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EFFECTS OF HYDROPHILICITY OF POLYMER MATRIX ON IN VITRO RELEASE RATE OF PILOCARPINE AND ON ITS MIOTIC ACTIVITY IN RABBIT EYES

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ABSTRACT

Pilocarpine release and the time course of miotic activity was studied in albino rabbit eye. ^{3}H-pilocarpine labelled matrices which contained pilocarpine base (14.2 %), glycerine (10%) and polymers (PVP, HPC or their mixtures) were prepared by solution casting. Increasing the amount of PVP in the matrices increased the release rate and hygroscopicity of the matrices. Rod-shaped nonradioactive 3.2 mg matrices with 0.45 mg pilocarpine base were applied into the inferior fornix of the rabbits and the miotic effect was followed.

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Despite in vitro differences, the time course of miotic response did not vary between the polymer matrices. Compared to aqueous eye drop (25 µl, 1.8 % pilocarpine), the polymer matrix administration delayed the onset of the peak effect, but did not affect its magnitude. The biophasic availability was increased 1.2-fold compared to the eye drops. The rod shape and the small size of the matrices diminished the favourable effect of polymer matrices on drug bioavailability. Administration of pilocarpine in polymer matrices probably caused conjunctival vasodilatation and subsequent systemic rather than intraocular drug absorption.

INTRODUCTION

Ocularly applied drugs are absorbed into the eye through the cornea. Ocular bioavailability of topically applied drugs is low when the drugs are instilled as aqueous solutions. This is due to the short corneal contact time of these solutions . Corneal contact and time for drug absorption have been prolonged by increasing the viscosity of the aqueous solutions (1) or by administering the drug in polymer matrices (2, 3).

The drug release from polymer matrices can be regulated by changing the polymer composition. The effects of changing the composition of polymer matrices on the ocular bioavailability has not been studied. In this study pilocarpine, an antiglaucoma agent that causes miosis, was administered ocularly in three gel forming, soluble polymer matrix formulations. Pilocarpine induced miosis after eye drop or polymer matrix administration was followed.

MATERIAL AND METHODS

In Vitro Studies

Pilocarpine base with ^{3}H-pilocarpine tracer (Radiochemical Centre, Amersham, England; 10-30 nCi/mg of pilocarpine) was used as the drug in the matrices. HPC (Aldrich Chemical Company, mw 100,000) and PVP (Fluka AG) K 60 (mw. 160,000) were used as matrix polymers.

Pilocarpine, tracer, plasticizer and polymers were dissolved in methanol and cast in a teflon coated petri dish. Circular matrices (0.318-0.463 mm thick and 18 mm diameter) were cut from the resulting films for the study of the drug release. The thickness of the matrices was measured with an electronic digital micrometer.

Matrices with 14.2 % of pilocarpine, 10 % of glycerine (plasticizer) and different amounts of HPC and PVP K 60 were prepared.

Dried circular matrices were mounted on a glass microscope slide with silicone vacuum grease. Slides were immersed in 200 ml of 32 ^{o} C iso-osmotic salt solution with pH 7.4. The solution was stirred with a magnetic stirrer. The pilocarpine concentration of 500 µl samples was measured using LSC. Five to six experiments were made with each composition.

The apparent diffusion coefficients were calculated using Eq. 1,

$$Q = 2 \cdot A \left(\frac{S}{V}\right) \left(\frac{Dt}{\pi}\right)^{\frac{1}{2}} \qquad (1)$$

where Q and A are the amounts of drug released at times t and infi-

nity respectively, S is the exposed area of the matrix, V is the volume of the hydrated matrix and D is the apparent diffusion coefficient of pilocarpine in the matrix. Because pilocarpine is a very water soluble drug, D was calculated using values of Q less than A/2. Particular emphasis should not be placed on the absolute values of apparent diffusion coefficients, because the S/V-ratio was assumed to be constant during the drug release though it was not verified experimentally.

Water absorption from the air to the placebo matrices was tested at room temperature in 79.5 % relative air humidity using a gravimetric technique.

In Vivo Studies

From the cast polymer matrices described above, rod-shaped matrices were cut. Three matrices with HPC/PVP K 60 -ratios of 100/0, 50/50 and 0/100 were used. Pilocarpine base eye drops were made iso-osmotic in phosphate buffers at pH of 7.0.

New Zealand White albino rabbits (3.6-4.4 kg) were used in the study. The animals were accustomed to the dim lighting and wooden restraint boxes 2 hours before the experiment.

25 µl of 1.8 % pilocarpine solution (drug dose 0.45 mg) was instilled onto the upper cornea of the rabbits, while the upper eye lid was slightly pulled aside. The matrices which contained 0.45 mg of pilocarpine were placed in the lower conjunctival fornix of the rabbits. Only one eye from each rabbit was used in the experiment.

Pupillary reaction to pilocarpine was followed with a video camera and monitor. The diameter of the pupil was measured from the monitor picture at fixed times. Pupillary constriction is related to the drug concentration in the iris sphincter muscle and thus pharmacokinetics of pilocarpine in the iris can be followed with pupillary response (5).

