of pilocarpine. The rate-limiting factor of the drug release was analyzed in each case with diffusional and dissolutional equations (Eqns. 2–4) using the data points after the initial swelling of the matrices but before 60% of drug release (Table 1).

When the proportion of HPC was at least 60% of the total polymer content in the matrices, pilocarpine release was best fitted (variance estimates, coefficients of determination and lag times) to the diffusional equation (Eqns. 1 and 4) (Table 3). In other cases, the best fits were obtained with the dissolutional equations (Table 3; Eqns. 2 and 3). The best fits by the dissolutional equations were obtained only with matrices that underwent attrition and in which constancy of the S/V-ratio could not be verified until 60% of the pilocarpine had been released (Fig. 1, Table 3). Dissolution-controlled drug release was, however, not obtained with an HPC-L matrix with a 40% content of PVP or with an HPC-M matrix with a 60% content of PVP, although PVP dissolved substantially from these matrices. In these cases substantial losses of matrix dry weight were observed only after 60% of the drug had been released (Fig. 1), and thus curve-fitting was not affected by polymer dissolution.

TABLE 3

FITTING OF THE SQUARE-ROOT OF THE TIME RELATIONSHIP AND CUBE-ROOT AND FIRST-ORDER EQUATIONS TO MEANS OF PILOCARPINE RELEASE FROM POLYMER MATRICES. LAG TIMES (min), COEFFICIENTS OF DETERMINATION (r^2), VARIANCE ESTIMATES (s^2), NUMBER OF DATA POINTS (n) AND SLOPES OF log(Q) vs log(t) PLOTS ARE PRESENTED

Polymer composition (%)		Diffusion eqn.			Cube-root eqn.			First-order eqn.			n	k[1]
		lag time	r^2	s^2	lag time	r^2	s^2	lag time	r^2	s^2		
HPC-L	*PVP*											
100	0	0.28	0.995	1.08	−7.92	0.987	2.65	5.86	0.991	1.55	11	0.589 ± 0.023
80	20	0.51	0.997	0.35	−2.39	0.993	0.75	1.60	0.996	0.46	5	0.683 ± 0.034
60	40	0.10	0.996	0.66	−3.24	0.982	3.15 *	2.45	0.989	2.02	6	0.602 ± 0.065
40	60	0.03	0.963	14.76	−0.10	0.999	0.35 **	−0.04	0.999	0.20 **	5	0.811 ± 0.081
20	80	0.01	0.967	15.95	−0.16	0.978	7.77	0.07	0.983	5.23	4	0.830 ± 0.016
HPC-M	*PVP*											
100	0	0.33	0.993	0.88	−10.80	0.988	1.61	7.69	0.991	1.14	8	0.540 ± 0.046
80	20	0.30	0.997	0.66	−7.85	0.985	2.89 *	5.94	0.992	1.73 *	10	0.559 ± 0.015
60	40	−0.08	0.989	1.71	−7.28	0.978	3.12	5.68	0.981	2.45	8	0.568 ± 0.030
40	60	0.20	0.986	1.61	−3.74	0.990	1.32	3.01	0.990	1.28	7	0.602 ± 0.040
20	80	1.09	0.961	9.34	0.70	0.979	5.61	−1.01	0.969	8.76	5	0.881 ± 0.117

[1] Means ± S.E. of 5 determinations.

* $P < 0.05$; ** $P < 0.001$.

Although statistically significant differences between the accuracies of the fits (Table 3) were obtained in only a few cases, the relation between PVP-concentration of the matrix and the mechanism of drug release seems consistent. The lack of statistical significance may be due to the slight upward curvature of the Q vs $t^{0.5}$ plots. This curvature is reflected as slopes of log(Q) vs log(t) plots (k) slightly above 0.5 and is caused by solvent-induced relaxation of the polymers (Park, 1968; Korsmeyer and Peppas, 1981). Relaxation of the polymer structure increases the diffusion coefficient of the drug and thus accelerates drug release. This causes a sigmoidal shape to the Q vs $t^{0.5}$ plots. Effects of the polymer relaxation on the k-values are, however, small compared to the substantial effect of polymer dissolution (Table 3, Fig. 1).

Polymer relaxation affects drug release and the value of k, when the velocities of relaxation and drug diffusion are in the same range (Frisch, 1980). The values of k come nearer to 0.5 when drug diffusion is substantially slower than the polymer relaxation (Frisch, 1980). On the basis of our k-values, with increased concentration and molecular weight of HPC, drug release apparently approaches a purely diffusion-controlled mechanism (Table 3). This might reflect increased resistance of drug diffusion by the hydrated layers of the matrix. The increased resistance could be due to the decreased diffusivity of the drug (D') or to the increased swelling of the matrix (S/V) (Table 1).

The effective diffusion coefficients were calculated for pilocarpine in the matrices that released the drug in the diffusion-controlled manner (Table 3). The exact values of these coefficients should not be emphasized too much, because relaxation of the polymers causes some time-dependence on the diffusion coefficients. The effective diffusion coefficients were in the same range ($D \sim 10^{-6}$ cm^2/s), with corresponding values for other drugs in hydrogels (Lapidus and Lordi, 1968; Korsmeyer and Peppas, 1981; Touitou and Donbrow, 1982b) (Table 4). Nevertheless, increased molecular weight of HPC apparently decreases the diffusivity of the drug in the gel (Table 4) in addition to increasing matrix swelling (Table 1). Based on Table 4, we conclude that the concentration of PVP did not affect the diffusivity of pilocarpine in the hydrated HPC–PVP matrices. In this case, increases in the rate of drug release are probably due to decreased swelling of the matrix.

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