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Design and Evaluation of Soluble Ocular Drug Insert for Controlled Release of Ciprofloxacin Hydrochloride

A. S. Mundada and B. K. Shrikhande
University Department of Pharmaceutical Sciences, Nagpur University Campus, Amaravati Road, Nagpur

ABSTRACT **Purpose**: Soluble ocular inserts of ciprofloxacin hydrochloride were prepared with the aim of achieving once a day administration. **Design**: Drug reservoir was prepared using natural hydrophilic polymer viz. gelatin while rate-controlling membrane was prepared using hydrophobic ethyl cellulose. Ocular inserts were evaluated for their physicochemical parameters like thickness, weight uniformity, drug content, percent moisture loss, and percent moisture absorption. The in vitro drug release studies were carried out using Bi-chambered donar receiver compartment model. Since targeted prolong release was observed in formulation CF2 and CF5, these formulations were further subjected to in vivo drug release study using rabbits as an animal model. In vitro drug release kinetic data was treated according to Zero, First, and Higuchi kinetics to access the mechanism of drug release. **Results**: Correlation between in vitro and in vivo drug release was found to be strong revealing the efficacy of the formulation. **Conclusion**: Formulation CF5 has achieved target of present study such as increase residence time, prolong drug release, reduction in frequency of administration, and, thus may improve the patient compliance.

KEYWORDS Soluble ocular insert, Ciprofloxacin hydrochloride, Gelatin, In vitro and In vivo release, Controlled release

INTRODUCTION

The eye is an interesting organ. The tear flow and blinking reflex maintains a good environment and removes foreign material from the eye. In ocular drug delivery, the physiological constraints imposed by protective mechanism of the eye lead to low absorption of drugs and sometimes short duration of therapeutics effect. One of the reasons for relatively low bioavailability of conventional eye drops is their short precorneal contact time. When drug solution is administered in the form of drops, effective tear drainage and blinking results in a ten-fold decrease in drug concentration in 4–20 min (Maurice, 1987). The drug absorption is also dependent upon the chemical nature of the

Address correspondence to A. S. Mundada, University Department of Pharmaceutical Sciences, Nagpur University Campus, Amaravati Road, Nagpur 440 033, India; Tel: +91-09224360591; E-mail: atishmundada@rediffmail.com

drugs since the corneal permeability depends upon molecular size and hydrophobicity of drugs (Grass & Robinson, 1984). By tear drainage the main part of administered drug is transported via the naso-lachrymal duct to the GI tract where it may be absorbed, sometimes causing the systemic side effects. Rapid elimination of administered eye drops often results in a short duration of therapeutic effect making a frequent dosing regimen.

In order to increase effectiveness of the drug, a dosage form should be chosen which increases the contact time of the drug in the eye. This may increase bioavailability, reduce systemic absorption, and reduce the need for frequent administration leading to improved patient compliance.

Ocular therapy would be significantly improved if precorneal residence time is increased and the most common way to achieve this is by increasing the viscosity of the solution (Grass & Robinson, 1984; Saettone et al., 1984). Gels and ointments moderately affect the contact time of the drug and have long residence time. They have a low patient compliance as they blur the vision and are recommended for bedtime use.

Ophthalmic inserts are thin disks or small cylinders made with appropriate polymeric material and fitting into the lower or upper conjunctival sac. Advantages and drawbacks of this interesting delivery system has been discussed in several reviews (Richardson, 1975; Shell, 1980; Chiou & Watanabe, 1982; Chien, 1982; Mikkelson, 1984; Buri, 1985; Lee & Robinson, 1986; Salminen, 1987; Lee, 1990; Bawa, 1993; Saettone, 1993; Gurtler & Gurny, 1995).

Ciprofloxacin hydrochloride is 1-cyclopropyl-6-fluro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid hydrochloride monohydrate. Ciprofloxacin hydrochloride is an extremely potent antibacterial agent with potent activity against most +ve gram and gram –ve bacteria. Ciprofloxacin is the best alternative to more toxic drugs such as aminoglycosides (Chambers, 2001).

Ciprofloxacin hydrochloride is among the most commonly used drug for the treatment of ocular infections. Presently it is available in the form of eye drops, which need to be administered 1–2 drops every 15–30 min initially in acute infection and 1–2 drops administered 6 times daily or more in severe conditions. To overcome these limitations associated with dosage regimen, an attempt has been made to formulate soluble ocular inserts (Saettone & Saleminen, 1995) that may not only improve the efficiency of the therapy but also patient compliance.

MATERIAL AND METHODS

Materials

Ciprofloxacin hydrochloride was obtained as a gift sample from Zim Laboratories, Nagpur. Ethyl cellulose was procured from S.D. Fine Chemicals (Boisar, India) and gelatin from Qualigens Fine Chemical. All other chemicals used were of analytical grade.

