



FORMULATION DEVELOPMENT AND EVALUATION OF LOTEPREDNOL ETABONATE AND TOBRAMYCIN LOADED OCULAR IN-SITU GEL

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ABSTRACT

The present study includes development of in-situ ophthalmic gel of Loteprednol etabonate and Tobramycin to be administered in the cul-de-sac of the eye using a combination of two polymers and optimization of the same. The pH triggered in-situ gel forming polymers selected for the study is Carbopol 940P. In the present work, Sodium alginate and Carbopol 940P were used as gelling agent that produced immediate gelation in presence of environmental stimuli like pH. Different formulations were prepared with varying concentrations of Sodium alginate and Carbopol 940P. These formulations were evaluated for the parameter like appearance, Viscosity, In-situ gelling capacity, In-vitro drug release study. A full factorial design was applied to check the effect of varying concentrations of Sodium alginate (X1) and Carbopol 940P (X2) on the dependant variables i.e Viscosity (Y1) and time required to release 100% (Y2). The pH values of in-situ gel formulations were between 5.5-6.0. The release profile of formulations exhibited a sustained release upto 8 hrs. Isotonicity and Eye irritation study (HET-CAM) was carried out for the optimized batch. Formulation F5 was selected as optimized formulation with concentration of sodium alginate (1.2%w/v) and carbopol 940P (1.5%w/v) showing release upto 8hrs, viscosity (cps) and sol-gel transition time seconds. After stability study of optimized formulations it was found that there were no significant changes in the evaluation parameters. On the basis of these findings, the in-situ gel may be considered as feasible alternative to conventional eye drops.

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INTRODUCTION

In-situ gel forming systems are liquid aqueous solutions which upon administration, under certain physiological conditions, turn into a gel. The major problem encountered with topical administration is the rapid pre-corneal loss caused by nasolacrimal drainage and high tear fluid turnover which leads to only 10% drug concentrations available at the site of actions. This type of gel combines the advantage of a solution being patient convenient with the favorable residence time of a gel for enhancing the ocular bioavailability. The principal advantage of in situ gels is that they can be easily administered with accurate and reproducible dose compared to that they can be easily instilled in liquid form, and are capable of prolonging the residence time.

In the last decade, greater attention has been focused on development of controlled and sustained drug delivery systems. Eye seems an ideal, easily accessible target organ for topical treatment.

However the eye is in fact well protected against absorption of xenobiotics, first by the eyelids and tear-flow and then by the cornea, which forms the physical-biological barrier.

Poor bioavailability of drugs from ocular dosage forms is mainly due to the tear production, non-productive absorption, transient residence time, and impermeability of corneal epithelium.

Most ocular treatments like eye drops and suspensions call for the topical administration of ophthalmic drugs to the tissues around the ocular cavity. These dosage forms are easy to instil but have the inherent drawback that the majority of the medication in them is immediately diluted. Extensive research has been carried in designing of polymeric drug delivery systems.

The development of *in-situ* gel systems has received considerable attention over the past few years and increasing number of *in-situ* gel forming systems have been investigated and in the tear film as soon as the eye drop solution is instilled into the *cul-de-sac* and is rapidly drained away from the pre-corneal cavity by constant tear flow and lacrimo-nasal drainage. For this reason, concentrated solutions and frequent dosing are required for the instillation to achieve an adequate level of therapeutic effect. One of the new classes of drug

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delivery systems, ophthalmic *in-situ* gels, which offer many advantages over conventional dosage forms, like increased ocular residence, possibility of releasing drugs at a slow and constant rate, accurate dosing, exclusion of preservatives and increased shelf life.

In present study Carbopol 940P and Sodium alginate were used as polymers. Carbopol 940P was used as a pH sensitive polymer and sodium alginate was used as mucoadhesive polymer. The limitation of conventional ophthalmic solution can be overcome by formulating In-situ ophthalmic formulation which have better contact and mucoadhesion.

