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THE SOFLENS® CONTACT LENS - AN EFFICIENT, CORNEAL LOADING, DRUG DELIVERY SYSTEM FOR ANTIGLAUCOMA DRUGS

V. F. Smolen*, R. Vemuri,
T. S. Miya+ and E. J. Williams
Purdue University,
Department of Industrial and Physical Pharmacy,
West Lafayette, Indiana 47907

ABSTRACT

The results of administering three antiglaucoma drugs to rabbits using drug-loaded Soflens® contact lenses as drug delivery systems demonstrated a marked enhancement in the miotic activity of the drugs relative to their administration as eyedrops. The use of the Soflens® systems virtually eliminated side effects of the drugs attributable to their systemic absorption. The lens system effects an efficient transfer of drug to the cornea within 15 minutes after which time it can be removed from the eye without loss of pharmacological activity.

The administration of aqueous solutions of ophthalmic drugs as eye drops is still the conventional method of dosing. Drug solutions, however, are rapidly washed out of the eye by tears; therefore, relatively concentrated solutions are required to produce an adequate level of therapeutic effect. The higher the concentration, however, the more likely it is that a sufficient amount of drug will be lost through lacrimal-nasal drainage passages and subsequent absorption to produce undesireable systemic side effects (1); also, frequent dosing is required with eye drops to maintain therapy. A variety of substances have been added to opthalmic drug solutions to mitigate these problems and to increase the efficiency of this mode of administration (2).

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This report presents results from an investigation in which a commercially available hydrophilic contact lens, the Bausch and Lomb Soflens, was used as an ophthalmic delivery system for the antiglaucoma drugs; pilocarpine, carbachol, and echothiophate (phospholine®) iodide. The results indicate that dosing rabbits with these drugs using drug loaded contact lenses markedly increases the drug induced peak miotic response intensity, the duration of miosis, and the areas under the temporal miotic response curves for all three drugs; the enhancement is greatest for echothiophate iodide and least for pilocarpine.

Materials and Methods

Materials - Carbachol powder was supplied by Alcon Laboratories and echothiophate iodide drug kits were supplied by Ayerst Laboratories. Pilocarpine hydrochloride powder was purchased from Mallinckrodt Chemical Company; pilocarpine ophthalmic solution (1% Isoptocarpine, Alcon Labs, Inc.) was purchased locally. All other chemicals were reagent grade. Distilled water was used in the preparation of the carbachol and pilocarpine solutions. Thin and thick Soflens contact lenses were furnished by the Bausch and Lomb Company. The lens diameter was approximately 13 millimeters and the average hydrated weights of the thin and thick lenses were 31 $\pm$ 1 mg and 46 $\pm$ 1 mg, respectively. Pupil diameter measurements were made with a Whitaker Model 800 pupilometer. An American Optical Company Tonomat applicator (Fig. 1) was employed to apply the drug-loaded lenses to the rabbit eyes; the lenses were removed with an optician's lens removal suction cup device. Male, New Zealand white rabbits, 3-4 months old and weighing 3-4 kilograms, were purchased from the Nicely Farms, Greenfield, Indiana. Teflon-coated magnetic stirring bars were used to stir the drug solutions during drug-loading of the lenses. A Cary Model 17 spectrophotometer and 2 cm path length teflon stoppered, quartz cells were used to assay for material leached from the contact lenses.

Preparation of Drug Solutions - 0.10% (W/V) carbachol and 1.0% pilocarpine solutions were prepared fresh by dissolving carbachol or pilocarpine hydrochloride powder in distilled water. NaCl was added to produce a final 0.3 isoosmolar solution which was diluted to volume with distilled water. The commercial ophthalmic pilo-

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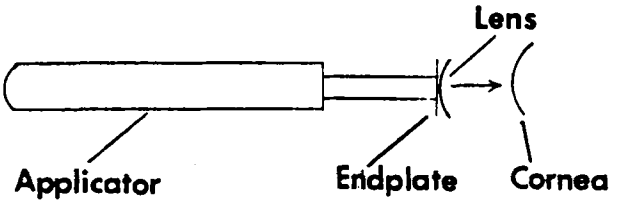

Fig. 1. Applicator for placing drug loaded Soflens contact lenses onto the corneas of rabbit eyes.

carpine solutions were used as is; ophthalmic echothiophate iodide solutions were prepared fresh by dissolving echothiophate iodide powder from the drug kit in the reconstituting liquid as directed in the package insert supplied with the product.