The percentual constriction of pupil was plotted against time. The magnitude of the peak response and its time delay were evaluated. The relative biophasic availability was measured as the area under the percentual change of pupillary diameter vs time curve (AUC) using trapezoidal method. The apparent elimination rate constant was determined with linear regression analysis from the natural logarithm of pupil constriction vs time curve.

RESULTS

Increased HPC-content and decreased PVP-content of the matrices decreased the rate of pilocarpine release. (Fig. 1 and Table 1). Increasing the amount of HPC in the matrices decreased the water absorption from the air, whereas addition of PVP increased the hygroscopicity of the matrix (Table 1).

The time course of the miotic response of pilocarpine was about equal after application in different polymer matrices. The time delay of the miotic response was significantly affected by HPC and HPC/PVP vehicles (Table 2). Statistically significant differences of the magnitude of peak response, AUC or apparent elimination rate were not observed between the test groups.

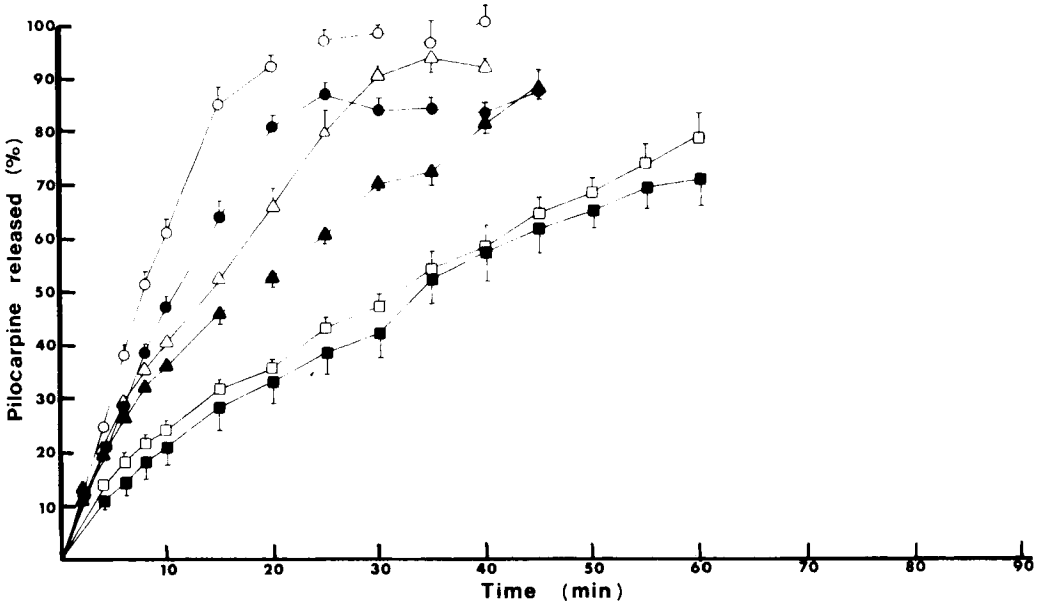

FIGURE 1

Release of pilocarpine base from polymer matrices prepared from mixtures of HPC and PVP K 60. The ratios of the amounts of HPC and PVP were 0/100 (open circles), 20/80 (closed circles), 40/60 (open triangles), 60/40 (closed triangles), 80/20 (open squares) and 100/0 (closed squares). Means ± S.E.s (n=6) are presented.

DISCUSSION

Increased PVP concentration and decreased HPC concentration accelerated pilocarpine release from the matrix (Table 1). Hygroscopicity of the matrix was increased in the same order as the drug release from the matrix. This was due to highly hydrophilic character of PVP molecule (6). PVP could increase pilocarpine release from the matrix by affecting penetration of water into the matrix or by changing the diffusion of the drug from the matrix. In our earlier study, water penetrated more quickly into the PVP than the HPC

TABLE 1

Apparent diffusion coefficients of pilocarpine release from HPC-PVP K 60 matrices and water absorption (%) to placebo matrices during 36 h. The initial pilocarpine concentration in the matrices of the release study was 14.2 %.

HPC/PVP-ratio	Apparent diffusion coefficient (10^{-6} cm^2/s)	Water absorbed [b] (%)
100/0	0.167 ± 0.017 (5)[a]	10.3 [c]
80/20	0.160 ± 0.016 (6)	11.7
60/40	0.271 ± 0.029 (6)	15.1
40/60	0.532 ± 0.028 (6)	17.0
20/80	0.814 ± 0.062 (6)	17.2
0/100	1.710 ± 0.128 (6)	19.9

[a] Means ± S.E.s of (n) determinations

[b] At 20°C and 79.5 % relative air humidity

[c] Mean of two determinations

TABLE 2

Pharmacokinetic parameters of miotic response induced by 0.45 mg of pilocarpine administered in aqueous solution and polymer matrices in albino rabbit eyes. Means ± S.E.s. of 4 determinations are presented.