MATERIALS AND METHOD

Chemicals

Loteprednol etabonate and Tobramycin was obtained from Sun Pharmaceuticals, Vadodara, Sodium alginate and Carbopol 940P from Astron chemicals Pvt. Ltd. And all other reagents and solvent used were of analytical grade.

Instruments

The following instruments were used for the study: UV spectrophotometer (Shimadzu 1800, Kyoto, Japan), Brookfield viscometer (Brookfield Eng. Lab, US), FT-IR (Shimadzu, Japan), Digital Weighing balance (Wensar, PGB300), Magnetic stirrer (Remi lab. Instruments), Franz diffusion apparatus (Orchid Scientifics, Pune).

Selection of solvent

The solubility of Loteprednol etabonate and Tobramycin were tested in various solvents, and it was determined that the Loteprednol etabonate was soluble in propylene glycol, methanol and Tobramycin was soluble in water, methanol than in any other solvent. The solubility was confirmed by analyzing the sample for quantitative determination by UV spectroscopy, with a scan of 200-400nm. Maximum absorbance was obtained for Loteprednol etabonate was at 245nm and for Tobramycin at 300nm.

Fourier Transform Infrared (FTIR)

The compatibility of drug and the excipients was determined by Fourier Transform Infrared spectroscopy (FTIR). The FTIR spectra of pure drug is compared with that of combination of the drug and all the excipients to check for interaction.

Formulation of In Situ Gel

Specified quantity of Loteprednol etabonate, Tobramycin, Sodium alginate, Carbopol 940P, Propylene Glycol, Sodium chloride, and Benzalkonium chloride were weighed accurately. Formulations containing Carbopol 940P as gelling agent were prepared by adding a weighed amount of Carbopol 940P in de-mineralized water and soaked overnight. Loteprednol etabonate was dissolved in propylene glycol and Tobramycin was dissolved in water. This mixtures were added into the solution containing Carbopol 940P. The formulation was made isotonic by adding required amount of sodium chloride to it. Benzalkonium chloride was added as a preservative.

Formulations containing sodium alginate as gelling agent were prepared by adding a weighed amount of sodium alginate in de-mineralized water and stirring continuously for about 10 min. Loteprednol etabonate was dissolved in propylene glycol and Tobramycin was dissolved in water. This mixtures were added into the solution containing Sodium alginate. The formulation

was made isotonic by adding required amount of sodium chloride to it. Benzalkonium chloride was added as a preservative.

For preparation of formulations containing both sodium alginate and carbopol 940P as gelling agents, weighed amount of sodium alginate was added to a solution of carbopol 940P in de-mineralized water. Loteprednol etabonate was dissolved in propylene glycol and Tobramycin was dissolved in water. This mixtures were added into the solution containing gelling agents. The formulation was made isotonic by adding required amount of sodium chloride to it. Benzalkonium chloride was added as a preservative.

Formulation of Trial Batches for optimization of polymers

Formulation of batches of Carbopol 940P

For the purpose of optimization of concentration of Carbopol 940P in the formulation of in-situ ophthalmic gel of Loteprednol etabonate and Tobramycin, five batches were prepared with varying concentrations of the polymer ranging from 0.5 to 2.5%w/v.

Table 1 Batches of Carbopol 940P

Ingredients(%w/v)	F1	F2	F3	F4	F5
Loteprednol etabonate	0.5	0.5	0.5	0.5	0.5
Tobramycin	0.3	0.3	0.3	0.3	0.3
Carbopol 940P	0.5	1	1.5	2	2.5
Propylene glycol	10	10	10	10	10
NaCl	0.9	0.9	0.9	0.9	0.9
Banzalkonium Chloride	0.02	0.02	0.02	0.02	0.02
Demineralised Water	Upto 100ml	Upto 100ml	Upto 100ml	Upto 100ml	Upto 100ml

Formulation of batches of Sodium alginate

For the purpose of optimization of concentration of sodium alginate in the formulation of in-situ ophthalmic gel of Loteprednol etabonate and Tobramycin, five batches were prepared with varying concentrations of the polymer ranging from 0.6 to 1.4%w/v.