Methods

Preparation of Drug Reservoir and Rate Controlling Membrane

Drug reservoir films containing different concentrations of the polymer and gelatin (Aryata & Sfeir, 1981) were prepared by solvent casting method using mercury as a substrate (Jayaprakash et al., 2000). Water was used as a casting solvent to prepare the solution of polymer and drug while glycerin was employed as a plasticizer. Glycerin was used in concentration of 70% w/w on the basis of weight of dry polymer. Drug reservoir film containing 50 mg of the drug was prepared using a ring of 4 cm diameter having 3 mL capacity. After drying at room temperature for 24 h, circular rings of 8 mm diameter each containing 2 mg of the drug were taken out.

Rate controlling membrane was prepared using three different concentration of ethyl cellulose and employing dibutyl phthalate as a plasticizer. Dibutyl phthalate was used in the concentration of 30% w/w based on the weight of dry polymer. Films were prepared by solvent casting method using methanol as a casting solvent. After drying at room temperature circular rings of 10 mm diameter were cut and used to seal both the sides of the drug reservoir to control release from the periphery (Ali & Sharma, 1991). The formulations so prepared were designated as CF1, CF2, CF3, CF4, CF5, and CF6.

Physicochemical Evaluation of Ocular Inserts

The prepared ocular inserts were evaluated for thickness, weight variation, drug content, percent moisture loss, and percent moisture absorption.

Uniformity of Thickness

Insert thickness was measured at three different points using Micrometer screw gauge (Mitutuya, Japan) and mean film thickness was noted (Table 2).

Uniformity of Weight

From each batch, three inserts were taken out and weighed individually using digital balance (A & D, Japan). The mean weight of insert was noted (Table 2).

Drug Content Uniformity

To check the drug content uniformity, three inserts were taken out from each film and drug content determined using the procedure of IP for ciprofloxacin hydrochloride (Pharmacopoeia of India, 1996).

Amount of ciprofloxacin hydrochloride in one insert is given by:

$$C = \frac{\mathrm{As} \times \mathrm{Cr}}{\mathrm{Ar}}$$

where, As is the absorbance of sample solution, Cr is the concentration of ciprofloxacin hydrochloride in standard solution, and Ar is the absorbance of standard solution of ciprofloxacin hydrochloride. The same procedure adopted for all the batches and drug content was noted (Table 2).

Percentage Moisture Absorption

Percentage moisture absorption test was carried out to check the integrity of the inserts (Graber, 1991). Individual inserts were weighed and placed in a desiccator maintained at high relative humidity using an excess amount of salt in solution. After three days the inserts were taken out and reweighed. The percentage moisture absorption was calculated using the formula

$$\%\ \text{Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage Moisture Loss

Percentage moisture loss was carried out to check the integrity of the film at dry conditions (Dhanaraju et al., 2002). Three inserts from each was taken for study. Inserts were weighed individually and kept in a desiccator containing anhydrous calcium chloride. After three days, inserts were taken out and reweighed. Percentage moisture loss was calculated using the formula

$$\%\ \text{Moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

In vitro Drug Release Study

The in vitro drug release studies were carried out using a bi-chambered donar receiver compartment model designed using commercial semipermeable membrane of transparent and regenerated cellulose type (Sigma dialysis membrane) (Jayaprakash et al., 2000; Saisivam et al., 1999; Aquil, 2005). Insert was placed in donar compartment and 7 μL of phosphate buffer pH 7.4 was maintained at the same level throughout study in donar compartment to simulate tear volume (Chien, 1993). Semipermeable membrane was used to mimic in vivo conditions like corneal epithelial barrier. The entire surface of the membrane is in contact with the reservoir compartment that contains 25 mL of phosphate buffer pH 7.4 stirred continuously using magnetic stirrer at 20 rpm to simulate blinking action (Chien, 1993; Robinson, 1993).

At periodic intervals, a defined quantity of sample was withdrawn from sampling port and replaced with equal volume of phosphate buffer pH 7.4. Drug content was analyzed using phosphate buffer pH 7.4 as blank on UV/Visible spectrophotometer (Shimadzu Inc., Japan) (Pharmacopoeia of India, 1996).

The release data obtained was treated as per Zero order, First order, and Higuchi release kinetics to access the drug release kinetic from the inserts (Table 3).

Draize Eye Irritancy Test

The inserts were sterilized using γ-radiation before Draize eye irritancy test and in vivo drug release studies. Pure ciprofloxacin hydrochloride, which was sterilized along with the inserts, was analyzed for potency to check the integrity after sterilization using TLC analysis and IR spectrophotometer.

