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Ocular inserts for controlled delivery of pefloxacin mesylate: Preparation and evaluation

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Pefloxacin mesylate is a flouroquinolone antibacterial drug effective in the treatment of bacterial conjunctivitis. The objective of the present work was to develop ocular inserts of pefloxacin mesylate and evaluate their potential for sustained ocular delivery. Reservoir-type ocular inserts were prepared by the film casting technique in teflon coated Petri dishes and characterized *in vitro* by drug release studies using a flow-through apparatus that simulated the eye conditions. Six formulations were developed, which differed in the ratio of polymers Eudragit RS 100 and Eudragit RL 100 used for the preparation of the rate controlling membrane. All formulations carried 0.72 mg pefloxacin mesylate, 2.69 mg polyvinyl pyrrolidone (PVP) K-30, plasticizers, propylene glycol (10% *m/m*) and dibutyl phthalate (15%, *m/m*). The optimized formulation was subjected to microbiological studies, *in vivo* studies, interaction studies, and stability studies to assess the effectiveness of the formulation. Cumulative drug released from the formulation ranged from 90–98% within 48 to 120 hours.

On the basis of *in vitro* drug release studies, the formulation with Eudragit RS 100/Eudragit RL 100 (4:1) was found to be better than the other formulations and it was selected as an optimized formulation. On the basis of *in vitro*, microbiological, *in vivo* drug release, interaction and stability studies, it can be concluded that this ocular insert formulation provided the desired drug release *in vitro* for 5 days and remained stable and intact at ambient conditions.

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Continuous delivery of drugs to the eye offers major advantages over conventional therapies that involve administration of drug solutions or suspensions as eye drops. Eye drop administration often results in poor bioavailability and therapeutic response due to rapid precorneal elimination of the drug and is also associated with patient compliance problems (1, 2). For this reason, several approaches have been reported and various oph-

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thalmic vehicles, such as suspensions, ointments, inserts and aqueous gels, have been investigated to extend the ocular residence time of topically applied medications (3). Ophthalmic inserts offer many advantages over conventional dosage forms, like increased ocular residence, possibility of releasing drugs at a slow and constant rate, accurate dosing, exclusion of preservatives and increased shelf life (4–6). Moreover, the use of these devices reduces systemic absorption, which otherwise freely occurs with eye drops. It also ensures better patient compliance due to lower frequency of administration and lower incidence of side effects (7–9). Baeyens *et al*. (10) developed soluble bioadhesive ophthalmic drug inserts for the treatment of external ocular diseases such as conjunctivitis, keratoconjunctivitis sicca and superficial corneal ulcers. Sasaki and co-researchers (11) prepared a unique one-side-coated insert that releases drug from uncoated side only. Ocular application of the one-side-coated insert produced constant concentrations of tilisolol in the tear fluid over 180 min.

The aim of this study was to prepare ocular inserts of pefloxacin mesylate (PM) and to demonstrate sustained antimicrobial action *in vitro* for 5 days.

EXPERIMENTAL

Pefloxacin mesylate (by courtesy of Ranbaxy Research Labs, India), polyvinyl pyrrolidone (PVP K-30) (Dabur, India), Eudragit RL 100 and Eudragit RS 100 (Pharmax, India), propylene glycol (C.D.H, India), silica gel (E.Merck India Ltd., India) and dibutyl phthalate (S.D. Fine Chemicals Ltd, India) were used. The reference standard of the drug was from Cipla Ltd. (India). All solvents were of analytical grade.

Preparation of ocular inserts

The preparation of ocular inserts involved three steps: (*i*) preparation of the drug-containing reservoir film of PVP K-30, (*ii*) preparation of rate controlling films of Eudragit, (*iii*) placing rate controlling films around the drug reservoir and sealing them to obtain ocular inserts.

