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Controlled release of pilocarpine from coated polymeric ophthalmic inserts prepared by extrusion

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Summary

A series of cylindrical ophthalmic inserts based on mixtures of PVA, glyceryl behenate and different polymers (xanthan gum, jota-carrageenan, hydroxypropyl methylcellulose, hyaluronic acid), and containing pilocarpine nitrate (PiN) were prepared by extrusion, and were subsequently coated with a mixture of Eudragit RL and RS. The inserts had the following characteristics: diameter, 1.5 mm; length, 3 mm; weight, 7 mg; PiN content, 1.16 mg. The applied coating was 4% of the inserts' weight. The inserts were submitted to release tests in vitro, and to miotic activity tests in rabbits. The uncoated inserts released 50% of the drug within 20–30 min, with predominantly diffusive kinetics. The release profiles of the four types of uncoated inserts were essentially similar. The coated units released 50% PiN in 3–5 h, depending on the core composition. Zero-order release kinetics were observed in the case of three of the four types of coated inserts. Release was incomplete in all cases: this was due, as shown by equilibrium dialysis tests, to PiN binding by the polymers. The uncoated inserts, when tested for miotic activity in albino rabbits, showed little or no sustained activity, and moderate AUC increases with respect to an aqueous solution of the drug. Conversely, the coated inserts showed miotic activity profiles indicating a prolonged-pulse or sustained release (9–10 h duration, shift of the peak time to 120–240 minutes, over 3-fold increases in AUC over the aqueous solution). The in vitro/in vivo relationships, the effects of different core compositions and coating thicknesses, and the possible mechanism governing release from the coated inserts are discussed. This preliminary study indicates the possibility of realizing, using relatively simple techniques and common pharmaceutical materials, ocular delivery devices showing substantially improved properties when compared with traditional ophthalmic vehicles.

Introduction

Two attractive potential features of solid ophthalmic dosage forms (inserts) are: (1) prolonged retention in the conjunctival cul-de-sac, producing an increased ocular drug bioavailability, and (2) a slow, controlled rate of drug release, resulting in optimum therapeutic efficacy. Reduction of systemic absorption, a third beneficial property, may result from the combined effect of the first two characteristics. Systemic absorption of drugs applied topically to the eye (the so-called 'oculosystemic' absorption) is known to occur rapidly and to a significant extent when instilled solutions are discharged into the nose and come in

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contact with the nasal mucosa (Lee, 1990; Salminen, 1990). The possible occurrence of oculosystemic absorption should not be ignored, particularly when administering potent agents such as β-blockers, cyclopentolate, etc., to cardiac patients and children. Solid delivery systems have been proven capable to reduce this phenomenon by restricting the drug access to the systemic absorption site (Urtti et al., 1985, 1990).

Although membrane-reservoir, insoluble inserts of the Ocusert® type can provide optimum, zero-order release rates for up to 1 week, the possibility of realizing simpler, monolithic soluble inserts exhibiting constant release rates for reasonable periods of time (up to 12–24 h) should not be disregarded. The latter slow-releasing devices, while obviating some drawbacks inherent to insoluble inserts (such as unnoticed expulsion), might: (a) ensure better patient compliance by replacing 4–8 instillations with a single daily application; (b) avoid undesirable drug concentration peaks in the ocular fluids and tissues; and, (c) reduce the risks of systemic absorption and toxicity.

A report on the properties of flat, one-sided coated pilocarpine (Pi) inserts prepared by compression was presented in a previous paper (Saettone et al., 1990). While significantly increasing the ocular bioavailability of Pi, these devices did not release the drug at a constant rate, and did not show optimum retention characteristics. Further investigations were stimulated by the consideration that cylinder-shaped inserts, besides being better retained in the eye with respect to flat ones (Katz and Blackman, 1977), can easily be coated by standard procedures used for solid oral dosage forms. Coating with appropriate materials might modify the release profile to approximate zero-order kinetics, as reported recently by Gazzaniga et al. (1991) for oral minimatrices.

