

DESIGN AND EVALUATION OF DICLOFENAC SODIUM OCUSERT

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ABSTRACT: Diclofenac sodium ocuserts were prepared by using different polymers such as hydroxy propyl methyl cellulose (HPMC), hydroxy propyl cellulose (HPC), methyl cellulose (MC) and ethyl cellulose (EC) at various concentrations and combinations using dibutyl phthalate (DBP) as plasticizer. The ocuserts is prepared by solvent casting technique. The prepared ocuserts were evaluated for moisture absorption, moisture loss, thickness, weight variation, folding endurance and drug content. The *invitro* drug release was studied using commercial semi permeable membrane. A zero order release formulation F3 were sterilized by ethylene oxide and subjected to in vivo studies. IR spectral observation show there is no interaction of drug with polymer which indicates the intactness of drug in formulation. Ocular toxicity test and accelerated stability studies were also carried out for the formulation F3.

Keywords: Diclofenac sodium, hydroxy propyl methyl cellulose, ocuserts, solvent casting technique, Once a day.

INTRODUCTION

Drugs administered in traditional topical ophthalmic formulation such as aqueous eye drops have poor bioavailability due to rapid precorneal elimination. To reach therapeutic levels frequent instillation of the drug are required, leading to a low patient compliance. Furthermore, the drug level in the tear film is pulsed, with an initial period of overdosing, followed by a longer period of underdosing^{1, 2}. Consequently, numerous novel ophthalmic drug delivery systems were developed to achieve a higher bioavailability of drugs. Among these formulations are in situ gelling polymer³⁻⁶, microspheres⁷⁻¹¹, nanoparticles¹²⁻¹⁵, liposomes¹⁶⁻¹⁹ and ocular inserts²⁰⁻²⁵. The advantage of ocular inserts, which are solid devices placed in the cul-de-sac of the eye in comparison with liquid formulations are numerous. Because of the prolonged retention of the devices and a controlled release, the effective drug concentration in the eye can be ensured over an extended time period. Dosing of the drug is also more accurate and the risk of systemic side-effects is decreased. Furthermore, solid devices have an increased shelf life and the presence of additives such as preservatives is not required. Nevertheless, despite all these advantages ocular inserts have so far not been widely used in ocular therapy.

Diclofenac sodium is an aryl-acetic acid derivative in the group of Non steroidal anti-inflammatory drugs. It is mainly employed for the inhibition of intraoperative miosis and post-operative inflammation in cataract surgery. In this study, an attempt was made to prepare diclofenac sodium ocular inserts with the target of increasing the contact time, reducing the frequency of administration, improving patient compliance and obtaining greater therapeutic efficacy^{26, 27}.

MATERIALS AND METHODS

Diclofenac sodium was obtained from M/s NATCO Pharma Ltd, Hyderabad, India. Polymers such as HPMC-15cps, MC, EC and HPC were obtained from Loba Chemicals, Mumbai as gift samples.

Preparation of drug reservoir

The reservoir film containing 6.25 mg of diclofenac sodium was casted with different polymers at various concentrations were dissolved in water and casted on glass plate using a ring 4 cm diameter having (an area of 12.571cm²) 3 ml capacity. Dibutyl phthalate (30 % W/W of polymer) used as a plasticizer. After drying, circular films of 8 mm diameter (an area of 0.5024cm²) each containing 250 mg of diclofenac sodium was cut. (Table 1)

Table 1: Composition of various polymers in different formulations per ring

Formulation code	Rate Controlling Membrane (%)	Drug Reservoir				Plasticizer
	EC	HPMC	HPC	MC	EC	
F1	3	4	-	-	-	DBP (30% W/W)
F2	3	-	4	-	-	
F3	3	3	1	-	-	
F4	3	2	2	-	-	
F5	3	1	3	-	-	
F6	3	-	-	4	-	
F7	3	-	-	-	4	
F8	3	-	-	3	1	
F9	3	-	-	2	2	
F10	3	-	-	1	3	

Preparation of rate controlling membrane

The rate controlling membrane was casted on a glass plate using ethyl cellulose which is dissolved in chloroform and dibutyl phthalate (30 % w/w of polymer) as plasticizer was prepared. Circular membranes of 10 mm diameter were cut using a special mould. Both the drug reservoir was sealed to control the release from the circumference²⁸.

