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FORMULATION AND EVALUATION OF IN SITU OPHTHALMIC GEL OF LOTEPREDNOL ETABONATE

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ABSTRACT

The aim of present study was to prepared ocular in-situ gel to increase the residence time of drug in cornea for improvement of ocular bioavailability of drug. In situ gel of Loteprednol etabonate was prepared by using carobopol 940 and different grades of HPMC in different ratios by pH triggered method. The prepared in situ gels were evaluated for pH, drug content, viscosity, gelling time, gelling strength spreadability and sterility testing. In vitro drug release study was carried by using diffusion cell with dialysis membrane. The drug content and pH of the formulation were found to be satisfactory. The gelling strength was found to be in the range of 34 seconds to 91 seconds. The viscosity and spredability of the formulations were found to be satisfactory. Formulation F5 containing 0.3 % carobopol 940 and 0.6 % HPMC K4M showed highest drug release of 80.30 %. The developed formulations showed sustained release of drug up to 8 hrs. From in-vitro drug release studies, it could be concluded that the developed in-situ gelling systems were thus a better alternative to conventional eye drops.

INTRODUCTION

Eye is the most critical organ of the body. The eye ball is cover through three layers: an outer fibrous protective layer (sclera and cornea), a middle vascular layer (choroid), and an inner nervous layer (retina). Eye goes through from a various problems like glaucoma, endopthalmitis, dry eye syndrome, trachoma, keratitis, conjunctivitis. Therefore, the drug required at ocular site in therapeutic dose has been one of the most challenging tasks until now [1]. Various factors such as nasolacrimal drainage of drug, binding of drug to lachrymal protein, induced lachrymation, availability of limited corneal area generate a barrier for absorption of drug through ocular routes [2,3]. The conventional ophthalmic drug delivery system in the form of eye drops, have a dynamic effect and high tear fluid income that causes rapid pre-corneal elimination of the drug and also only 1-10% of topically applied drug get absorbed that frequently results in poor bioavailability and therapeutic response [4].

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Various formulations like inserts, ointments, suspensions, and aqueous gels, have been developed in order to get longer the residence time of instilled dose and improve the ophthalmic bioavailability [5]. because of low patient observance in using the inserts and the side effect of using an ointment such as blurred vision, these ocular drug delivery systems has not been used. This new drug delivery systems that have been developed established by ophthalmologists is in-situ gel systems. In-situ gel forming system have been showed their potential in lengthen the residential time because of bio adhesiveness of formed gel that have been produced. Additionally, polymers used to achieve in-situ gelling may result in sustained release of drug molecules.[6-8] In-situ gelling systems are described as low viscosity solution that phase transition in cul-de-sac to form viscoelastic gel. This sol-to-gel phase transition happen due to conformational changes of polymer in response to a physiological environment. In-situ formulations are more suitable for patient because they are administered as solution or suspension which immediately undergoes to gelation as coming in contact with the eye. Loteprednol etabonate is used as an anti-inflammatory agent. It belongs to BCS class II drug and half life of 2.8 hours. It has very slightly soluble in water, soluble in methanol.

MATERIALS AND METHODS

Material

Loteprednol etabonate was obtained as a gift sample from Yarrow Chem Product, Mumbai. All other ingredients were used of analytical grade.

Formulation of in situ gel

The in-situ gelling polymer was added slowly in distilled water with continuous stirring until completely dissolved. Another polymeric solution (carbopol 940 solution) was made and allowed to hydrate overnight. After mixing and complete hydration of polymers, drug was added to the polymeric solution. The resultant solution was thoroughly mixed until uniform and clear solution was formed. Final volume was made by adding required volume of distilled water. Different grade of HPMC used as viscosifying agent and carbopol 940 used as pH inducing agent/ gelling agent.

EVALUATION OF IN SITU GEL

pH of in-situ gel: pH of each formulation was determined by using pH meter which was previously calibrated using standard buffer of pH 4 and pH 7. pH was measured by taking 1 ml formulation which was diluted with simulated tear fluid pH 7.4. [9]

Drug content: 1 ml of formulation was taken in 10 ml of volumetric flask and at that point diluted with simulated tear fluid pH 7.4 up to 10 ml. Yet again 1 ml quantity from this solution was taken and diluted with 10 ml of simulated tear fluid pH 7.4. Lastly, the absorbance of prepared solution was measured at 212 nm against blank reagent using UV visible spectrophotometer. [10]

Viscosity measurement: Viscosity of prepared formulation was determined using Brookfield viscometer with spindle no. 62 at 50-100 rpm at temperature 37±0.5° C. Spindle was lowered perpendicularly into gel placed in a beaker taking care that the spindle does not touch the bottom of beaker. Reading were recorded after 30 sec. [11]

Gelling time: The gelling time was determined by dropping the formulation in a test tube containing 2.0 ml of freshly prepared simulated tear fluid pH 7.4 and the gelation was observed by visual examination. [12]