The present paper is concerned: (a) with the preparation, by a simple extrusion method, of cylindrical polymeric ocular inserts containing pilocarpine; (b) with coating of the said inserts with polymeric films controlling release; and (c) with a study of the in vitro release characteristics and in vivo miotic activity in rabbits of both coated and uncoated devices. These studies were considered as an essential preliminary to further investigations on systemic absorption. Some of the polymers used for the manufacture of the insert cores were polysaccharides (xanthan gum, carrageenan), whose ocular use has been hitherto little explored: an investigation on their potential as ocular matrix materials was also considered of interest.

Materials and Methods

Materials

The following materials were all used as received: pilocarpine nitrate, PiN (m.p. 176–178°C, Sigma Chemical Co., St. Louis, MO, U.S.A.); polyvinyl alcohol, PVA (Mowiol® 4-88, Hoechst AG, Frankfurt/Main, Germany); xanthan gum, XG (Keltrol® TF, Kelco, Chicago, U.S.A.); carrageenan, JC (Jota-carrageenan, Sanofi Bio-industries, Paris, France); hydroxypropyl methylcellulose, HPMC (Methocel® K4M Premium, Col-

TABLE 1

Composition of the inserts (% w/w)

No.	PVA	XG	JC	HPMC	HA	GB	PiN	ACR/DEP
1	37.52	23.45	–	–	–	23.45	14.07	–
2	37.52	–	23.45	–	–	23.45	14.07	–
3	37.52	–	–	23.45	–	23.45	14.07	–
4	37.52	–	–	–	23.45	23.45	14.07	–
1C	36.00	22.50	–	–	–	22.50	13.50	4.00
2C	36.00	–	22.50	–	–	22.50	13.50	4.00
3C	36.00	–	–	22.50	–	22.50	13.50	4.00
4C	36.00	–	–	–	22.50	22.50	13.50	4.00

orcon Ltd, Orpington, U.K.); hyaluronic acid sodium salt, MW 5.9×10^5, HA (Hyalectin®, Fidia S.p.A., Abano Terme, Italy); glyceryl behenate, GB (Compritol® 888 ATO, Gattefossé SA, Saint Priest, France); a 30% aqueous dispersion of acrylic copolymers, ACR (10% v/v Eudragit® RL 30 D and 90% v/v Eudragit RS 30D, Rohm Pharma, Darmstadt, Germany), and diethyl phthalate, DEP (Fluka Chemie AG, Buchs, Switzerland).

Preparation of the inserts

Inserts 1–4, whose per cent final w/w composition is illustrated in Table 1, were prepared as follows. PiN (0.60 g) was dissolved in a 16% w/w solution of PVA in 50% w/w aqueous ethanol (10 g). To the solution were added 1.0 g of one of the polymers (XG, JC, HPMC or HA) and 1.0 g GB. The resulting mixture was homogenized (Ultra Turrax X1020, Ystral GmbH, Göttingen, Germany), then gently evaporated under a current of warm air from a hair dryer, while kneading in a glass mortar, until it acquired the consistency of a thick paste (residual solvent content, as determined by weight loss, $\approx 20\%$). The paste was subsequently placed in a die, whose bottom was fitted with a Teflon® cap bearing a 1.5 mm hole. After a brief pre-compression (100 kg/cm^2, Perkin-Elmer P/N 15.011 press, Specac Lim., Orpington, U.K.), the paste was extruded from the die in the form of spaghetti-like rods, 5–6 cm long. The extruded rods were cut into 3 mm portions, which were subsequently dried in an evacuated dessicator. The final inserts had the following characteristics: water content, 1.5% (determined by the Karl Fischer method); average weight, 7 mg $\pm$ 5%; diameter, 1.5 mm; average PiN content, as monitored by HPLC, 1.16 mg $\pm$ 0.095.