Table 2 Batches of Sodium alginate

Ingredients (%w/v)	F1	F2	F3	F4	F5
Loteprednol etabonate	0.5	0.5	0.5	0.5	0.5
Tobramycin	0.3	0.3	0.3	0.3	0.3
Sodium alginate	0.6	0.6	1	1.2	1.4
Propylene glycol	10	10	10	10	10
NaCl	0.9	0.9	0.9	0.9	0.9
Banzalkonium Chloride	0.02	0.02	0.02	0.02	0.02
Demineralised Water	Upto 100ml	Upto 100ml	Upto 100ml	Upto 100ml	Upto 100ml

Formulation of Full Factorial Batches (3² full factorial design)

After optimization of the concentrations of both the polymers individually, a 3² full factorial design was adopted to formulate batches with combination of polymers

Table 3 Full factorial Batches

Experimental run	X ₁	X ₂
F1	-1	-1
F2	0	-1
F3	1	-1
F4	-1	0
F5	0	0
F6	1	0

F7	-1	1
F8	0	1
F9	1	1
	Actual values	
	X ₁	X ₂
Coded values	Conc. of Sodium alginate(%w/v)	Conc. of Carbopol 940P (%w/v)
-1	1	1
0	1.2	1.5
1	1.4	2

Table 4 Formula for full factorial batches

	F1(%w/v)	F2(%w/v)	F3(%w/v)	F4(%w/v)	F5(%w/v)	F6(%w/v)	F7(%w/v)	F8(%w/v)	F9(%w/v)
Loteprednol etabonate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Tobramycin	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Carbopol 940P	1	1.2	1.4	1	1.2	1.4	1	1.2	1.4
Sodium alginate	1	1	1	1.5	1.5	1.5	2	2	2
Propylene glycol	10	10	10	10	10	10	10	10	10
NaCl	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
BKC	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
DM Water	Upto 100 ml	Upto 100 ml	Upto 100 ml	Upto 100 ml	Upto 100 ml	Upto 100 ml	Upto 100 ml	Upto 100 ml	Upto 100 ml

Evaluation

Appearance and clarity

The formulations were evaluated for its clarity by viewing it against black and white background.

Drug Content

It is calculated using equation generated from the standard calibration curve. The formulation were shaken for 2-3 min and 1ml of formulation was transferred to 100ml volumetric flask and volume was made up with artificial tear fluid pH 7.4 and shaken vigorously. Aliquot of 1ml was withdrawn and further diluted to 10 ml with same artificial tear fluid pH 7.4. The concentration of both the drugs were determined at 245nm and 300nm by using UV-Visible spectrophotometer.

Gelling time

Gelling time was determined by placing a drop of formulation on a slide already wet with simulated tear fluid, and observing the time taken for the formation of gel.

Gelling capacity

In these studies the gelling capacity (gelling speed and extent of gelation) for all formulations were determined. Gelation characteristics were assessed ranging between + (poor), ++ (acceptable), +++ (good), ++++ (very good), +++++(excellent)

Viscosity

The viscosity values of prepared formulations were measured by using Brookfield viscometer at room temperature.

In vitro diffusion study

The In-vitro release studies of the formulations were studied through the cellophane membrane using a modified dissolution apparatus. The dissolution medium used was freshly prepared artificial tear fluid (pH 7.4). A cellophane membrane previously soaked overnight in the dissolution medium was tied to one end of the specially designed glass cylinder (open at both end). One ml volume of the formulation was precisely pipette into this assembly. The glass cylinder was suspended in 100 ml of dissolution medium at 37. So that the membrane just touches the receptor medium surface. Stirring of receiving medium was done at 50 rpm to avoid diffusion layer effects. A sample was placed evenly on the surface of the membrane in

the donor compartment. Aliquots of 5 ml volume were withdrawn at hourly interval and replaced by the volume of dissolution medium and analyzed by UV Spectrophotometer at 254nm and 300nm.