Table I: Formulation composition of in situ gel

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
LE* (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Carbopol 940 (%)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
HPMC K15M (%)	0.4	0.6	0.8	-	-	-	-	-	-	-	-	-
HPMC K4M (%)	-	-	-	0.4	0.6	0.8	-	-	-	-	-	-
HPMC E15LV (%)	-	-	-	-	-	-	0.4	0.6	0.8	-	-	-
HPMC E50LV (%)	-	-	-	-	-	-	-	-	-	0.4	0.6	0.8
Methyl Paraben (%)	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Distilled Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

*LE= Loteprednol etabonate

Gelling strength: The prepared gel was placed in 100 ml measuring cylinder the probe was placed on the gel and a weight was placed on the probe. The probe was allowed to penetrate at a distance of 5 cm and time required for penetration was noted as a gelling strength. [13]

Spreadability: Excess of sample was applied in between 2 glass slide and was compressed to uniform thickness by placing 100-gram weight over the upper glass slide for 5 minutes. Weight 50 gram was added to pan. Time required separating the two slides i.e. the time in which the upper glass slide move over the lower plate was taken as measure of spreadability [14]

$$S = \frac{m \times 1}{t}$$

Where, S= Spreadability; m= weight tied to upper slide; t= time taken, 1= length moved on upper glass slide

In vitro drug release: The drug release of the Loteprednol etabonate in-situ ophthalmic gel was measured using Franz diffusion cell with dialysis membrane (mol. Wt. 12000D) as a barrier. Assembly was set and the temperature was maintained at 37±0.5°C, then 2 ml of in-situ ophthalmic gel of Loteprednol etabonate was filled in the donor compartment, which was separated from the receptor compartment with the dialysis membrane.

The receptor compartment was filled with the simulated tear fluid pH 7.4. 1 ml aliquots of sample were withdrawn at regular time intervals and replaced with an equal volume of simulated tear fluid pH 7.4 as fresh receptor medium. The samples were appropriately diluted with simulated tear fluid pH 7.4 and analyzed spectrophotometrically at 212 nm. [15]

Table 2: Evaluation parameters of batches F1 -F12

Batch no.	Drug Content (%)	pH	Gelling Time (sec)	Spreadability gcm/sec
F1	96.67 ± 0.16	6.48±0.18	7.4 ± 0.250	38.62 ± 0.20
F2	97.51 ± 0.14	6.45±0.11	10.2 ± 1.124	33.33 ± 0.18
F3	97.28 ± 0.25	6.6±0.24	11 ± 0.062	28.61 ± 0.21
F4	97.45 ± 0.04	6.75±0.15	8.1 ± 1.413	26.61 ±0.11
F5	98.80 ± 0.30	6.8±0.05	4.5±0.932	30.42 ± 0.15
F6	97.77 ± 0.19	6.53±0.12	9.1 ± 0.045	22.46 ± 0.10
F7	94.49 ± 0.18	6.08±0.1	10 ± 0.206	37.69 ± 0.22
F8	96.61 ± 0.21	6.55±0.20	7.9 ± 0.120	36.57 ±0.15
F9	94.35 ± 0.18	6.71±0.09	6.0 ± 0.566	31.52 ± 0.25
F10	96.46 ± 0.26	6.6±0.24	9.2 ± 1.145	45.55 ± 0.27
F11	96.21 ± 0.26	6.75±0.15	7.5 ± 0.120	42.55 ± 0.02
F12	97.01 ± 0.01	6.55±0.20	4.5 ± 0.932	37.62 ± 0.20

***Each observation values are expressed as mean ±S.D. of n=3**

RESULT AND DISCUSSION

Drug content of all the formulation was establish to be in the range of 94.24 to 98.80 %. The loteprednol etabonate content in all formulation was almost stable F5 shows highest drug content. The drug content was carried out in triplicates.

pH of solution at time of instillation of all formulations was found to be in the range of pH 6.08 to 6.80. Spreadability of formulation indicates that ease of application of drug. Spreadability of all the formulation was found to be in range from 26.61 to 45.55 gcm/sec. In all of the above formulations, viscosity increases as the polymer concentration increases.

The viscosity for solution was found in the range of cps 68 to 225 cps and the viscosity for gel was found to be in the range of cps 171 to 430 cps. Gelling strength of the formulation was found in the range from 30 sec to 86 sec.

Amongst all these formulations, the maximum drug release was found to be 98.41% for F5 and it was also observed that drug release decreases by increasing the concentration polymers.

