RESEARCH PAPER

Accepted 16 August 2005
Revised 17 February 2005
Received 3 September 2004
Indian J. Pharm. Sci., 2005, 67(4): 473-476

Formulation and Stability Evaluation of Diclofenac Sodium Ophthalmic Gels

V. SANKAR*, A. K. CHANDRASEKARAN, S. DURGA, K. G. PRASANTH, P. NILANI, G. GEETHA[1], V. RAVICHANDRAN[2], A. VIJAYAKUMAR[2] AND S. RAGHURAMAN[3]

Department of Pharmaceutics, PSG College of Pharmacy, Coimbatore-641 004
[1]Department of Pharmacology, PSG Institute of Medical Sciences and Research, Coimbatore-641 004
[2]Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore-641 035
[3]Department of Medicinal Chemistry, Kakathiya University, Warangal-506 009

An ophthalmic gel of diclofenac sodium, a potent non-steroidal antiinflammatory drug was formulated using polymers of hydroxypropyl methylcellulose, sodium carboxymethylcellulose and methylcellulose. The gels were sterlized and assessed for various parameters like clarity, pH, physical appearance, physical stability, viscosity and uniformity of drug content. Almost 96% of drug was released from the hydroxypropylmethylcellulose formulation within a period of 9 h. Drug release obeys zero order kinetics. *In vitro* release for different gel formulation after 9 h is expressed in the decreasing order as follows hydroxypropylmethylcellulose gel>methylcellulose gel>sodium carboxymethylcellulose gel. Ocular irritation on score basis study in rabbits reveals that none of the gel formulation showed any redness, inflammation (or) increased tear production when compared with placebo. Diclofenac formulation was found to be more stable in hydroxypropylmethylcellulose gel compared to methylcellulose gel and sodium carboxymethylcellulose gel at ambient, refrigerator and incubator temperature. The stability of the gel was evidenced by the degradation rate constant. Formulated ophthalmic gel with hydroxypropylmethylcellulose proves to be a viable alternative to conventional eye drops as it offers longer precorneal residence time and excellent ocular tolerance.

Ophthalmic formulations are usually administered in the form of eye drops, a dosage form consisting of buffered isotonic aqueous solutions (or) suspensions of the drug. These medicaments present the inconvenience of a low bioavailability (only 0.5-2% of the applied drug penetrates the cornea) and of pulsed drug delivery[1]. Due to the unsatisfactory bioavailability obtained with the conventional eye drops, viscous liquid and semisolid preparations were utilized as an alternative therapeutic system[2]. Several authors suggest that the use of ophthalmic vehicles based on natural, semisynthetic (or) synthetic hydrogels proved to enhance the ocular bioavailability, prolong the drug duration and reduce the patient non compliance problems[3].

Diclofenac sodium is available as tablets, infusions and eyedrops (0.1%w/v). Topical administration of diclofenac sodium eyedrop is useful in the treatment of mydriatics, cycloplegics, conjunctivitis and post-cataract inflammatory conditions[4]. It can be seen that this dosage form has several drawbacks such as loss of drug from tear flow, lacrimal and nasal drainage, lesser absorption, lesser contact time, increased frequency of administration and patient non compliance. The objective of the present study was to formulate and evaluate ophthalmic gels of diclofenac sodium using different polymers with the aim to overcome

*For correspondence
E-mail: sansunv@yahoo.co.in

the above mentioned drawbacks.

MATERIALS AND METHODS

Diclofenac sodium was a gift sample from Pharma Fabricon (P) Ltd, Madurai. The polymers sodium carboxymethylcellulose-60 cps (SCMC, 60 cps), hydroxypropylmethylcellulose-15 cps (HPMC, 15 cps), methyl cellulose-40 cps (MC, 40 cps) were purchased from Genuine Chemical Co., Mumbai. Dialysis membrane (cut off 12,000) was procured from the Sigma Chemical Co., St. Louis, USA. All other ingredients were of analytical grade.