For preparation of the drug-containing reservoir film, polymeric solutions were prepared by dissolving 1.0, 1.5, 2.0, 3.5 and 4.0% of PVP K-30, along with 0.38% (*m/V*) of pefloxacin mesylate (PM) and propylene glycol (10%, *m/m*), in doubly distilled water (film codes A, B, C, D and E). The solutions were poured into a glass ring of 5.5 cm diameter placed in a Teflon coated Petri dish. The solvent was allowed to evaporate by placing it inside an oven maintained at 35 ± 2 °C, 30 ± 0.5% RH for 24 h.

To prepare the rate-controlling films, Eudragit RS 100 and Eudragit RL 100, in the ratio of 1:1, 1.6:1, 3:1, 4:1, 5.6:1 and 9:1 (in formulations a, b, c, d, e and f, respectively along with 15% (*m/m*) of plasticizer, dibutyl phthalate were dissolved in ethanol/acetone (80:20) mixture. Final concentration of Eudragits RS and RL, and dibutyl phthalate were 4.0% and 0.6%, respectively. The solutions were poured into a glass ring of 5.5 cm diameter placed in a teflon coated Petri plate. The solvent was allowed to equilibrate at 25 ± 0.5 °C, 45 ± 0.5 % RH for 24 h.

Elliptically shaped ocular inserts were cut out of medicated reservoir film with the help of a stainless steel die. These ocular inserts were placed on a rate-controlling mem-

brane and another rate controlling membrane was kept over it. The two rate-controlling membranes containing the reservoir film between them were placed over a beaker saturated with ethanol/acetone vapours (60:40) for 1–2 minutes. This procedure resulted in sealing the two rate-controlling membranes containing the medicated reservoir film between them. The final ocular inserts consisted of three films (mass: 8.83 ± 0.0081 mg (n = 6); length: 13.2 ± 0.0050 mm; width: 5.8 ± 0.0065 mm; thickness: 0.184 ± 0.0081 mm). Each ocular insert contained 0.72 mg of the drug. The ocular inserts were stored in an airtight container under ambient conditions.

In vitro *drug release studies*

A flow-through apparatus designed for *in vitro* release studies on ocular inserts was modified (12). The apparatus consisted of a jacketed 250-mL capacity conical flask, jacketed flow-through cell, magnetic stirrer, peristaltic pump, a flow regulator device and a constant-temperature water bath. The ocular insert was placed in the jacketed cell. The dissolution medium was isotonic phoshate buffer (IPB) of pH 7.4 and the apparatus was equilibrated at 37 ± 0.5 °C. The flow rate of IPB through the jacketed cell was regulated to 0.4 mL min^{-1} and samples were withdrawn at appropriate time intervals up to 120 h and analyzed at 273 nm spectrophotometrically (Beckman DU-64 spectrophotometer, USA).

The *in vitro* release studies were done on reservoir films A, B, C, D and E (Fig. 1). The ocular inserts were prepared with the drug reservoir, which showed maximum drug release (code B), and two rate-controlling membranes. These ocular inserts (code X-1, X-2, X-3, X-4, X-5 and X-6) were subjected to *in vitro* release studies (Fig. 2).

Interaction studies

Interaction studies were conducted on the optimized formulation (X-4) by comparing it with the pure drug and the placebo formulation (without drug) on the basis of the assay, ultraviolet, infrared and thin layer chromatography analyses.

The optimized ocular insert of the drug was powdered in the mortar and extracted with IPB (pH 7.4). The extract was transferred to the volumetric flask of 50 mL capacity and made to the volume. It was then filtered through Whatman filter paper No. 42. The absorbance of the filtered solution was determined spectrophotometrically.

The solutions of pure drug, medicated and placebo formulations were prepared in IPB of pH 7.4 and filtered through Whatman filter paper No. 42 and scanned for UV absorption between 200 and 400 nm.

The IR absorption spectra of the pure drug, medicated and placebo formulations were taken in the range of 400–4000 cm^{-1} by KBr disc method using IR spectrophotometer (Hitachi, Japan).