Inserts 1–4 were coated to give the corresponding inserts 1C–4C, using an experimental, specially designed air-suspension apparatus which will be the object of a separate communication. Coating was effected by spraying over the inserts the aqueous ACR dispersion, to which 23% w/w DEP (amount calculated on dry lacquer substance) had been added. Prior to spraying, the ACR/DEP mixture was vigorously stirred in order to assist dispersion of the plasticizer into the polyacrylate aqueous blend. In order to define the most appropriate coating thickness, preliminary tests were carried out on JC cores by applying 2, 4 and 10% w/w coatings (as percent weight increase over the initial weight of the cores). After verifying the release data of these inserts, a 4% coating was applied to all other types of inserts.

The determination of PiN in the inserts was performed, after dissolution in water and ultrafiltration (Sartorius Utrasart Cell 10, SM 14539 Sartorius filter, Sartorius GmbH, Göttingen, Germany), by HPLC (Shimadzu apparatus with LC 6A Pump and 20 μl Rheodyne injector, SPDM 6A photo-diode array detector and computer integrating system, Shimadzu Corp., Kyoto, Japan). The column (30 cm $\times$ 3.9 mm) was packed with μ-Bondapak C 18 (pore size 10 mm, Waters, Milford, MA, U.S.A.). The mobile phase (flow rate 1 ml/min) was 30% v/v aqueous methanol containing 0.005 M/l hexanesulphonic acid (Low UV Pic B6 reagent, Waters). Under these conditions, the retention time of Pi was 5.6 min. The determination was performed at 219 nm.

Release tests in vitro

For these tests, two inserts were placed in a small stainless steel, woven wire basket (50 mesh, diameter 18 mm, height 20 mm) rotating at 20 rpm. The receiving solution consisted of 5 ml of pH 7.4, 1.33 mM phosphate buffer, thermostated at 30°C. Samples of the solution (2.0 ml) were withdrawn at intervals and replaced with fresh buffer. Analysis of PiN in the samples was carried out by HPLC after ultrafiltration, as indicated before.

Pilocarpine binding by the polymers

Equilibrium dialysis tests were carried out essentially as described by Patel and Kostenbauder (1958). Solutions of PiN in pH 7.4, 1.33 mM phosphate buffer (10 ml) were introduced in prehydrated cellophane dialysis bags (Spectra/Por, cutoff Mol. Wt 6000–8000, Spectrum Medical Ind., Inc., Los Angeles, CA, U.S.A.), and the bags were placed in bottles containing 10 ml of dispersions of the polymers (PVA, XG, JC,

HPMC or HA) in the same buffer. The stoppered bottles were agitated in a thermostated shaking bath at 30°C for 24 h. Separate experiments carried out in the absence of polymers proved that binding of PiN by the cellophane membrane was negligible. The PiN content of the solutions inside the bags was determined by HPLC according to the method previously indicated.

Miotic activity tests

The medicated inserts were applied into the lower conjunctival sac of one eye of non-anaesthetized, male New Zealand albino rabbits weighing 2.5–3.0 kg. A commercial PiN solution (Pilocarpina 2%, Farmigea, Pisa, Italy) of which 50 μl were instilled, was used as reference standard.

The miotic activity measurements were performed under standardized light conditions, by estimating, at appropriate intervals, the horizontal diameter of the pupil to the nearest 0.1 mm. The contralateral, untreated eye served as control. Each preparation was tested at least on six different animals. All tests were performed in accordance with the NIH guidelines and the ARVO resolution on the use of animals in research.

Results and Discussion

Composition of the inserts

Some of the polymers used in the present study (PVA, HA, HPMC) have been investigated as ingredients of ophthalmic vehicles by the present (Saettone et al., 1984, 1989a) or other investigators (Zaki et al., 1986). There is scanty information, however, of the ocular use of the other materials, XG and JC. In a previous investigation (Saettone et al., 1989b), analogous polysaccharides were found to display muco-adhesive properties, potentially useful in ocular delivery systems.