In vitro release studies

The *in vitro* release studies were carried out using a bi chambered donor receptor compartment model designed using commercial semi-permeable membrane of transparent and regenerated cellulose type (Sigma dialysis membrane). It was tied at one end of the open-end cylinder, which acted as the donor compartment²⁹. The ocuserts was placed inside the donor compartment. The semi permeable membrane was simulated ocular *in vivo* conditions like corneal epithelial barrier. In order to simulate the tear volume, 0.7 ml of pH 7.4 isotonic phosphate buffer was placed and maintained at the same level through out the study in the donor compartment, which contain 25 ml of pH 7.4 isotonic phosphate buffer. The drug content was analyzed at 276 nm using Shimadzu 1201 UV/Vis spectrophotometer.

Evaluation of ocuserts

The prepared ocuserts were evaluated for moisture absorption³⁰, moisture loss³⁰, thickness, weight variation, folding endurance and drug content. Formulation F3 was sterilized by using ethylene oxide. The test for sterility of formulation F3 was carried out according to the method prescribed in Indian Pharmacopoeia for detecting the presence of viable forms of Bacteria, fungi and yeast using fluid thioglycollate media and chopped meat medium having positive and negative control. Accelerated stability studies were carried out exposing the formulation F3 to the temperature of 4⁰ C, 37⁰ C and 60⁰ C for 42 days. Ocular toxicity test were conducted in 6 male healthy rabbits weighing about 1.5 kg. The eyes were washed with all glass double distilled water warmed to body temperature..

The medicated disc was placed in cul-de-sac of right eye keeping the left eye as control.

RESULTS AND DISCUSSION

In the present study, efforts have been made to prepare ocuserts of Diclofenac sodium using different polymers such as HPMC, HPC, MC and EC³¹ (Table 1). The ocuserts were prepared as membrane permeation controlled devices with the drug loading sufficient enough for 'Once a day' therapy.

F7 and F10 exhibit low percentage moisture absorption which could be due to its low degree of hydrophilicity than other formulations. The formulation F3 and F1 had more percentage moisture absorption due to HPMC, which is hydrophilic in nature. Moisture loss study revealed that F7 and F10 show low moisture loss, which is due to low moisture degree of hydrophilicity of polymer compared to other formulations. F1 and F3 show maximum moisture loss due to its hydrophilicity. All the batches were formulated to have thickness as minimum as possible in order to minimize irritation to the eyes. All batches were found to have thickness in the range of 0.172±0.02mm to 0.227±0.22mm and weight uniformity in the range of 19.38 to 24.83mg with minimum intra batch variations. Folding endurance and content uniformity values avowed the fact that the process used in the study is capable of giving films with uniform drug content with unsubstantial differences in targeted drug loading in addition to the physical stability of the film against the mechanical stress. The drug content analysis data revealed that all batches having the maximum drug loading (Table 2). The minimum standard deviation values revealed the fact that process used in the study is capable of giving film of uniform magnitude.

In vitro dissolution study of formulation F3 was found to release 94.76% of drug in a zero order pattern for the extended period of 24 hrs (Fig 1 & 2). Hence it was considered as the formulation of choice for *in vivo* studies. The *in vivo* release was found to be 73.80% of

loaded drug at the end of 24 hrs. To establish the correlation between *in vitro* – *in vivo* release data regression analysis was carried out. The correlation value of 0.9972 indicated correctness of the *in vitro* method followed and adaptability of the delivery system to the biological system where it can release the drug in concentration independent manner fig 3. Formulation F3 passed the test for sterility.