Isotonicity Test

The eye formulation should have isotonicity so that it does not damage the eye cornea and other integral parts. Sodium chloride 0.9% w/v was added for the isotonicity.

Along with NaCl other buffer salts and drug may also contribute to the tonicity of formulation. To check the isotonicity following test was conducted. First one to two drop of blood was taken on slide with sterile blood lancet. Two drops of Low molecular weight Heparin was mixed with blood to avoid clotting. Then it was observed under optical microscope for the integrity of RBCs. On another slide blood and Heparin were taken in similar manner and two drops of in situ gel formulation were mixed. It was observed under the optical microscope in similar manner for integrity of RBCs. RBCs should remain intact with formulation. Presence of burst or shrunken RBCs indicates lack of isotonicity.

Sterility Test

The test for sterility is an important aspect for ophthalmic preparations. The test for sterility is intended for detecting the presence of viable forms of bacteria, fungi and yeast in sterilized preparations Sterility test was performed according to I.P (Indian Pharmacopoeia) by using both alternate Thioglycoate and Soya-bean casein digest medium. Fluid thioglycolate media was used to check growth. Aseptic conditions were maintained during performing sterility test.

Ocular Irritation (Het-Cam Test)

Ocular irritation of the optimized batch was checked by hen's egg chorioallantoic membrane test which is rapid, insensitive and inexpensive test. Testing with an incubated egg is borderline case between in vivo and in vitro systems and does not conflict with the ethical and legal obligations. The chorioallantoic membrane of the chick embryo is complete tissue including veins, arteries and capillaries and technically very easy to study. It responds to injury with a complete inflammatory process, a process similar to that induced in the conjunctival tissue of the rabbit eyes. Briefly, fertilized hen's egg weighing between 50-6-g were obtained from poultry farm. These eggs were incubated and on 10th day a window (2 * 2 cm) was made on the eggs through which formulation (0.5 ml) were instilled. Optimized formulation was compared with those obtained using normal saline, which was used as a control that is supposed to be practically non irritant.

Stability study of Optimized Formulation

A short term stability study of selected formulation was done as per ICH Q1AR2 guide lines. These studies are designed to

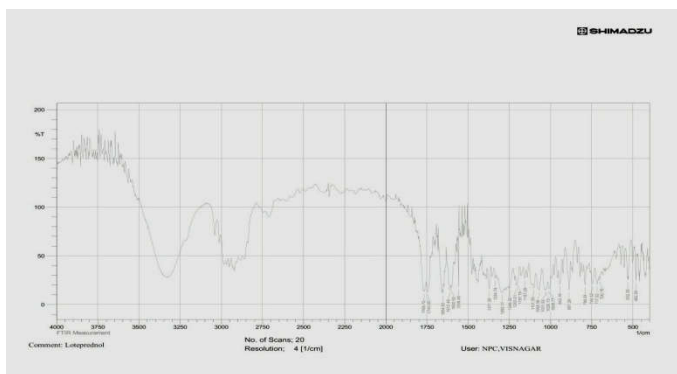
increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions. The short term stability study for In situ gel were done by keeping selected formulation at 40 °C ±2 °C temperature and 75% RH ±5%. Formulation was evaluated for gelling time, gelling capacity, viscosity, %assay and in vitro drug release study after 30 days storage.