Preparation of the Lenses - Each Soflens was rinsed and leached for five days in distilled water. The water was changed every day and analyzed spectrophotometrically to determine how much leaching was required to remove extraneous materials from the lenses.

Drug Loading of Lens - A Soflens was immersed in 7.0 ml of drug soaking solution contained in a stoppered vial. The lens and soaking solution were stirred at room temperature, 23 $\pm$ 1° C, with precautions being taken to avoid frictional heating of the solutions during the stirring by elevating the vial on a platform above the stirrer so that an insulating air space was interposed between the vial and stirrer. Soaking times were as follows: pilocarpine, 24 hours; carbachol, 1 hour; and phospholine iodide, 1 hour. Thick lenses were used for pilocarpine and thin lenses for carbachol and phospholine iodide.

Rabbit Preparation and Lens Application - To minimize intersubject variations, rabbits were screened for: (1) pupilary response to drug; (2) clarity of definition of the pupil; (3) general behavior and degree of cooperation to application of a lens. Selected rabbits were preconditioned to wearing a lens in the testing environment before their first lens-dosing experiment. Rabbits were fasted overnight prior to each experiment and for the duration of the experiment. At the beginning of each experiment a rabbit was removed from his cage, placed in a restrainer, weighed, and

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moved to the testing laboratory; it was necessary to immobilize the heads of the rabbits in order that their right eye would remain in proper alignment with the pupilometer TV camera and infra-red illuminator (Fig. 2). After a rabbit had been acclimated for 30 minutes in the quiet, darkened testing environment, 30 - 60 minutes of predrug pupilary measurements were obtained. A drug loaded lens was removed from the soaking solution, shaken carefully to remove clinging drops of the soaking solution, placed on the right eye of the rabbit, and positioned over the cornea. Carbachol and echothiophate iodide loaded lenses were removed after 15 minutes; pilocarpine loaded lenses were left on the cornea for the entire experiment (5-6 hours). Rabbits were allowed a recovery period of approximately one week between experiments. At the conclusion of each experiment the rabbit eye was examined visually and checked with freshly prepared fluorescein stain solution to determine whether the lenses had abraded the cornea. The eye was also examined the next day.

Eye Drop Dosing - Following the rabbit acclimation period and predrug pupilary measurements, 0.01 ml of drug solution was instilled into the conjunctival sac of the right eye of the rabbit and the eye lids were held together for 30 seconds.

Pupilometric Measurements - Postdrug pupil diameter measurements were begun immediately after lense application. Measurements were made at approximately 3-minute intervals during the first hour after dosing and then periodically for the remainder of the experiment. All measurements were made in a quiet, darkened room. A rheostated microscope light was used to adjust the predrug pupil diameter to 4.5 mm.(Fig. 2). Prolonged exposure of the pupil to the microscope light resulted in a gradual change in pupil diameter. To avoid this problem the pupil was routinely illuminated for a standard time of 1 minute before each pupilometric reading. The miotic response intensity, I, was calculated using equation 1, where D_o is the average predrug pupil diameter and D_t is the pupil diameter at any time, t, after dosing (2).

$$I = \frac{D_o - D_t}{D_o} \qquad \text{Eqn. 1}$$

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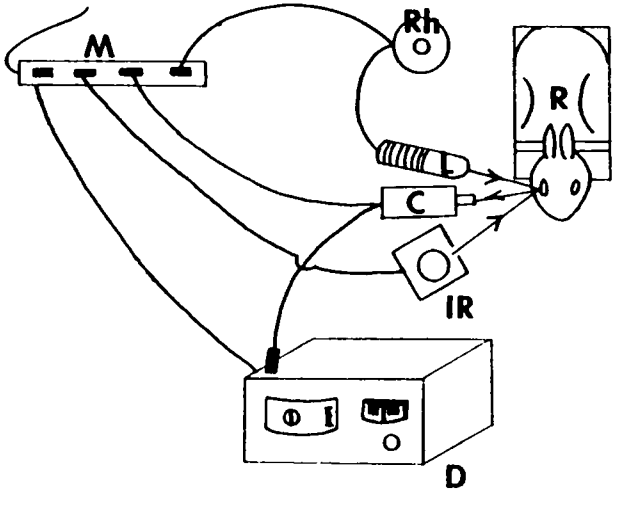

R - Rabbit in Restrainer
L - Microscope Lamp
Rh - Rheostat
C - TV Camera
IR - Infra-red Illuminator
D - Discriminator and
Pupil Image Monitor
M - Multi-way Plug Pin

Fig. 2. Experimental arrangement for making pupil diameter measurements on rabbits.