The Draize eye irritancy test is currently the most valuable and reliable method for evaluating hazard or safety of a substance introduced into or around the eye. Eye irritancy potential of a substance was determined on the basis of its ability to cause injury to the cornea, iris, and conjunctiva when a substance is applied to the

eye (Draize et al., 1944). Testing was carried out on adult albino rabbits weighing about 2.5 to 3.5 kg of either sex. All rabbits were maintained under 12 h light and dark cycles and were fed with green vegetables throughout the course of study. Food and water was allowed ad libitum. A series of six rabbits were used for testing the eye irritation potential of the polymer.

One placebo insert was made up of gelatin sandwiched using films of ethyl cellulose devoid of the drug placed into the cul-de-sac of the rabbit while other eye served as a control.

In vivo Drug Release Study

Inserts sterilized using γ-radiations were used for in vivo drug release studies. Two groups containing 10 and 12 healthy rabbits were used to study the drug release in vivo from formulation CF2 and CF5 which showed the desired in vitro drug release, respectively. Each rabbit was kept in good hygienic condition in order to avoid vulnerability to any disease including ophthalmic type. Sterilized insert was placed in the cul-de-sac of each rabbit while the other eye served as a control. At periodic intervals the inserts were taken out carefully from the cul-de-sac of each rabbit and analyzed for the remaining drug content (Sane et al., 1992; Dandagi et al., 2004).

RESULTS AND DISCUSSION

In the present study an attempt has been made to formulate soluble ocular insert of ciprofloxacin hydrochloride using different polymer concentrations for preparing the drug reservoir and rate controlling membrane.

Preparation of Ocular Insert

Ocular inserts of ciprofloxacin hydrochloride were prepared using two different concentrations of gelatin for preparing the drug reservoir. Ethyl cellulose has been employed in three different concentrations to prepare the rate controlling membrane. Gelatin has been chosen, as it is a natural polymer having good film forming property. Glycerin and dibutyl phthalate were utilized as plasticizers for preparation of gelatin and ethyl cellulose flexible films, respectively. The prepared batches (Table 1) were found to be uniform and flexible proving the efficiency of the solvent casting method for preparing the inserts.

Physicochemical Evaluation

Physicochemical evaluation studies (Table 2) revealed that all batches were uniform with respect to

TABLE 1 **Formulation Chart**

Formulation code	Gelatin concentration % w/v	Ethyl cellulose concentration % w/v	Glycerin concentration % w/w	Dibutyl phthalate % w/w
CF1		3		
CF2	16	4		
CF3		5	70	30
CF4		3		
CF5	18	4		
CF6		5		

TABLE 2 **Physicochemical Evaluation**

Formulation	Thickness* (mm)	Weight* (mg)	Drug content* (mg)	% moisture loss*	% moisture absorption*
CF1	0.170 (0.01)	12.38 (0.21)	1.977 (0.02)	6.79 (0.13)	9.03 (0.36)
CF2	0.170 (0.01)	12.39 (0.13)	1.978 (0.03)	5.23 (0.16)	10.53 (0.7)
CF3	0.175 (0.02)	12.39 (0.25)	1.977 (0.02)	4.70 (0.21)	11.94 (0.37)
CF4	0.190 (0.02)	12.42 (0.35)	1.980 (0.01)	7.59 (0.03)	14.37 (0.21)
CF5	0.193 (0.03)	12.45 (0.24)	1.980 (0.02)	7.05 (0.08)	13.86 (0.17)
CF6	0.193 (0.09)	12.46 (0.41)	1.977 (0.07)	6.10 (0.10)	12.50 (0.4)

* Indicates average of three readings.
The S.D. values are given in the parentheses.

thickness, weight of individual insert, and drug content. The minimum standard deviation values suggest that the process was reproducible given uniform thickness, weight, and drug content of inserts. Formulation CF4 showed high moisture absorption which may be attributed to a high concentration of gelatin and less concentration of ethyl cellulose. This is assumed that less concentration of ethyl cellulose offered minimum hindrance to the transfer of moisture. While formulation CF3 had shown low moisture absorption which may be due to the high concentration of ethyl cellulose as a rate controlling membrane, moisture loss study revealed that formulation CF4 showed high moisture loss may be due to less hindrance offered by ethyl cellulose. Formulation CF1 showed high moisture loss might be due to high gelatin and low ethyl cellulose concentration.

In vitro Drug Release Study

In vitro drug release study (Fig. 1) reveals that formulations CF2 and CF5 are capable of extending the drug release up to 12 h as this fulfills the aim of the present study of once a day therapy for ciprofloxacin hydrochloride. These two formulations were further selected for in vivo drug release study.

Draize Eye Irritancy Test

All γ-irradiated inserts were found to pass sterility test IP. Results of Draize eye irritancy test reveals that all inserts prepared using gelatin as reservoir and ethyl cellulose as a rate controlling membrane were non-toxic and non-irritating to the eye. Total score was zero. As inserts were not expelled out of the cul-de-sac of the rabbits it suggests that the insert's dimensions were appropriate for use.

