

Design and Evaluation of Diclofenac Sodium Ophthalmic Inserts

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Abstract

Diclofenac sodium ophthalmic inserts were prepared by using methyl cellulose (MC), sodium carboxymethyl cellulose (SCMC) alone and in combination. Weight variation, thickness, drug content, ocular irritation and stability of medicated inserts were evaluated. *In vitro* study was carried out by using a semipermeable dialysis membrane. According to the results, 97 % of drug was released from the formulation containing 4% SCMC and 1% MC in combination over a period of 12 h. Release followed zero order kinetics. Medicated inserts were subjected to UV irradiation and *in-vivo* drug release studies. No significant change was observed in the drug content and physical features during storage at 30°C and 40°C for 2 months. From this study it was concluded that ophthalmic inserts prepared with 4% SCMC and 1% MC in combination showed sustained release and were found to be stable.

Key words: Diclofenac sodium, ocuserts, *in vitro*, *in vivo* evaluation.

Introduction

Eye drops and eye ointments are conventional ocular dosage forms. They have certain disadvantages like frequent administration, poor availability, massive and unpredictable doses, drainage of medication by tear and nasolacrimal fluid (Lee and Robinson, 1979; Udupa, 1993; Rastogi *et al.*, 1996). These factors requires to formulate a controlled release ocular drug delivery system which maintains a steady state drug release. The literature survey reveals good scope of work in this direction. In the present study, an attempt was made to formulate ocuserts of diclofenac sodium using polymers like methyl cellulose, sodium carboxymethyl cellulose and a formulation with the combination of these two polymers.

Material and Methods

Diclofenac sodium (I.P.) was kindly provided by Tablets India (P) Ltd., Chennai. The polymers MC, SCMC were purchased from S. D. Fine Chemicals (P) Ltd., Boisar. Glycerin and methanol was procured from Merck India (P) Ltd., Mumbai. Dialysis membrane (cut off 12,000) was purchased from the Sigma Chemicals Co., St. Louis, USA. All other ingredients were of analytical grade.

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Preparation of ocular Films: A series of ocular films containing 122 mg of diclofenac sodium with varying percentages of polymer were casted on a glass plate (area of 49 cm² having 7 ml capacity). 1 ml of glycerin was used as plasticizer for 10 ml of polymer solution. After drying at room temperature for 24 h, circular films of 8 mm diameter (an area of 0.56 cm²) each containing 2 mg of drug were cut for evaluation (Manikandar et al., 1998).

Preparation of rate controlling membrane: A rate controlling membrane was casted on a glass plate using the polymer ethyl cellulose (6 %) by incorporating 1 ml of glycerin as plasticizer and circular membranes of 10 mm diameter were cut by using a special mould.

Preparation of ocuserts: The reservoir films containing the drug were sandwiched in between the rate controlling membrane to control the release and they were fixed with reservoir film by applying chloroform on the edges of the controlling membrane.

Drug Content: Ophthalmic inserts were dissolved in distilled water by shaking and this solution was kept for 10-15 min to get a clear solution. Drug content was then determined spectrophotometrically at 276 nm after proper dilution (Babu et al., 2001). The results given are the mean of five determinations.

In vitro release: Semipermeable membrane obtained from Sigma which has molecular wt cut off 12,000 Daltons, was used in this study. This membrane was tied to one end of the open cylinder which acts as donor compartment. The ophthalmic disc was placed inside the compartment. The semipermeable membrane acted as corneal epithelium. Then the open-ended cylinder was placed over a beaker containing 50 ml of distilled water which acted as receptor compartment. This was continuously stirred using a magnetic stirrer at 50 rpm. The temperature was maintained at 37 ± 1°C. 1 ml of the sample was withdrawn at hourly intervals from the receptor compartment and the same quantity was replaced with distilled water. The cumulative percentage of drug released was determined spectrophotometrically at 276 nm. The experiment was carried out in triplicate and average values are reported.

In vivo studies: Among three formulations, formulation F₃ (matrix containing 4 % SCMC and 1 % MC in combination) was chosen for the animal studies. 8 male healthy rabbits (*Orytolagus Cuniculus*) (Ali, 1991) weighing 1-2 kg each were divided into 2 equal groups. They were kept in 2 cages with husk bedding and were fed with rodent pellet diet and water as much as required. A dark and light cycle of twelve hours was maintained. To the first group plain discs (without drug) were placed in the cul-de-sac of the left eye. To the second group medicated discs were placed in the cul-de-sac of the left eye. Before inserting the discs into the eye the sides of the plain discs and medicated discs were sterilised under UV light for 15 min at a 0.305 m height from a fixed UV lamp (Kannan, 1996). The eyelids were closed by using cotton and non irritant adhesive tape until sampling. After 8 h, the plain discs and medicated discs were taken out, dried at room temperature and estimated for remaining amount of drug spectrophotometrically by using plain discs as control. All experimental protocols involving laboratory animals were approved by IAEC.