The pupil diameter of the left eye of each rabbit was measured before and periodically after dosing so that miotic activity in this eye, which could be attributed to nonspecific systemic absorption of the drugs, could be detected. The times of onset and the duration of any systemic side effects including salivation, lacrimation, nasal drainage, abnormal respiration and urination, were noted wherever these side effects occurred.

RESULTS

Figs. 3, 4, and 5, together with Table I, provide a comparison of the miotic effect produced by drug-loaded contact lenses versus eyedrop dosing for pilocarpine, carbachol and phospholine iodide. The lenses increased the peak miotic response intensity, overall miotic effect (as indicated by the areas under the temporal miotic response curves), and the duration of miosis of all three drugs. Lens administered carbachol (Fig. 4) and particularly echothiophate iodide (Fig. 5) produced a very large enhancement of miosis considering the low concentrations of these drugs in the soaking solution. The pilocarpine results (Fig. 3), although significant, are less dramatic. Table 2 demonstrates that the wearing of the lenses itself does not cause miosis and provides an indication of the precision of repeated pupilometric measurements on different rabbits.

There was no evidence of corneal tissue injury; rabbits which were repeatedly used in subsequent experiments yielded data which were indistinguishable from that obtained using new rabbits, again indicating that the application and wearing of these soft contact lenses did not appear to damage the cornea. These lenses have been approved by the FDA and prescribed for human use for more than two years. No side effects, including miosis in the left (control) eyes, were evident following administration of any of the drugs using drug loaded lenses even though the miosis induced in the drug treated eyes was quite pronounced. Systemic side effects did occur following eye drop dosing with the 1% pilocarpine solution.

A simple qualitative experiment was performed which demonstrates the rapidity and efficiency with which therapeutic amounts of ophthalmic drug can be transferred to the cornea when a

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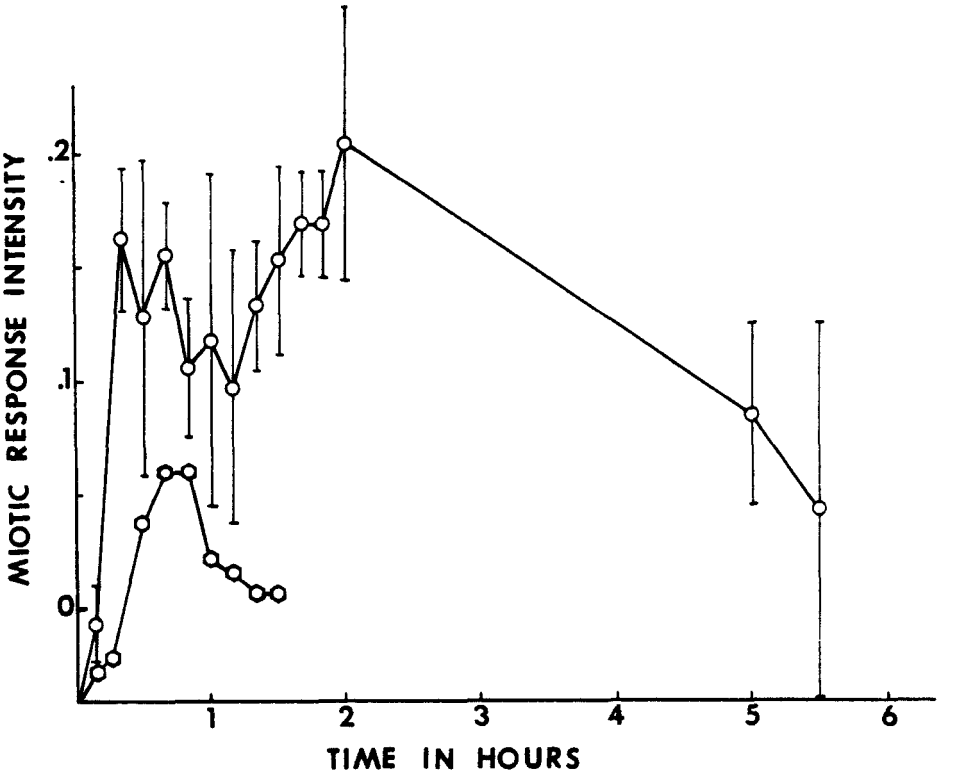