Xanthan gum (XG) is a high-molecular weight (Mol. Wt > 2 million) polysaccharide, produced in a pure culture fermentation process by the microorganism *Xanthomonas campestris*. Each repeating unit of XG contains five sugar units, i.e., two glucose units (which constitute the main chain), two mannose units and one glucuronic acid unit (as a mixed potassium, sodium and calcium salt). The main chain of the polymer, built up by the glucose units, has a chemical structure identical to that of cellulose. Applications of this material, which shows unique properties in controlling the rheological properties of aqueous fluids, in the food, cosmetic and pharmaceutical industry have been reported (Cottrell et al., 1980).

Jota carrageenan (JC) is a polysaccharide extracted from the red seaweed *Euchema spinosum*. Its repeating unit consists of β-D-galactose-4-sulfate linked in 1 and 3, and of 3,6-anhydro-α-D-galactose-2-sulfate linked in 1 and 4. The sodium salt is water-soluble, while the calcium salt gives elastic, thixotropic gels. This material, which has a number-average molecular weight in the region of 100 000, also finds applications in the food, cosmetic and pharmaceutical industry as thickening, suspending and gelling agent (Guiseley et al., 1980).

The composition of the inserts is indicated in Table 1. All uncoated cores contained fixed proportions of PVA and of GB (37.52 and 23.45% w/w, respectively); the former material acted as binder, and the latter as lubricant assisting extrusion. The other components were one of the polymers (XG, JC, HPMC or HA, 23.45% w/w) and PiN (14.07% w/w). This composition was established after several tests, in which the proportions of the excipients were tentatively adjusted.

Coating of the inserts was performed with ACR, an aqueous 30% w/w dispersion of copolymers of acrylates and metacrylates, with a small content of quaternary ammonium groups. The latter are present as salts, and are responsible for the water permeability of the applied films. The polymeric blend used for coating was made up of two components, one readily permeable to water, and the other much less permeable. The ratio of the two components, defined after a series of preliminary tests, was 10:90; thus, the less permeable acrylic polymer prevailed strongly. The ACR blend also contained an appropriate amount of diethyl phthalate (DEP), added as plasticizer.

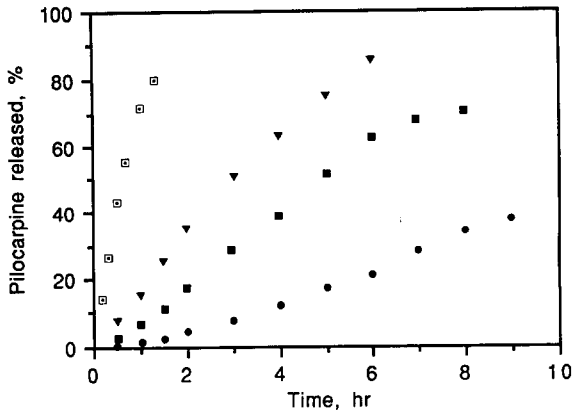

Fig. 1. In vitro release of pilocarpine from JC inserts, uncoated and with different coating thickness. (⊡), Uncoated cores; (▼) 2% coating; (■) 4% coating; (●) 10% coating.

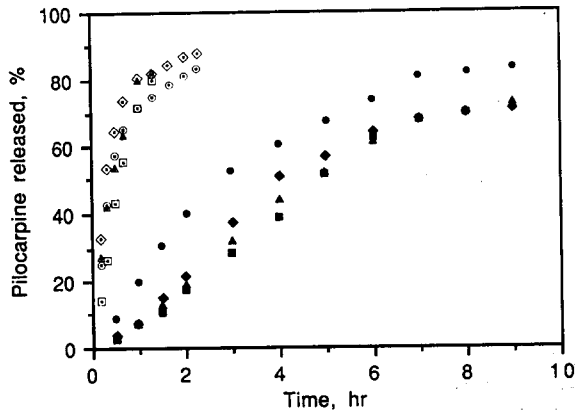

Fig. 2. In vitro release of pilocarpine from uncoated and 4% coated inserts. (⊙) 1; (●) 1C; (⊡) 2; (■) 2C; (◇) 3; (◆) 3C; (△) 4; (▲) 4C.