Preparation and drug content determination of gels:

The polymer (quantity of each polymer with the drug were specified in Table 1) was taken in a mortar and water was added. This was allowed to soak for about 24 h and to this required amount of drug and other additives was added. The trituration was continued to get a homogeneous dispersion of the drug in the gel. The gels were buffered at a pH of 7.2±0.05 and these were sterlised by autoclaving at 15 lbs, 121° for 20 min. These were aseptically filled in sterile plastic containers and labeled. Drug content was determined by dissolving accurate weighed quantity of gel in purified water. After suitable dilution absorbance was recorded by uv/vis spectrophotometer at 276 nm. Drug content was determined using slope of the standard curve previously plotted.

TABLE 1: FORMULATIONS OF VARIOUS DICLOFENAC SODIUM GELS

Ingredients	NACMC gel (g)	HPMC gel (g)	MC gel (g)
Diclofenac sodium	0.10	0.10	0.10
SCMC	-	-	1.0
MC	-	-	3.0
HPMC	-	4.0	-
Disodium edetate	0.01	0.01	0.01
Benzalkonium chloride (%)	0.01	0.01	0.01
Propylene Glycol (%)	10.00	10.00	10.00
Potassium Dihydrogen orthophosphate	0.908	0.908	0.908
Disodium hydrogen orthophosphate	2.38	2.38	2.38
Purified water (q.s)	100.00	100.00	100.00

Compositions of various ophthalmic gels prepared are given in the table. NACMC represents sodium carboxy methyl cellulose, HPMC denotes hydroxy propyl methyl cellulose and MC indicates methyl cellulose.

pH and viscosity:

Accurately 2.5 g of gel was weighed and dispersed in 25 ml of purified water. The pH of the dispersion was measured using pH meter (Systronics Digital -DI-707). Viscosity of the gels was determined using a Brookfield viscometer. In the present study, we selected the rate of shear (G) of 6 rpm. All the formulated gels were sheared at 6 rpm for 5 min. The shear stress (F) was recorded for each formulation

In vitro release study:

Semipermeable membrane (obtained from Sigma Chemicals) having a molecular weight cut off 12,000 was used for this study. The membranes used were transparent and regenerated cellulose type, which were permeable to low molecular weight substances. The semipermeable membrane was tied to one end of open ended cylinder (diameter 1.8 cm) which acts as donor compartment. Ten grams of gel was kept inside the compartment. The semipermeable membrane acts as corneal epithelium. The entire surface of the membrane was in contact with the receptor compartment containing 25 ml of isotonic buffer pH 7.2. The receptor compartment was continuously stirred (50 rpm) using a magnetic stirrer. The temperature maintained was 37±1°. The study was carried out for 9 h. The samples were withdrawn at predetermined time intervals and the same volume was replaced with fresh buffer medium. The absorbance of the withdrawn sample was measured after suitable dilution at 276 nm[5] to estimate diclofenac sodium. The experiment was carried out in triplicate and average values are reported.

Ocular irritation test:

The potential ocular irritancy effects of the formulations were evaluated by observing them for any redness, inflammation (or) increased tear production. Each formulation was tested on six rabbits (*Orytolagus cunniculus*), the treatment was performed by single instillation 0.02 g of gel under test into the conjunctival sac of left eye every 24 h for three days. Plain gel base was instilled into the right eye. Both eyes of the rabbit under test were examined for any signs of irritation before treatment and up to 10 h after instillation.

TABLE 2: DRUG CONTENT, pH. AND VISCOSITY OF VARIOUS GELS

Formulation	Drug content (g)	pH	Viscosity centipoise (cps)
NACMC gel	98.2±0.1	7.15	4784
MC gel	96.8±0.2	7.13	5132
HPMC gel	95.2±0.2	7.11	13146

Viscosity was determined using brookfield viscometer at a shear rate of 6 rpm for 5 min.

Evaluation was done as per the draize[6] scale technique. All experimental protocols involving laboratory animals were approved by the IAEC.