Fig. 3. Temporal variation of miotic response intensity following dosing of rabbits with Soflenses impregnated with 1% (W/V) pilocarpine, ○, and with 1% Isoptocarpine solution, ⬡. Each point is an average of data from 3 experiments; the standard error is shown.

suitable substrate, impregnated with drug, is placed in intimate contact with the cornea for only a short time. A transparent lens, approximately 13 mm in diameter, was cast from acrylic nail lacquer onto the rounded end of an 8-inch test tube; the curvature of this "lens" approximated that of the rabbit cornea. A disk of cellulose, millipore filter (pore size = 0.22 microns), 5 millimeters in diameter, was soaked in 3% carbachol solution, the filter disk was removed from the soaking solution, freed of adhering liquid, and placed inside the

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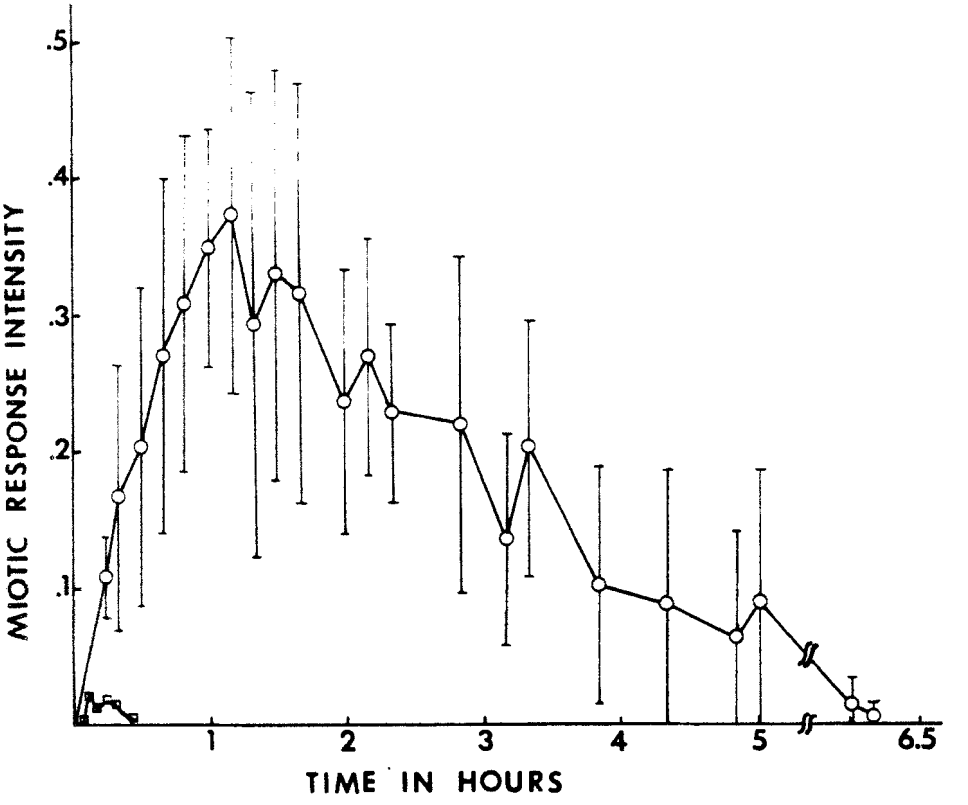

Fig. 4. Temporal variation of miotic response intensity following dosing of rabbits with Soflenses impregnated with 0.10% (W/V) carbachol, ○, and with 0.10% (W/V) carbachol ophthalmic solution, □. Each point is an average of data from three experiments; the standard error is shown.

artificial lens which had been well rinsed and stored in distilled water for two days. The drug loaded filter disk assembly was then placed on the eye of the rabbit with the drug loaded disk held in contact with the cornea by the "lens" for 15 minutes. At the time the assembly was removed, the pupil diameter, relative to its predrug value, had decreased 70% (from 5.0 mm to 1.5 mm); 26 hours later miosis was still evident. Similar results were observed