Table 3: Evaluation parameters of batches F1 -F12

Batch	Viscosity (cps)		Gelling Strength (sec)
	Solution	Gel	
F1	92 ± 0.57	165 ± 0.35	45 ± 0.30
F2	131 ± 0.57	320 ± 0.18	61 ± 0.19
F3	157 ± 0.20	341 ± 0.17	72 ± 0.20
F4	68 ± 0.16	171 ± 0.19	30 ± 0.20
F5	85 ± 0.21	237 ± 0.01	45 ± 0.30
F6	103 ± 0.06	325 ± 0.17	66 ± 0.36
F7	79 ± 0.19	215 ± 0.05	42 ± 0.31
F8	150 ± 0.25	370 ± 0.07	53 ± 0.21
F9	225 ± 0.28	430 ± 0.01	59 ± 0.10
F10	95 ± 0.04	225 ± 0.11	50 ± 0.20
F11	126 ± 0.07	270 ± 0.07	65 ± 0.30
F12	143 ± 0.30	342 ± 0.17	86 ± 0.09

*Each observation values are expressed as mean ±S.D. of n=3

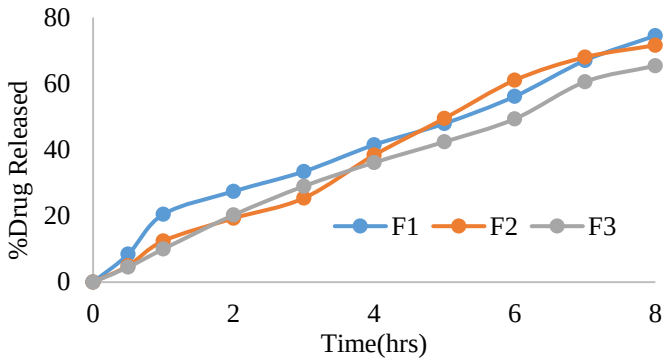

Figure 1: In vitro drug released of F1 – F3

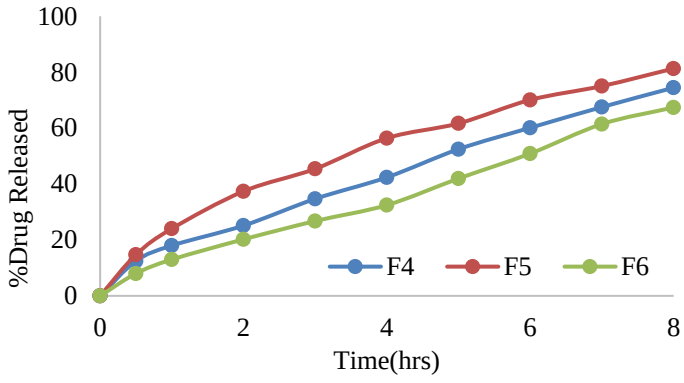

Figure 2: In vitro drug released of F4-F6

CONCLUSION

To overcome reduced corneal permeability of steroid cyclodextrin, inclusion complexes was developed. Aqueous solubility and corneal perfusion are increased. β-CD, one of the natural unsubstituted cyclodextrins, was employed for solubility enhancement of the drug. Eight hour in vitro drug release diffusion studies showed controlled released affected by the drug concentration gradients.

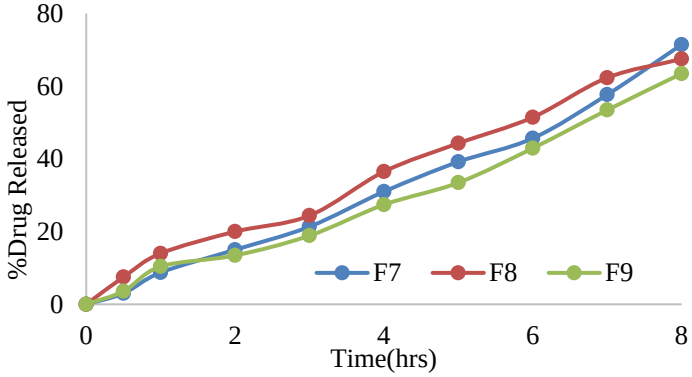

Figure 3: In vitro drug released of F7-F9

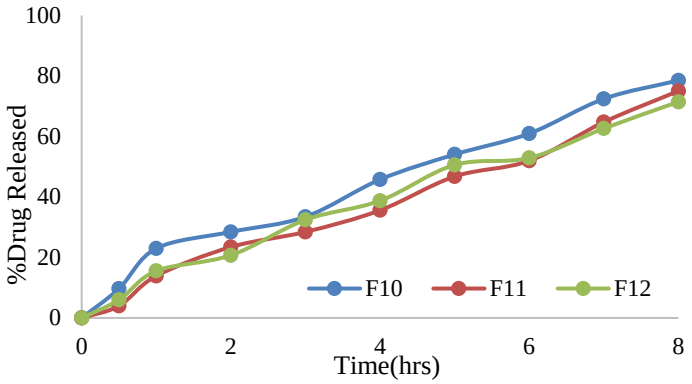

Figure 4: In vitro drug released of F10-F12

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Shaikh shoaeba has conducted the laboratory experiment. Hitesh Jain and Asit shahu has designed and guided shaikh shoaeba for overall study and in preparing the manuscript. D.B.Meshram supervised the overall study and the manuscript.

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