As said, a 4% coating was applied to all inserts: the average amount of coating (ACR/DEP) applied to each insert was 1.58 mg/cm^2, based on an average area of 0.177 cm^2 per insert.

Pilocarpine release in vitro

The results of preliminary release tests carried out on JC cores (2, Table 1) to which had been applied coatings of increasing thickness are illustrated in Fig. 1. While a 2 or 10% ACR/DEP coating resulted in release being either too rapid or too slow, a 4% coating was considered as the most suitable, since it allowed 50% of the drug to be released in about 5 h, vs 32 min for the uncoated cores. Release of Pi from the 10% coated cores was less than 40% after 10 h.

The subsequent release experiments carried out with the uncoated (1–4) and 4% coated (1C–4C) inserts are illustrated in Fig. 2. The effect of coating on liberation of the drug appears clearly from the graphs. In the case of the uncoated inserts, 50% drug was released within 20–30 min, while the coated inserts released the same percentage of PiN in 3–5 h, depending on the core composition. It can also be observed from Fig. 2 that drug release was incomplete in all cases, and ranged from 80–85% for the uncoated inserts to 70–80% for the coated ones.

The results of equilibrium dialysis tests, reported in Table 2, indicate that drug binding by the polymers might be responsible for the failure of the inserts to release all the contained drug. The dialysis tests were performed using two polymer-drug w/w ratios: one reproducing the composition of the inserts, and another which was doubled with respect to the former. As shown in Table 2, no binding was observed in the case of PVA, while all other polymers bound the drug to varying extents (XG, 17%; JC, 26%; HPMC, 15%; HA, 23%). Doubling the polymer/PiN ratio with respect to that present in the inserts produced in two cases (XG, HPMC) only a moderate increase in the amount of bound drug. The final release

TABLE 2

Results of the equilibrium dialysis tests

Polymer	R (g/g) [a]	Pilocarpine bound (%)
PVA	2.7 (1)	0
PVA	5.4 (2)	0
XG	1.7 (1)	17
XG	3.2 (2)	19
JC	1.7 (1)	26
JC	3.2 (2)	39
HPMC	1.7 (1)	15
HPMC	3.2 (2)	18
HA	1.7 (1)	23
HA	3.2 (2)	35

[a] Polymer/PiN ratio, R, corresponding (1) to the composition of inserts; (2) to a value doubled with respect to the composition of inserts.

TABLE 3

In vitro release parameters

Matrix	n	K	$t_{30\%}$ [a] (h)	$t_{50\%}$ [b] (h)	R 30% [c] (mg/h)	R 50% [d] (mg/h)
1	0.52	0.73				
2	0.86	0.71				
3	0.51	0.87				
4	0.50	0.72				
1C	0.74	0.196	1.75	3.48	0.12	0.10
2C	1.16	0.070	3.49	5.40	0.10	0.11
3C	1.12	0.082	3.16	4.98	0.10	0.11
4C	1.04	0.086	3.32	5.41	0.09	0.09

[a] Time required for release of 30% and [b] 50% PiN. [c] Instantaneous release rate at time of 30% and [d] 50% release of PiN.

values in Fig. 2 do not reflect exactly the different binding capacities of the polymers, probably because the release experiments, carried out under sink conditions, were discontinued at relatively early times, while the binding data were obtained at equilibrium.

An analysis of all release data, performed using the semi-empirical equation $M_t/M_\infty = Kt^n$, proposed by Peppas (1985) and Korsmeyer and Peppas (1983), is presented in Table 3. In the equation, M_t/M_∞ denotes the fraction of drug released at time t, the exponent n is indicative of the release kinetics, and K represents a constant, characteristic of the system. A value of n equal to 0.5 indicates Fickian diffusion to occur, while $n = 1$ is indicative of zero-order kinetics. Values of n between 0.5 and 1 indicate anomalous (non-Fickian) transport.