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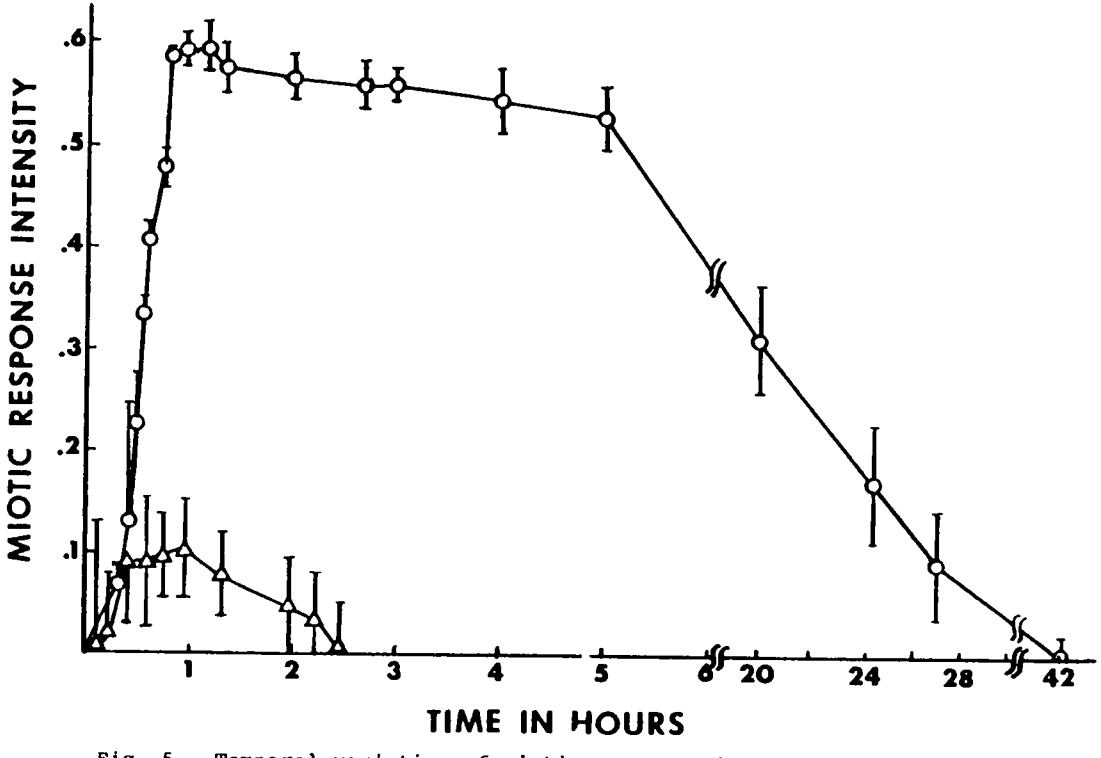

Fig. 5. Temporal variation of miotic response intensity following dosing of rabbits with Soflenses impregnated with 0.03% (W/V) echothiophate iodide, ○, and with 0.03% echothiophate iodide ophthalmic solution, △. Each point is an average of data from three experiments; the standard error is shown.

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I

Comparison of the Miotic Effect Produced in Rabbits by Soflens and Eyedrops Administered Antiglaucoma Drugs. Each Value is an Average of Three Experiments with Different Rabbits

Drug Concentration	Miotic Response Parameters					
	Eye Drop Dosing			Soflens Dosing		
	I_{max} *	AUC+	Duration, hours†	I_{max}	AUC	Duration, hours
1% (W/V) Pilocarpine	0.088	30	1.5	0.203	400	6.0
0.10% (W/V) Carbachol	0.023	15	0.5	0.37	860	6.5
0.03% (W/V) Phospholine Iodide	0.13	147	2.5	0.59	9700	42.0

*Maximum miotic response intensity value.

+Area (in arbitrary units) under the temporal miotic response intensity curves; obtained by Planimetry.

†Time required for pupil diameter to return to predrug value.

II

Miotic Response Data for Soflens Soaked in Distilled Water.