Dosage form (HPC/PVP-ratio)	Peak effect		AUC (% · h)	Apparent elimination rate constant/h^{-1}
	Time delay (min)	Magnitude (%)		
Aqueous solution	22.0 ± 3.2	51.5 ± 1.9	105.9 ± 10.9	0.51 ± 0.06
Polymer matrices (100/0)	32.0 ± 2.2*	55.7 ± 1.8	129.9 ± 9.1	0.47 ± 0.06
(50/50)	41.0 ± 0.6*	51.0 ± 1.9	131.0 ± 12.5	0.58 ± 0.05
(0/100)	28.0 ± 1.8	55.6 ± 4.2	133.3 ± 9.6	0.52 ± 0.19

* $P < 0.05$ (Mann-Whitney's U-test)

matrix, but also the gel layer of the HPC matrix seemed to retard pilocarpine release more efficiently than the gel layer of the PVP matrix (4). Biophasic availability of pilocarpine increased 2.5-3.5 times when the drug was administered in hydrophilic polymer matrices with approximately equal release characteristics to the matrices of this study (3, 7). Availability of pilocarpine to the biophase of iris was increased 1.4 fold even with aqueous eye drops with the viscosity of 4.2 cps (1) and 1.9-2.7 fold with pilocarpine impregnated contact lenses from which the drug release was rapid in vitro (8). The polymer matrices of this study did not show a vehicle-controlled absorption of pilocarpine, because the absorption phase of the matrix delivered drug is indistinguishable from that of the drug administered in eye drops (Fig. 2). The prolonged contact of the drug with corneal surface delays the onset of the peak effect (9). According to Mishima (10) sustained effect of pilocarpine in the eye is achieved only when the precorneal loss of the drug is slower than its elimination from the biophase of iris. Thus it seems that the precorneal loss of pilocarpine was faster than 0.5 h^{-1} in this study.

The discrepancy between the results of biophasic availability of this study and earlier studies (2, 7, 8) is explained by the poor access of pilocarpine to the corneal site of drug absorption from a small rod-shaped device in the bottom of lower (inferior) conjunctival fornix. When the corneal absorption of pilocarpine in rabbits was blocked, drug absorption to the iris-ciliary body decreased by about 80 % (11). According to Lee and Robinson (12) drainage of the

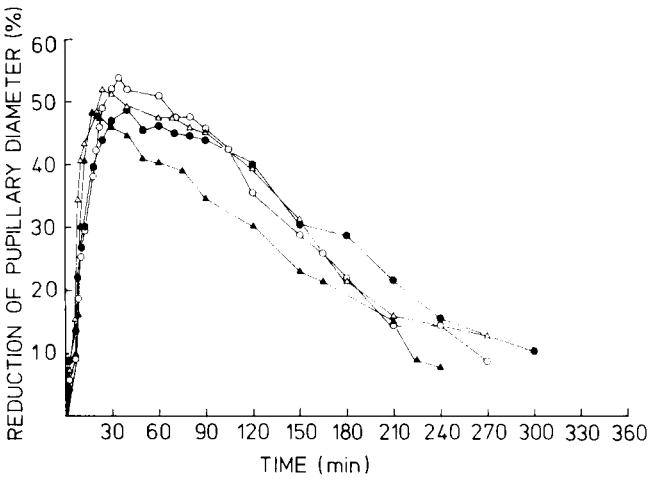

FIGURE 2

Time course of pupillary diameter reduction (%) in albino rabbit eye after 0.45 mg of pilocarpine administered in aqueous eye drops (closed triangle), in HPC matrix (open circles), in HPC-PVP matrix (closed circles) and PVP matrix (open triangels). Means of 4 determinations are presented. Standard deviations are omitted for the sake of clarity.

instilled solution and the drug induced conjunctival vasodilatation are the most important factors that contribute to the precorneal loss of pilocarpine instilled as an eye drop. In the case of polymer matrices drainage factor is absent, and the role of the systemic absorption of pilocarpine in the precorneal drug loss is emphasized. Pilocarpine must diffuse via the conjunctiva up to corneal surface, in order to penetrate into the eye. Systemic absorption of pilocarpine from the conjunctiva is rapid and substantial both after eye drop and HPC-matrix administration (13). Small soluble inserts dissolve more rapidly in tear fluid than corresponding larger inserts and the resulting polymer solution has lower viscosity. Consequently, pilocarpine and polymers are more rapidly washed off in the tear fluid.

Polymer matrices have been widely studied as a prolonged action dosage form for ophthalmic drug delivery. In order to diminish the foreign body sensation after application of a solid insert, small unmedicated rod-shaped HPC-inserts have been used for treatment of keratitis sicca (14) (Lacrisert^{R} , Merck, Sharp & Dohme, West Point, USA). The effect of the size and shape of the insert on ocular bioavailability of drugs has not been described. In rabbits the small rod-shaped (3 mg) pilocarpine inserts increased ocular bioavailability less than the 5-15 mg slab shaped inserts in our earlier studies (3, 7). Although the blinking frequency and precorneal fluid kinetics are different in rabbits and humans, rabbit data may be considered predictive of the situation in humans (15).

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