Inspection of Table 2 shows that the n values for the uncoated inserts 1, 3 and 4 were in the range 0.50–0.52, while the n value for insert 2 was 0.86. This indicates that liberation of PiN from the former three inserts took place via a diffusional mechanism, while release from matrix 2 (JC) occurred by an anomalous mechanism. All uncoated inserts, however, behaved similarly after immersion in water: they underwent rapid hydration and swelling, becoming a lump of jelly within 5–10 min. In the case of the coated inserts, the data in Table 3 indicate release to occur at an approximately constant rate for inserts 2C, 3C and 4C ($n = 1.16$, 1.12 and 1.04, respectively; R 30% $\approx R$ 50%) at least for the first 50% of release. The n value for insert 1C (XG) was 0.74, which indicates an anomalous, non zero-order rate. Inspection of Fig. 2 shows that the coated inserts 2C–4C indeed display analogous release profiles, while release from 1C was faster and essentially non-linear (R 30% = 0.12; R 50% = 0.10).

On visual inspection, it was noticed that the 1C inserts, soon after being placed in phosphate buffer, underwent considerable swelling, and rupture of the polymeric coating. This was considered a reasonable explanation for the anomalous release behavior of these inserts. The constant-rate release observed in the case of inserts 2C–4C, on the other hand, might be attributed to the

TABLE 4

Summary of the miotic activity data of the inserts and of the reference aqueous solution

Matrix no.	Peak time (min)	I_{max} (mm) (±95% C.L.)	Duration (min)	K_e [a] (mm/min)	AUC (cm^2) (±95% C.L.)	Relative AUC
AS	20	2.58 ± 0.61	180	0.012	47.54 ± 11.63	1
1	15	2.08 ± 0.69	330	0.0042	62.08 ± 23.00	1.30
2	30	3.08 ± 0.39	300	0.0065	98.37 ± 10.90	2.07
3	30	2.33 ± 0.27	360	0.0053	87.87 ± 13.72	1.85
4	30	3.25 ± 0.28	270	0.0081	78.25 ± 11.28	1.64
1C	120	2.25 ± 0.28	540	0.0048	145.60 ± 23.80	3.06
2C	240	2.16 ± 0.27	600	0.0055	149.90 ± 24.43	3.15
3C	180	2.16 ± 0.27	540	0.0066	152.50 ± 21.31	3.20
4C	240	2.33 ± 0.27	600	0.0080	177.50 ± 29.75	3.73

[a] Apparent elimination rate constant, determined from the ln(Δ pupillary diameter) vs time graphs. Only the data points after I_{max} were used.

physical restriction exerted by the coating film on core swelling: a mechanism which was first described and investigated by Colombo et al. (1985) and by Gazzaniga et al. (1988, 1991), to whose papers we refer for fuller details.

Miotic activity in rabbits

All inserts (coated and uncoated) were well retained in the lower cul-de-sac of the animals; at the end of the experiments no irritation of the treated eyes could be detected on inspection with a slit lamp.

A summary of the miotic activity parameters of the inserts under study is presented in Table 4; the miotic activity profiles of the uncoated and coated inserts, and of the reference solution AS are illustrated in Figs 3 and 4, respectively.

As shown by the data in Table 4 and in the relevant graphs (Fig. 3), the uncoated inserts produced only a moderate improvement of the activity parameters with respect to AS. Some, however (inserts 2–4), doubled (or almost doubled) the duration of activity and showed significantly increased ($p < 0.05$) AUC values when compared with the reference aqueous solution. The slightly reduced apparent elimination rate constants (0.0042–0.0081 vs 0.012 mm/min for AS) also indicate that the uncoated inserts exerted some control on the ocular absorption and distribution phases of pilocarpine (Salminen et al., 1983).