Time after lens application, minutes	Miotic Response Intensity				
	Rabbit 1	Rabbit 2	Rabbit 3	Average	Standard Error
4	0.022	-0.102	0	-0.027	0.066
6	-0.022	-0.020	0	-0.014	0.012
8	-0.088	0.041	0	-0.016	0.066
10	-0.088	-0.122	-0.022	-0.077	0.051
12	0.022	-0.141	-0.022	-0.014	0.032
20	-0.060	-0.061	-0.087	-0.069	0.015
25	0	0	-0.087	-0.029	0.050
30	-0.020	0.022	-0.022	0.013	0.059
35	-0.020	0.041	0.087	0.036	0.054
40	-0.040	0.020	0.022	0.001	0.035
45	-0.020	0.061	0	0.014	0.042
60	-0.040	0.020	0	-0.007	0.031

when a clean, unused Soflens was used to hold a similarly loaded filter disk in place on the cornea.

The discovery that new Soflens lenses contained leachable water-soluble impurities occurred during a preliminary attempt to develop a direct spectrophotometric assay for the carbachol contained in carbachol impregnated lenses. Fig. 6 is a plot of the absorbance at 210 nm of these impurities versus leaching time; the figure shows that most of the material is easily removed from the lenses by soaking them in distilled water. When a lens was taken from the final leaching solution and placed in distilled water with stirring at 94° C for 10 minutes, the spectrophotometric absorbance of this

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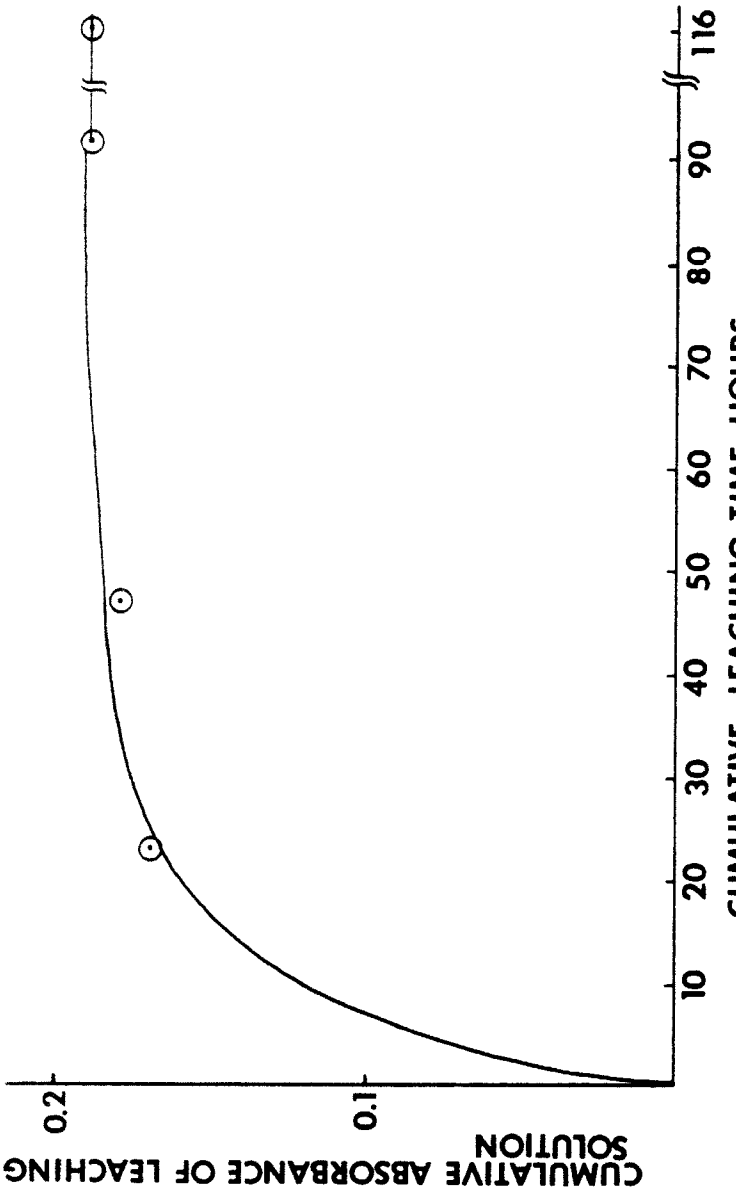

Fig. 6. Time course of the absorbance of extraneous material leached from sterile packaged Soflens contact lenses into distilled water.

high temperature leaching liquid was negligible suggesting that the leachable material is not due to thermal degradation of the polymeric lens material during sterilization of the lenses.