Stability studies:

Formulated gel preparations were kept at different temperature[7] conditions like ambient temperature (temperature in the working area) 25° to 28°, 8±1° (refrigerator temperature), 37±2° (temperature in the incubator) for 6 w. The following parameters[8] of the gel such as color, consistency, drug content and degradation rate constant (K) were studied.

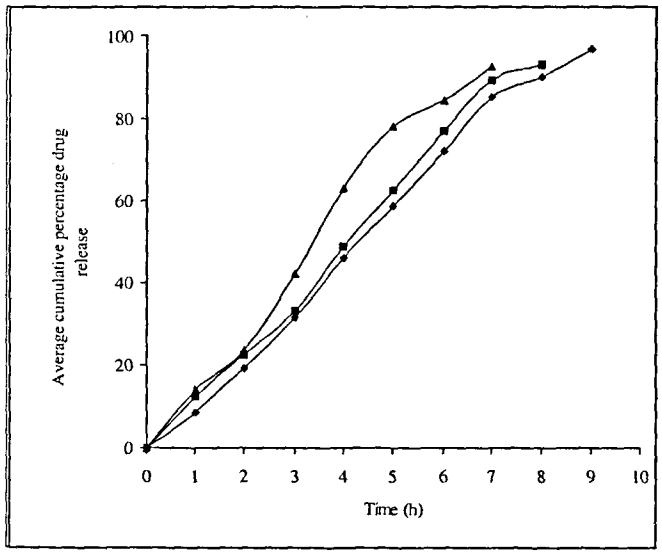

Fig. 1: Comparative *in vitro* release profile of diclofenac sodium from different gel bases

(-♦-) release of diclofenac sodium from HPMC gel. (-■-) Release of diclofenac sodium from MC gel. (-▲-) Release of diclofenac sodium from NACMC gel.

RESULTS AND DISCUSSION

In the present study efforts were made to prepare ophthalmic gels of diclofenac sodium using polymers like HPMC, SCMC and MC. Ophthalmic gels prepared with HPMC were found to be white, translucent and homogeneous. But gels prepared with SCMC, MC was found to be off white and homogeneous. Drug content values of the formulations were well within the range between 95-99% (Table 2) and pH 7.13±0.02 (Table 2). The viscosity of various formulated diclofenac sodium gels was measured using a Brookfield viscometer. Viscosities of different formulations are presented in Table 2. All the gels were found to have non Newtonian type of flow. The results of the *in vitro* release study from different gels across the dialysis membrane are depicted in (fig. 1). *In vitro* release for all the formulations showed a linear relationship between average cumulative % release Vs time. Ninety six percentage of drug was released from HPMC formulation through a semipermeable membrane within a period of 9 h. Drug release obeys zero order kinetics (fig. 2).

Though SCMC, MC formulation shows the quick release within 6 h and within 7 h the amount of drug released was less compared to the drug release from HPMC formulation. The extended and zero order release from the gel might be due to the hydroxypropyl and methoxy substituents of HPMC that render HPMC hydrophobic. The order of *in vitro* release for different gels is expressed in the de-

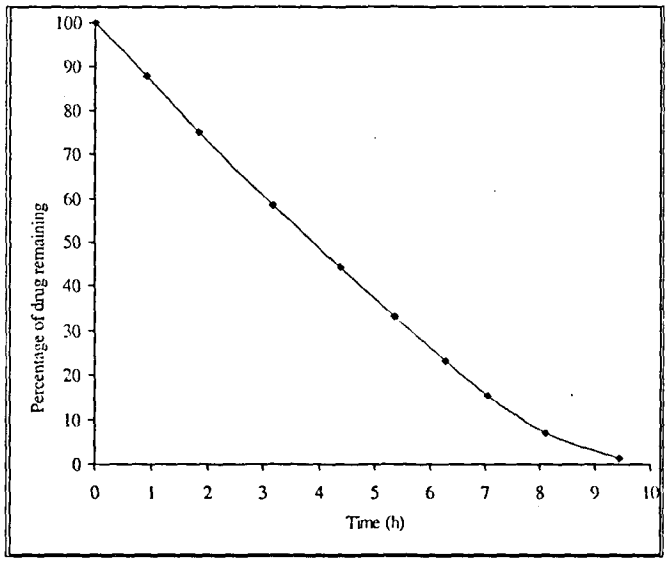

Fig. 2: Zero order release pattern of diclofenac sodium from HPMC gel

(-♦-) release of diclofenac sodium from HPMC gel.