In vivo Drug Release Study

In vivo drug release study from insert formulations CF2 and CF5 were found to be in accordance with that of in vitro drug release study (Fig. 2). The correlation between in vitro and in vivo drug release study was found to be strong and positive revealing the efficacy of the formulation (Jayaprakash et al., 2000) (Fig. 3).

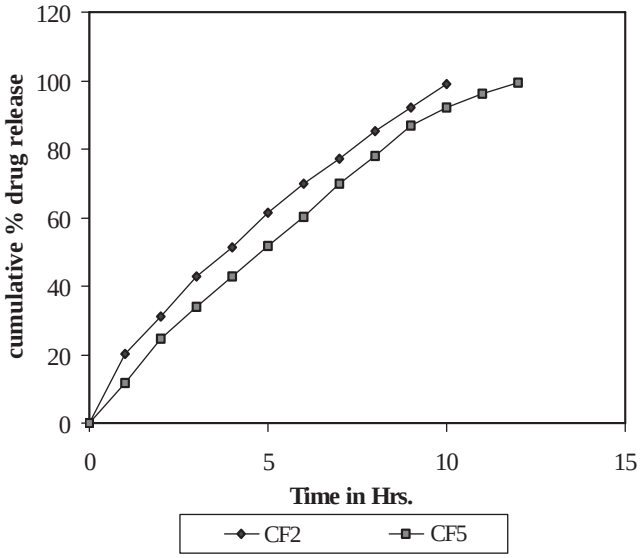

FIGURE 2 In Vivo Drug Release Study.

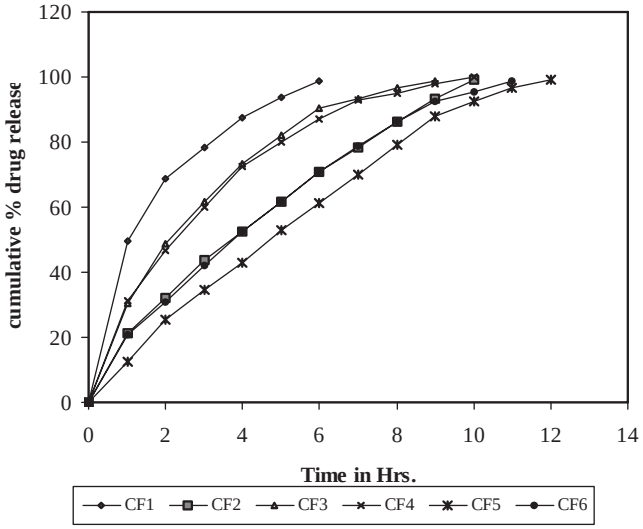

FIGURE 1 In Vitro Drug Release Study.

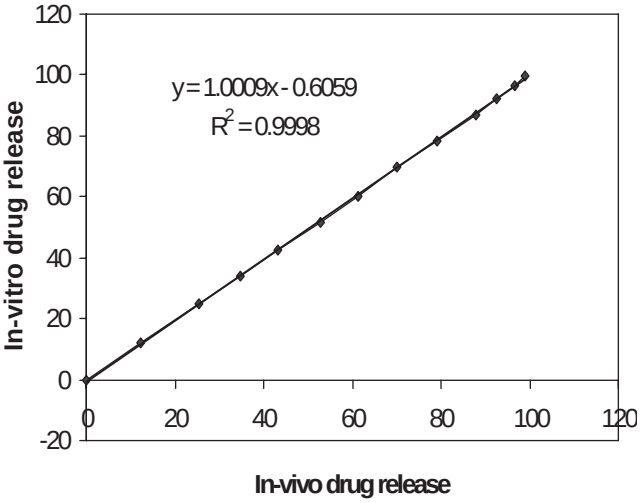

FIGURE 3 In Vitro and In Vivo Correlation Study.

TABLE 3 Regression Coefficient

Formulation	Zero order	First order	Higuchi kinetics
CF1	0.8245	0.9279	0.9825
CF2	0.9768	0.7990	0.9802
CF3	0.8837	0.957	0.9882
CF4	0.8701	0.8451	0.9857
CF5	0.9807	0.8603	0.9634
CF6	0.9634	0.8991	0.9823

In vitro drug release was found to follow square root of time (Higuchi release) kinetics indicating drug release was taking place by diffusion mechanism from the inserts (Saettone, 1993) (Table 3).

CONCLUSION

From the results of the study, it may be concluded that a formulation containing 18% gelatin sandwiched between a 4% ethyl cellulose membrane has achieved targets such as increase residence time, prolong drug release, reduction in frequency of administration, and thus, may improve the patient compliance.

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