The sterilized ocuserts were tested for their sterility. It was found visually that the fluid thioglycollate media containing sterilized ocuserts and chopped meat medium containing sterilized ocuserts were free from turbidity. This confirms the absence of aerobic bacteria and anaerobic bacteria and fungi. From this ethylene oxide sterilization was found to be convenient for

sterilizing ocuserts. The rabbit eye subjected to ocular toxicity test did not show any signs of irritations or inflammations. The results of accelerated stability studies indicate that they are stable both physically and chemically at 4⁰ C and 37⁰ C. The period of expiry for the formulation F3 was determined by FREE and BLYTHE method. By this method it is known that the time to 90% potency is 114 days if the F3 is stored at 25⁰C.

CONCLUSION

Formulation F3 has achieved the targets of present study as prolonged zero order release, increase in contact time and reduction in frequency of administration and thus improve patient compliance.

Table 2: Physicochemical Evaluation of different formulations

Formulation code	*Percentage Moisture Absorption ±SD	* Percentage Moisture Loss ± SD	*Thickness in mm ± SD	* Weight uniformity in mg ± SD	* Folding Endurance ± SD	* Drug content in mg ± SD
F1	7.37±0.365	1.672±0.11	0.227±0.002	23.14±0.095	93±2.52	0.2567±0.0227
F2	5.95±0.118	12.61±0.096	0.168±0.0043	19.38±0.09	74±2.08	0.2532±0.0159
F3	7.25±0.318	11.57±0.057	0.217±0.0052	21.53±0.056	87±1.15	0.2488±0.02217
F4	6.44±0.227	14.14±0.046	0.180±0.0046	21.71±0.0568	82±1.53	0.2546±0.0180
F5	6.13±0.02	13.67±0.06	0.172±0.0047	20.74±0.454	70±2.52	0.2594±0.0145
F6	6.98±0.134	14.79±0.137	0.232±0.0026	24.83±0.121	95±3.05	0.2563±0.0165
F7	3.74±0.096	10.18±0.0488	0.178±0.01	22.18±0.168	72±1.73	0.2505±0.267
F8	5.97±0.103	12.82±0.07	0.224±0.0025	24.11±0.226	90±1.00	0.2527±0.0222
F9	4.30±0.0268	12.72±0.031	0.218±0.0044	23.24±0.098	78±0.577	0.2459±0.0321
F10	4.14±0.0473	11.49±0.229	0.193±0.0053	22.36±0.245	75±2.00	0.2648±0.1237

Average of three determinations

Fig 1: In vitro drug release for prepared ocusert from F1-F5

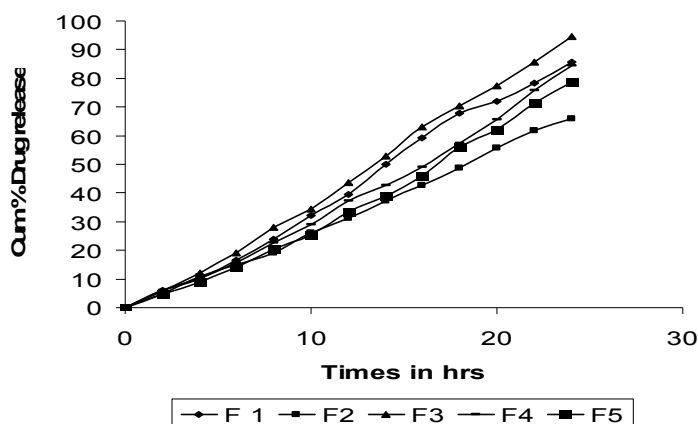
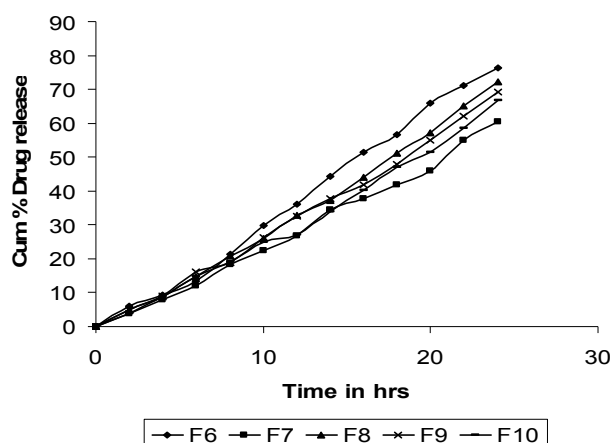
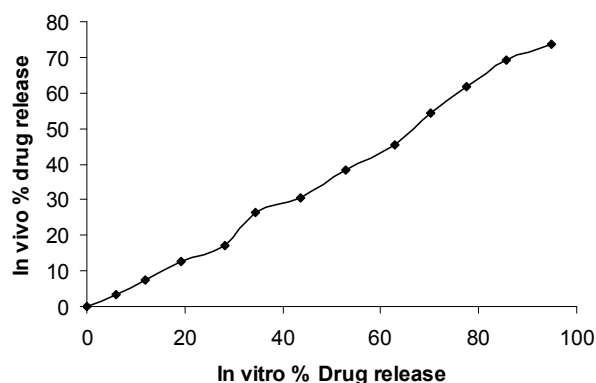