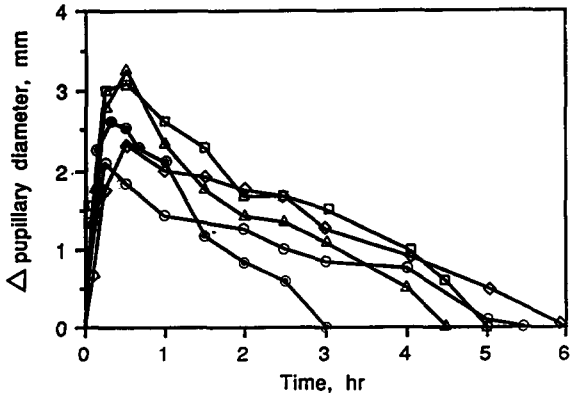

Fig. 3. Miotic activity in rabbits of the reference aqueous solution (AS) and of the uncoated inserts. (⊙) AS; (○) 1; (□) 2; (◇) 3; (△) 4.

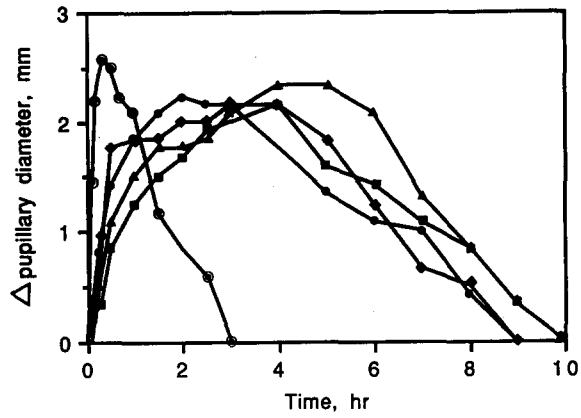

Fig. 4. Miotic activity in rabbits of the reference aqueous solution (AS) and of the 4% coated inserts. (⊙) AS; (●) 1C; (■) 2C; (◆) 3C; (▲) 4C.

The effect of 4% polymer coating on the miotic activity of the inserts was: (i) to shift the peak time of activity from 30 min (inserts 2–4) to a maximum of 240 min; (ii) to prolong the duration to 9–10 h vs 5–6 h for the uncoated inserts, with activity plateaus particularly evident for inserts 3C and 4C; and (iii) to produce statistically significant AUC increases for each coated insert with respect to the corresponding uncoated counterpart. The apparent elimination rate constant of Pi from the coated inserts, however, did not show any further decrease with respect to the uncoated ones. When considered together, all these data offer evidence that enveloping the inserts with a polymer covering provided a significant control of release of PiN, and modified the precorneal pharmacokinetics of the drug from a modest pulse-entry (aqueous solution and uncoated inserts) to a sustained-entry or a sustained pulse-entry.

When examining possible in vitro–in vivo relationships, it should be observed that matrix 1C, which had shown a faster in vitro release and anomalous release kinetics, demonstrated, as might be expected, the shortest peak time in vivo. Other activity parameters (I_{max}, AUC), however, did not differ significantly from those of the other coated inserts. The best overall activity parameters were shown by matrix 4C, containing as core material, besides 36% PVA, 22.5% low molecular

weight (5.9×10^5) HA, a polymer marketed as a 'viscosurgery aid'. The present results, besides showing the essential role of coating in the in vitro and in vivo behavior of the inserts, indicate that the core materials might have some relevance to release in vivo and to biological activity of the coated inserts, even if statistically significant differences among inserts with different core composition could not be detected, possibly as a consequence of the relatively large variations inherent to biological tests.

Conclusions

The present preliminary study indicates the possibility of realizing, by relatively simple techniques, involving apparatus and materials of common use in the pharmaceutical industry, coated ocular inserts showing substantially improved properties (constant-rate release, prolonged activity) when compared with simpler, uncoated inserts or with standard eyedrops. It is hoped that additional investigation now in progress, dealing with different drugs, coating materials and coating thickness, and with an evaluation of oculosystemic absorption, will further define the usefulness and the possible range of application of these inserts.

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