creasing order after 9 h is as follows HPMC gel>MC gel>SCMC gel. The difference in release rate could also be due to the difference in the viscosity (or) due to the difference in the solubility of diclofenac sodium in different polymer.

Ocular irritancy effects of the formulations were evaluated on score basis. Eyes of each animal were observed during the study for the following parameters. Redness of mucous membrane of eye 0 to 4. 0-absent, 1-mild, 2-moderate, 3-severe, 4-very severe. Lacrimal secretion from 0 to 3. 0-normal, 2-more than normal, 3-abnormally more than normal. Swelling of eye lid from 0 to 2. 0-absent, 1-slight, 2-more. Results reveal none of the gel formulation showed any redness, inflammation or increased tear production when compared with placebo formulation.

The fading of the color was observed for the prepared gels. It was prominent in case of SCMC gel. The consistency of NACMC gel was found to be same especially at ambient and 8° temperature but at 37° there was slight decrease in the consistency of NACMC gel after one month. In the case of MC gel the consistency was changed dramatically at all three temperature conditions, especially there was a dramatic change in the consistency of the MC gel at 37° temperature. The gel consistency of HPMC gel formulation was found to be satisfactory up to six weeks at the selected temperatures.

Diclofenac sodium was found to be more stable in HPMC gel compared to MC gel and NACMC gel as evidenced by the degradation rate constant (k). The k values for HPMC gel at ambient, refrigerator and incubator temperature were 0.0319, 0.0216 and 0.0513 per day, respectively. Similarly k values for MC gel 0.0416, 0.0262 and 0.0583 and for NACMC gel 0.0451, 0.0314 and 0.0612 per day respectively. Physical stability of the gels was evaluated by freeze thaw cycling. Gels were observed for synersis. Diclofenac sodium gel prepared with SCMC showed instability due to synersis. In conclusion, ophthalmic gel formulated with HPMC proves to be a viable alternative to conventional eye drop as it offers increased contact time, decreased frequency of administration and excellent ocular tolerance and thus improved patient compliance.

ACKNOWLEDGEMENTS

The authors sincerely thank Pharma Fabricon, Madurai for providing gift sample. We wish to thank PSG management for providing necessary facilities, constant encouragement and support.

REFERENCES

1. Amin, P.D., Tayade, P.T. and Dhavse, V.V., **Eastern Pharmacist.,** 1998, 486, 127.
2. Saeftone, M.F., Giannaccini, B., Savigni, P. and Wirth, A., **J. Pharm. Pharmacol.,** 1980, 32, 519.
3. Chrai, S.S. and Robinson, J.R., **J. Pharm. Sci.,** 1974, 63, 1219.
4. Mandell, G.L. and Sande, M.A., In; Goodman, L.S., Gillman, A.G., Raul, T.W and Murad, F., Eds., Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 9th Edn., Mc Graw-Hill, New York, 1996, 637.
5. Pharmacopoeia of India, 3rd Edn., Vol. I, Controller of Publications, Govt. of India, New Delhi, 1996, 244.
6. Draize, J.H., Woodward, G. and Calvery, H.O., **J. Pharmacol. Exp. Ther.,** 1944, 82, 377.
7. Pandey S., Praveen, S.H. and Dupa, N., **Indian J. Pharm. Sci.,** 2000, 62, 376.
8. Kusum Devi, V., Asha, A.N., Mahesh, G.N. and Vijayalakshmi, P., **Antiseptic,** 2003, 100, 283.