TLC analysis was conducted according to BP 2000 (13). Silica gel (1 mm thick, E. Merck India Ltd., India) plate was used as the stationary phase and the mobile phase consisted of water/ammonia/butanol/acetone in the ratio of 1:2:4:13. Solutions of pure drug, medicated formulations (0.38%) and placebo were compared with the drug reference standard. The depth of thin layer was 2.5 cm. For visualization, a solution of bromocresol purple in 50% (*V/V*) alcohol (0.4 g L^{-1}) was used as spray reagent and the plate was observed under UV light.

Stability studies

Stability studies were conducted according to ICH guidelines (14) by storing replicates of the ocular inserts at 40 ± 0.5 °C and 75 ± 5% RH for 6 months. The samples were withdrawn on days 0, 30, 60, 90 and 180 and analyzed by HPLC (Shimadzu, Japan). The column was C18 Finepak (particle size 10 micrometers).

The mobile phase consisted of 0.025 mol L^{-1} phosphoric acid and acetonitrile (85:15). The solution pH was adjusted between 2.8 to 3.0 with triethylamine. Flow rate was adjusted to 2 mL per minute and the eluent was monitored at 278 nm (UV detector). Under these conditions, the retention time for pefloxacin mesylate was 5 min.

The ocular insert was taken out off the package, ground with 1 mL of water for HPLC in a mortar, filtered through 0.22 μm membrane filter and 20 μL of filtrate containing 0.0144 mg of drug was injected into the chromatographic system. The quantity of drug was estimated from the calibration curve.

In vivo *studies*

Approval for the use of animals in the study was obtained from the Jamia Hamdard Animal Ethics Committee (Hamdard University, New Delhi, India). New Zealand rabbits of either sex weighing 2.8 to 4.1 kg were used to measure the *in vivo* release of the drug in the eye. The rabbits were housed singly in restraining boxes during the experiment and allowed food and water *ad libitum*. Free leg and eye movement was allowed.

There were 9 animals in the experimental group and 3 animals in the control group. Both eyes of the control group animals received normal saline. The ocular inserts were inserted in both eyes of all animals in the experimental group. Three ocular inserts were removed after each 24 hours from eyes of animals of the experimental group. This was repeated for 5 days, namely at each 24-h timepoint. The amount of drug remaining in each ocular insert was determined as per the assay method of drug in ocular inserts given in interaction studies. Cumulative percent drug released *in vivo* was calculated.

Microbiological studies

The optimized ocular insert was evaluated microbiologically for controlled drug release for 5 days. The test microorganisms were *E. coli* (460×10^7 cfu) and *S. aureus* (450×10^7 cfu). The clinical isolates of the bacterial species were procured from the Patel Chest Research Institute (Delhi, India). A layer of seeded agar (10 mL) was allowed to solidify in the Petri plate. An ocular insert was removed from the pack and carefully placed over the agar layer and a second layer of seeded agar (10 mL) was applied to cover the insert. After solidification, the Petri plate was incubated in inverted position for 24 h at 37 ± 0.5 °C. After incubation, the length, width and area of zone of inhibition were measured around the ocular insert. Then the same insert was transferred to a fresh plate seeded with microorganisms and a second layer of seeded agar was applied to cover the insert. The same procedure was repeated for 5 days, *i.e.*, by transferring the same insert to a fresh Petri plate at an interval of 24 h. Normal saline served as a negative control.

RESULTS AND DISCUSSION

The reservoir type of the ocular insert consisted of three layers of films, the inner reservoir film containing the drug and two-rate controlling films surrounding the reservoir. The ocular inserts are composed of a central reservoir of drug enclosed in specially designed semipermeable or microporous membranes that allow the drug to diffuse from the reservoir at a precisely determined rate. For the preparation of the drug containing reservoir film, PVP K–30 was chosen as the polymer. Propylene glycol used as plasticizer was found to be compatible with the drug and PVP K-30. Best films were obtained when the plasticizer concentration was 10% (*m/m*) of the dry mass of the polymer. The content of the drug of 20 ocular inserts was estimated to be 0.72 ± 0.0003 mg.