DISCUSSION

Echothiophate iodide appears to be the drug most benefited by lens administration as judged from a comparison to eye drop adminsitration. Carbachol appears to be the next drug of choice for this mode of dosing, while pilocarpine is least affected. This may be due in part to a lower miotic potency of pilocarpine; that is, the pilocarpine impregnated lenses may sorb approximately the same amount of pilocarpine as carbachol or echothiophate iodide, despite the lens soaking solution concentration of pilocarpine being much higher. O'Brien and Swan have demonstrated that pilocarpine is less effective than carbachol in lowering intraocular pressure and as a miotic agent (3).

It is also conceivable that pilocarpine is less effectively transferred from the lenses to the cornea relative to carbachol and echothiophate iodide. The physiologically active carbachol and echothiophate quaternary ammonium cations are not subject to a pH dependent extent of ionization as is pilocarpine (PKa = 7.1). In the physiological pH 7.4 environment which prevails at the corneal surface, the majority of cationic pilocarpine hydrochloride has been deprotonated. Smolen, et al., have demonstrated that fixed anionic tissue sites, which are present on the net negatively charged corneal surface, are involved in the binding and transcorneal passage of carbachol cations (4) and probably other cationic drugs as well (4-6). Unionized pilocarpine cannot interact electrostatically with these sites and may become bound to the corneal tissue colloids to a lesser degree and permeate the cornea by a less efficient mechanism than site-to-site migration (4).

Other investigators have studied soft contact lenses as drug delivery systems for pilocarpine (7-9). Leaders and co-workers using rabbits, examined the miotic enhancement of pilocarpine loaded Bioplex lenses relative to eye drop dosing with pilocarpine solutions containing benzalkonium chloride (9). The degree of miosis was greater than was observed with the Soflens; conceivably this was because the more permeable Bioplex lens polymer matrix

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sorbs more pilocarpine from a soaking solution than does the Soflens. Podos and co-workers (8) have reported that Bionite soft lenses soaked in 0.5% and 1% pilocarpine effectively lowered the intraocular pressure in glaucoma patients. One disadvantage of highly permeable lenses in drug delivery is their tendency to pick up and retain excess drug and also unwanted water-soluble material which makes it more difficult to cleanse such lenses between successive applications.

The effectiveness of the brief, 15 minute, cornea-lens contact time for carbachol and echothiophate iodide loaded Soflenses indicates that the transfer of drug from Soflens to cornea is rapid for this lens and these drugs. The lenses prevent tears from washing away the drugs (10), serve as drug reservoirs (9), load the cornea with drug (4-5), and probably facilitate corneal drug absorption by stimulating or perturbing the external epithelial layer of the cornea (11) as well as the precorneal tear film (12). The ease of removal of leachable material from Soflens also suggest that drugs which are sorbed by these lenses from soaking solutions are not strongly sorbed onto the lens polymer matrix indicating that drug loaded Soflens quickly release and efficiently transfer the drug from the lens to the cornea.

The ability of drug loaded Soflens to produce pronounced miosis and presumably a concomitant decrease in intraocular pressure (IOP), without accompanying side effects, is quite advantageous from a therapeutic point of view. Presumably a glaucoma patient could wear a drug loaded Soflens for fifteen minutes or less each morning to receive a therapeutic dose of the drug for the day and remove the lens. Both the systemic side effects and frequent dosing characteristics of eye drops are obviated. Pilocarpine and carbachol function as antiglaucoma drugs because of their transient cholinergic activity; echothiophate iodide, however, is an irreversible cholinesterase inhibitor and, although its antiglaucoma action is more prolonged, it also produces more serious side effects. Therefore, any lens promoted increase in therapeutic efficiency which does not concomitantly increase toxicity is especially advantageous for echothiophate iodide.

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CONCLUSIONS

Drug loaded Soflens contact lenses are an efficient drug delivery system for antiglaucoma drugs, and probably other ophthalmic drugs as well. The magnitude and duration of drug induced miosis is enhanced markedly, particularly for echothiophate iodide and carbachol, as compared to ophthalmic solution dosing. Moreover, side effects are virtually eliminated. Apparently, small therapeutic amounts of lens sorbed carbachol and echothiophate iodide are rapidly and efficiently transferred directly from the lenses to the cornea.

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*Department of Industrial and Physical Pharmacy and to whom reprint requests should be addressed.

+Department of Pharmacology and Toxicology.

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