Ocular irritation: The potential ocular irritation and/or damaging effects of the ocusert under test were evaluated by observing them for any redness, inflammation (or) increased tear

production. Formulation was tested on five rabbits by placing the inserts in the cul-de-sac of the left eye. Both eyes of the rabbits under test were examined for any signs of irritation before treatment and were observed up to 12 h (Kaur *et al.*, 2000).

Stability studies: The ophthalmic insert was stored in the amber colored glass bottles at 2 different temperatures (30°C and 45°C) for a period of 2 months (Narasimhamurthy, 1997). The samples were withdrawn at every 10 day intervals and the physical features of the samples were analysed. Percentage of drug content was determined.

Results and Discussion

In the present study, efforts were exerted to prepare ophthalmic inserts of diclofenac sodium using polymers like MC, SCMC. The films were casted on a glass plate using distilled water as solvent. Ethyl cellulose (6 %) was used as a rate controlling membrane.

The physicochemical evaluation of ophthalmic inserts indicates that thickness values were in a range of 0.197 ± 0.01 mm - 0.215 ± 0.02 mm (Table 1). The thinnest and thickest formulations were F₁ containing 3% MC and F₃ containing 4% SCMC and 1% MC in combination, respectively. Thickness of ocuserts slightly increased as the concentration of polymer increased. The formulations were not very thick and hence did not cause irritation. Use of less amount of plasticizer was observed to cause brittleness in the medicated discs, but use of greater amount of plasticizer (1ml plasticizer per 10 ml) displayed little opaqueness and good folding endurance. The weight of the ophthalmic inserts varied between 14.38 ± 2.28 mg and 20.16 ± 1.30 mg. The drug content of the formulations was uniform with a maximum variation of 0.3%. The drug content was 1.68 ± 0.22 mg and 1.60 ± 0.12 mg before and after UV irradiation, respectively. It confirmed that insignificant loss was observed in the drug content after UV irradiation. *In vitro* diffusion study revealed that 97% of drug released from the formulation F₃ containing 4% SCMC and 1% MC in combination through an semipermeable dialysis membrane over an extended period of 12 h as depicted in Fig. 1.

Table 1: Physicochemical features of diclofenac sodium ocuserts (n = 5)

Physicochemical parameters	F ₁	F ₂	F ₃
Thickness * ± S.D in mm	0.197 ± 0.01	0.201 ± 0.02	0.215 ± 0.02
Weight ** ± S.D in mg	14.38 ± 0.28	14.45 ± 0.61	20.16 ± 0.30
Drug content** ± S.D in mg	1.67 ± 0.30	1.68 ± 0.12	1.68 ± 0.02

F₁: matrix film containing 3%MC; F₂: matrix film containing 3% SCMC; F₃: matrix film containing 4% SCMC and 1% MC in combination.

*n = 10

**n = 5

A linear relationship between average percentage of cumulative drug released vs time was observed. Drug release from formulations F₁ and F₂ was faster compared to formulation F₃ during 7 h.

The extended period of drug release may be due to the slow diffusion of drug from the combined polymeric ophthalmic insert (Formulation F₃). Moreover, formulation F₃ exhibited zero-order release pattern as shown in Fig. 2. Hence this formulation was proved to be of great interest and it was further taken for animal studies.

The *in vivo* studies showed about 47% of drug release from the ocusert after 8 h. Plain ocuserts placed in the cul-de-sac of the animal confirmed the withstanding capacity of the polymers in the eye for 8 h without irritation. The medicated discs were stable at two different temperatures. The drug content was found to be 99.93%, 99.89% in formulation F₃ at the end of 1st and 2nd months, respectively. The degradation constant (K) for 30°C and 40°C were 0.0112 and 0.0189 per day, respectively.