Fig 2: In vitro Drug release for prepared Ocuserst from F6-F10**Fig 3: In vitro - In vivo Correlation****REFERENCES**

- Baudoin C. Side effects of antiglaucomatous drugs on the ocular surface. *Curr. Opin. Ophthalmol.* 1996; 7:80-6.
- Topalkara A, Gurtler C, Arici DS, Arici MK. Adverse effects of topical antiglaucoma drugs on the ocular surface. *Clin. Exp. Ophthalmol.* 2000; 28:113-7.
- Gurny R, Ibrahim HP, Buri. *Ocul. Drug Delivery, Biopharm.* In: P.Edman (Ed), CRC Press, Boca Raton, Fl, 1993, 81-90.
- Cochan S, Lobel E, Trevgoda A, Oeled Y. A novel *in situ* forming ophthalmic drug delivery system from alginates undergoing gelation in the eye. *J. Control. Rel.* 1997; 44:201-8.
- Rozier A, Mazuel C, Grove J, Plazonnet B. Functionality testing of gellan gum, A polymeric excipients materials for ophthalmic dosage forms. *Int. J. Pharm.* 1997; 153:191-8.
- Srividya B, Cardoza RM, Amin PD. Sustained ophthalmic delivery of ofloxacin from a pH triggered *in situ* gelling system. *J. Control. Rel.* 2001; 73:205-11.
- Zimmer A, Kreutedr J. Microspheres and nanoparitcles used in ocular delivery system. *Adv. Drug. Deliv. Rev.* 1995; 16:61-73.
- Durrani AM, Farr SJ, Dellaway IW. Precorneal clearance of mucoadhesive microspheres from the rabbit eye. *J. Pharm. Pharmacol.* 1995; 47:581-584.
- Genta I, Conti B, Perugini P, Pavanetoo F, Spadaro A, Pulisi G. Bioadhesive microspheres for ophthalmic administration of acyclovir. *J. Pharm. Pharmacol.* 1997; 49:737-42.
- Giunchedi P, Conte U, Chetoni P, Saettone MF. Pectin microspheres as ophthalmic carriers for piroxicam; Evaluation in vitro and in vivo in albino rabbits. *Eur. J. Pharm. Sci.* 1999; 9:1-7.
- Chiang CH, Tung SM, Lu DW, Yeh MK. In vitro and in vivo evaluation of an ocular delivery system of 5-fluorouracil microspheres. *J. Ocul. Pharmacol. Ther.* 2001; 17:545-53.
- Gurny R, Boye T, Ibrahim H. Ocular therapy with nanoparticulate system for controlled drug delivery. *J. Control. Rel.* 1985; 2:353-61.
- Langer K, Zimmer A, Kreter J, Acrylic nanoparticles for ocular drug delivery. *STP Pharma Sci.* 1997; 7:445-51.
- De Campos AM, Sanchez A, Alonso MJ. Chitosan naoparitcles: a new vehicle for the improvement of the drug to the ocular surface. Application to cyclosporine A, *Int. J. Pharm.* 2001; 224:159-68.
- Cavalli R, Gasco MR, Chetoni P, Burgalassi S, Saettone MG. Solid lipid nanoparitcles (SLN) as ocular delivery system for tobramycin. *Int. J. Pharm.* 2002; 238:241-45.
- Meisner D, Mezei M. Liposome ocular delivery systems. *Adv. Drug Deliv. Rev.* 1995; 16: 75-93.
- Nagarsenker MS, Londhe V, Nadkarni GD. Preparation and evaluation of liposomal formulation of tropicamide for ocular delivery. *Int. J. Pharm.* 1999; 190:63-71.
- Law SL, Huang KJ, Chiang CH. Acyclovir-containing liposomes for potential ocular delivery; Corneal penetration and absorption. *J. Control. Rel.* 2003; 63:135-40.
- Pleyer U, Groth D, Hinz B, Keil O, Bertelmann E, Rieck P, Reszka R. Efficiency and toxicity of liposomes diated gene transfer to corneal endothelial cells. *Exp. Eyes Res.* 2001; 73:1-7.
- Gurtler F, Gurny R. Patent literature review of ophthalmic inserts. *Drug Dev. Ind. Pharm.* 1995; 21: 1-18.
- Saettone MF, Salminen L. Ocular inserts form topical delivery. *Adv. Drug Deliv. Rev.* 1995; 16:95-106.