To prepare rate controlling films, combinations of Eudragit RS 100 and RL 100 were assayed in different ratios and dibutyl phthalate was chosen as plasticizer. Flexible, uniform and transparent films were obtained containing 15% (*m/m*) of plasticizer per dry mass of polymer.

The *in vitro* release studies were performed using the drug reservoir (without rate-controlling membranes, code A, B, C, D and E). The drug reservoir that showed a fast drug release rate was chosen for the preparation of final ocular inserts. The fastest release rates were observed in the case of reservoir code B (Fig. 1). Therefore, code B was selected as the drug reservoir and it was sandwiched between two rate-controlling membranes (codes a, b, c, d, e and f) to make the final ocular inserts (codes X-1, X-2, X-3, X-4, X-5 and X-6). Ocular inserts X-1, X-2, X-3, X-4, X-5 and X-6 were subjected to *in vitro* release studies (Fig. 2).

For *in vitro* drug release studies, the slope(s) of the log (percent drug release) *vs*. log (time) plots were calculated from the fitted linear regression lines. A slope of 1.0 indicates zero order release kinetics, while a slope of 0.5 indicates diffusional square-root--of-time kinetics (14).

Drug release from the drug reservoir code D follows the first order kinetics [R = 0.9939, k = 0.0051, t = 15.622 (tabular t at p = 0.05, two tails, df = n–2, is 3.182)], which indicates that the drug release from the reservoir is proportional to the amount of drug remaining in its interior.

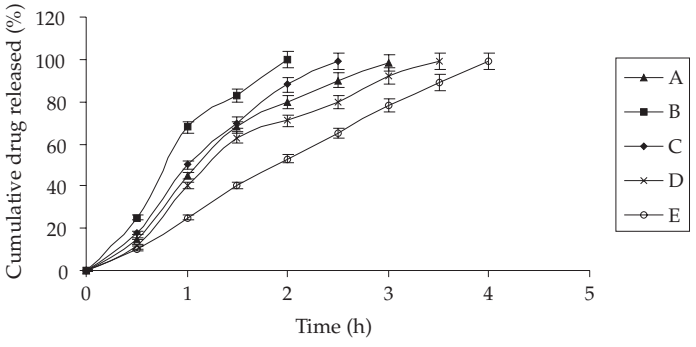

Fig. 1. Cumulative drug released *vs.* time from drug reservoirs. Mean ± SD are presented (*n = 3).*

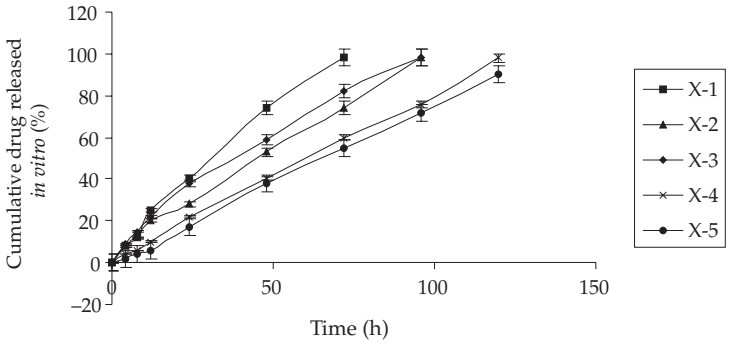

Fig. 2. Cumulative drug released *in vitro vs.* time from ocular inserts. Mean ± SD are presented (n = 3).

The ocular insert that showed maximum drug release for 120 h was selected. As shown in Fig. 2, 99.0% cumulative drug was released from formulation X-1 (48 hours), 98.6% from formulation X-2 (72 hours), 98.0% from formulation X-3 (96 hours), 98.0% from formulation X-4 (120 hours), and 90.0% from formulation X-5 (120 hours). Hence, formulation X-4 was selected as the optimized formulation. The drug was released from all ocular insert formulations according to zero order kinetics (k = 0.8 to 1.2, Table I). In order to understand the drug release mechanism from the optimized formulation, the release data were tested assuming common kinetic models (Table II). For the optimized formulation X-4, the best-fit kinetic model was the zero order kinetic model (R = 0.9996, k = 0.3422). There was no sufficient linearity for the diffusion model, Hixon Crowell and first-order kinetic models. The drug release from such system is controlled by the dissolution fluid permeating through the membrane until a sufficient internal pressure is reached to drive the drug out of the reservoir.