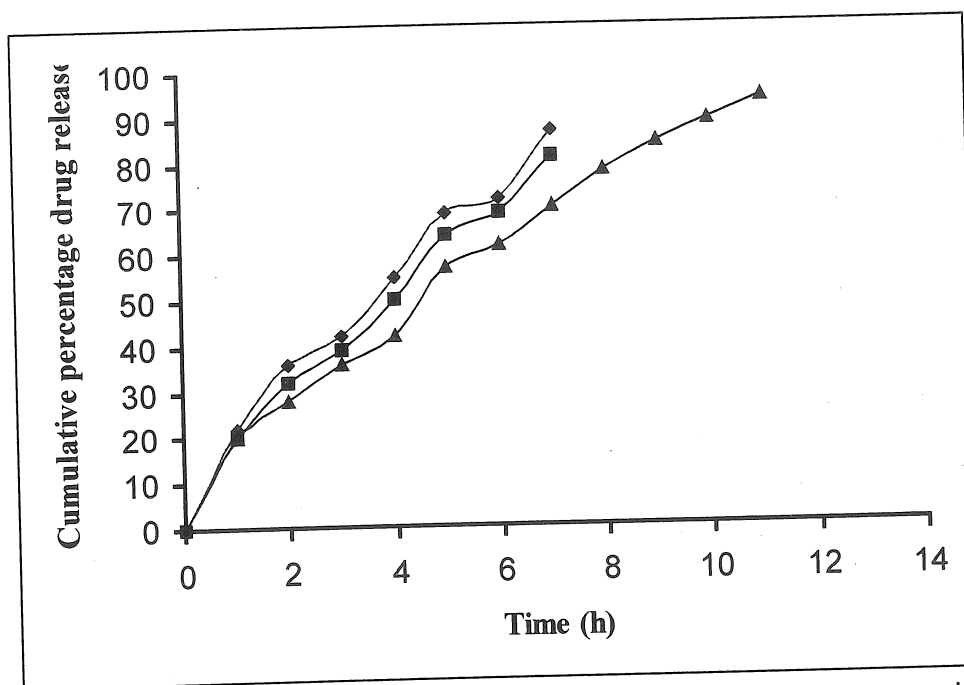


Figure 1. *In vitro* release of diclofenac sodium from ophthalmic inserts containing 3% MC (-◆-); 3% SCMC (-■-); 4% SCMC and 1% MC in combination (-▲-).

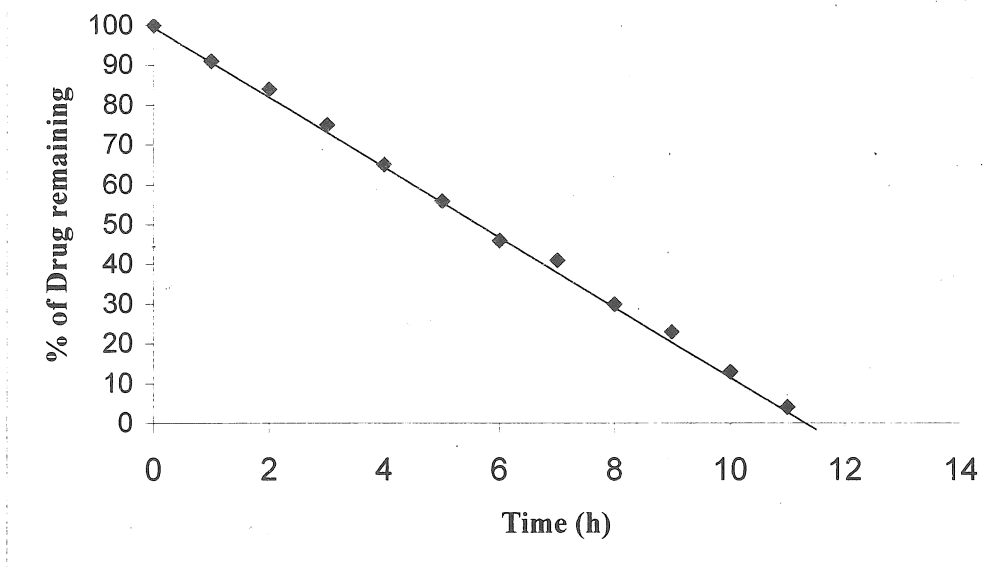


Figure 2. Zero order drug release pattern from formulation F₃

The rabbits subjected to ocular irritation tests did not show any signs of irritation, inflammation and abnormal discharge. Behavior of these animals was slightly agitated when compared with that of the normal animals, but the intake of food and water was normal.

As a conclusion, these results indicated that the formulations of diclofenac sodium were achieved the objectives of increased contact time, prolonged drug release and decreased frequency of administration.

It is evident that a successful attempt can be made to treat ocular disorders using an ophthalmic insert containing 4% SCMC and 1% MC in combination according to the data of this study. Patient compliance can also be improved to a greater extent with the use of such ophthalmic inserts.

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