22. Gurtler F, Kaltsatos V, Boisrame B, Gurny R. Long-acting soluble bioadhesive ophthalmic drug insert (BODI) containing gentamicin for veterinary use: optimization and clinical investigation. *J. Control. Rel*, 1995; 33:231-236.
23. Lee YC, Millard JW, Negvesky GJ, Butrus SL, Yalkowsky SH. Formulation and in vivo evaluation of ocular inserts containing phenylephrine and tropicamide. *Int. J. Pharm*, 1999; 182:121-26.
24. Kawakami S, Nishida K, Mukai T, Yamamura K, Nakamura J, Sakaeda T, Nakashima M, Sasaki H. Controlled release and ocular absorption of tilisolol utilizing ophthalmic insert incorporated lipophilic prodrugs. *J. Control. Rel*, 2001; 76:255-63.
25. Ceulemans J, Vermeire A, Adriaens E, Remon JP, Lwudwig A. Evaluation of a mucoadhesive tablet for ophthalmic use. *J. Control. Rel*, 2001; 77:333-4.
26. Rastogi SK, Vaya N, Mirsha B. A novel concept in rate controlled oral drug delivery. *Eastern pharmacist*, 1995; 38: 79.
27. Gupta SK, Jingan S, Madan Mohan. Non steroidal anti-inflammatory drugs. *Eastern Pharmacist*, 1996; 39: 71.
28. Ale A, Sharma SN. Fabrication of a through flow apparatus for in vitro determination of drug from ophthalmic preparations. *Indian drugs*, 1991; 29:157-60.
29. S. Jayaprakash, D. Dachinamoorthi, S. Ramkanth, M. Nagarajan, K. Sangeetha., Formulation and evaluation of Gentamicin sulphate ocuserts. *The Pharma Review*, 2006; 131-34.
30. Alam AS, Parrot EL. Effects of adjuvants on tackiness of PVP film coating. *J. Pharm. Sci.* 1972; 61:265-69.
31. *Hand Book of Pharmaceutical Excipients*, American Pharmaceutical Association, USA and the Pharmaceutical society of Great Britain, London, 2nd edition, 1986. p. 84.