A relationship was found between the polymer (type and concentration) and the rate of release. The release rates were found to decrease by increasing the concentration of Eudragit RS 100 and decreasing the concentration of Eudragit RL 100 in rate-controlling membranes in formulations X-1 to X-5. This might be due to the lower permeability of Eudragit RS 100 and higher permeability of Eudragit RL 100. Formulation X-4 was found to be better, since constant and complete release of drug was observed up to 120 h.

Table I. Release of pefloxacin mesylate from ocular inserts in isotonic phosphate buffer pH 7.4 (37 °C)

Code	k ± SD[a]	p
X-1	1.24 ± 1.01[b]	< 0.0001
X-2	1.14 ± 0.06[b]	< 0.0001
X-3	0.97 ± 0.01[b]	0.0132
X-4	0.95 ± 0.01	–
X-5	0.89 ± 0.01[b]	0.0002

[a] k-slope of log percent drug released *vs.* log time, n = 3.
[b] Significantly different with respect to rate constant of X-4.

Table II. Kinetic models for formulation X-4 (16–18)

	R	*k*
Zero order	0.9996	0.3422
(t-test)	94.545	(passes)
1st order	–0.9996	–0.0034
(t-test)	93.633	(passes)
Matrix	0.9612	0.2749
(t-test)	9.219	(passes)
Peppas	0.9999	0.3432
(t-test)	215.307	(passes)
Hixon Crawell	–0.9996	–0.0011
(t-test)	93.935	(passes)
t at $p = 0.05$ (two tails), df = n–2: 2.365		

Drug and polymers were found to possess different λ_{max} values. The polymer solutions did not show absortion at wavelengths other than their λ_{max}, suggesting that polymers do not interfere with UV determination of the drug.

Interaction studies were carried out to ascertain any kind of interaction of the drug with the excipients used in the formulation of ocular inserts. For this purpose, the optimized formulation X-4, placebo formulation and the pure drug were subjected to the assay, UV, IR and TLC analyses. The principal spot in TLC obtained with the test solution was similar in position, colour and size to the chromatogram obtained with the reference standard of the drug.

R_f value of 0.54 was obtained with the medicated formulation and drug reference standard. The UV absorption maximum for the pure drug and the medicated formulation was found to be at 273 nm. The spectra recorded were taken as qualitative in order to assess the change in peaks, pattern of curve, *etc*. No major differences were observed in the IR spectra of the pure drug and the medicated formulation. The IR spectrum of the pure drug and the medicated formulation showed characteristic absorption bands for carboxylic group (3500, 3400 cm^{-1}), carbonyl group in a six membered ring (1722 cm^{-1}), unsaturation (1635 cm^{-1}) and bands for aromatic rings (1480, 895, 855, 810 cm^{-1}). The UV and IR spectra of the placebo formulation showed absorption profiles exclusive of those for the pure drug and medicated formulations. On performing the assay, 99.14% ± 0.01% ($n = 6$) of the drug was recovered from the medicated formulation. The results of the assay, UV, IR and TLC analyses indicated that there was no chemical interaction between the drug and the excipients in the ocular inserts.

A very low degradation rate constant ($k_1 = 6.909 \times 10^{-5}$ $days^{-1}$) was observed on performing the stability studies according to ICH guidelines (15). It could be assumed that negligible degradation occurred, and a shelf life of 2 years could be assigned to the ocular insert.

In vivo drug released from the ocular insert was observed for 5 days by placing the ocular insert in the rabbit eye and removing it after every day for 5 days for determination of drug content. Cumulative drug released *in vivo vs.* time showed a straight line

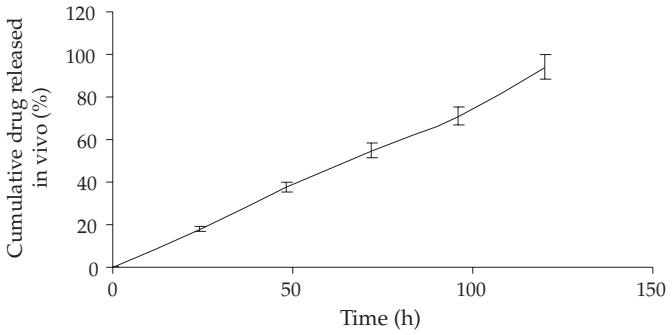

Fig. 3. Cumulative drug released *in vivo vs.* time from ocular inserts. Mean ± SD are presented (n = 3).

(Fig. 3). It was concluded that drug release *in vivo* occurred by zero order [n = –0.8417, *t*-test = 3.118 (tabular *t* at p = 0.05, 2 tails, df = n–2, is 2.776]. Scatter diagram between *in vitro* and *in vivo* release showed high correlation (R = 0.998).

The optimized ocular insert showed antimicrobial activity when tested microbiologically on solidified agar (Table III). The controlled release of the drug from ocular insert was observed for 5 days.

Table III. In vitro *inhibition of the growth of microorganisms by an optimized ocular insert*[a]

Day	Area of zone of inhibition (mm^2)	
	Staphyloccocus aureus	*Escherichia coli*
1	440	450
2	435	446
3	436	445
4	300	440
5	290	110

[a] An optimized ocular insert is that which showed the maximum drug release for the intended period of time, *i.e.*, 120 hours (5 days), n = 3.

CONCLUSIONS

Reservoir type ocular insert consisting of a polyvinyl pyrrolidone reservoir with pefloxacin mesylate and rate-controlling membranes of Eudragit RS 100 and Eudragit RL 100 mixtures demonstrated sustained release of the drug in the eye for 5 days. The *in vivo* results suggest that the lower hydrophilicity of rate-controlling membrane plays an important role in retarding the release of the drug from reservoir ocular inserts. The drug remained intact and stable in the ocular insert in storage, with no apparent chemi-

cal interaction between the drug and the excipients. Further work is in progress to establish the therapeutic utility of these systems by pharmacokinetic and pharmacodynamic studies in human beings.

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S A Ž E T A K

Okularni umeci za kontrolirano oslobađanje pefloksacin mesilata: Priprava i ispitivanja

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Pefloksacin mesilat je fluorokinolonski antibakterijski lijek učinkovit u liječenju bakterijskog konjunktivitisa. Svrha ovog rada bila je razviti okularne umetke pefloksacin mesilata s kontroliranim oslobađanjem ljekovite tvari. Okularni umeci tipa spremišnih sustava pripravljeni su lijevanjem filma u Petrijevu zdjelicu obloženu teflonom. Ispitano je oslobađanje pefloksacina *in vitro* u uređaju koji simulira uvjete u oku. Razvijeno je šest pripravaka koji se međusobno razlikuju po udjelu Eudragita RS 100 i RL 100 upotrebljenog u pripravi membrane koja kontrolira oslobađanje. Sve formulacije sadržavale su 0,72 mg pefloksacin mesilata, 2,69 mg polivinil pirolidona (PVP) K-30, plastifikatore, propilen glikol (10% *m/m*) i dibutil-ftalat (15%, *m/m*). Provedena su mikrobiološka ispitivanja te *in vivo* ispitivanjima interakcija i stabilnosti. Ukupno se iz pripravaka oslobodilo 90–98% ljekovite tvari u razdoblju od 48 do 120 h. Ispitivanja su pokazala su da je pripravak s udjelom RS 100/RL 100 (4:1) najprihvatljiviji. Tim oblikom okularnog umetka postignuto je *in vitro* oslobađanje pefloksacina tijekom 5 dana. Za to vrijeme pripravak je stabilan u ambijetalnim uvjetima.

Ključne riječi: pefloksacin mesilat, okularni umetak, *in vitro* oslobađanje, *in vivo* ispitivanja

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