RESULTS AND DISCUSSION

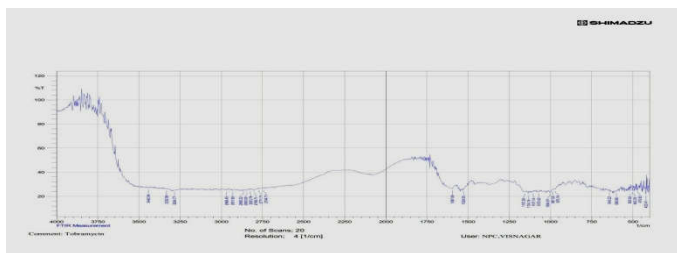
FTIR studies

The results of the FTIR study show that the major peaks present in the pure drug sample were present in the mixture of the drug and the polymers, which indicates that there is no interaction between the drug and the excipients.

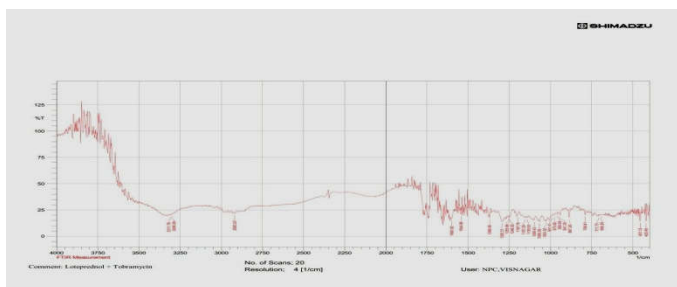
Loteprednol etabonate



Tobramycin



Loteprednol etabonate + Tobramycin



Loteprednol etabonate + Tobramycin + Carbopol 940P + Sodium alginate

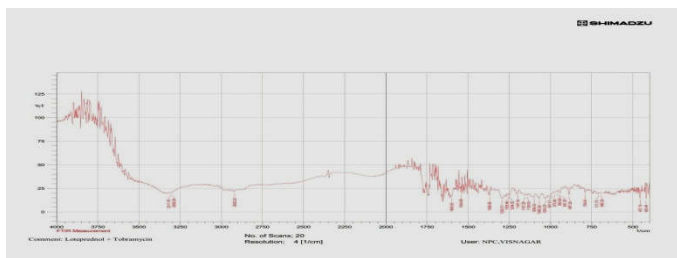


Table 5 Comparative FTIR data

Vibration	Analytical range	Loteprednol etabonate	Tobramycin	Loteprednol+Tobramycin+sodium alginate+carbopol940P	Interaction
OH	3650-3450	3539.30	3640.87	3529.06	No
C-H	2900-3000	2945.21	2962.98	2978.63	No
C=O	1700-1740	1721.11	1711.30	1711.28	No
NH	3400-1580	1725.57	1843.89	1889.51	No

Observations of batches containing Carbopol 940P

The batches containing Carbopol 940P in the concentration ranging from 0.5-2.5%w/v were evaluated and the results are summarized in table 6 and table 7

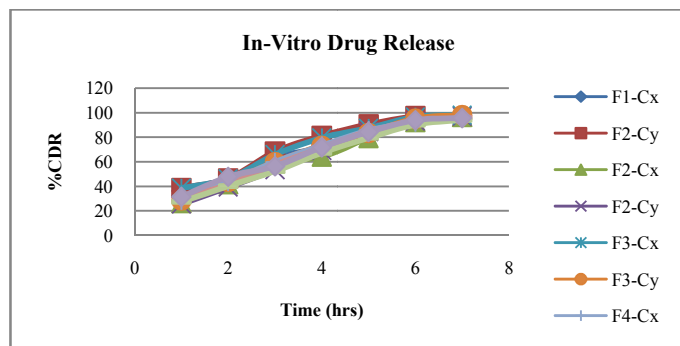
Table 6 Evaluation of batches containing Carbopol 940P(n=3)

Batch code	Apperance & Clarity	pH	Gelling time (sec)	In-vitro gelling capacity	Viscosity in cps at 12 RPM
F1	Clear	5.96	18	+	240
F2	Clear	5.82	15	++	280
F3	Clear	5.75	13	+++	320
F4	Clear	5.71	10	+++	440
F5	Clear	5.63	9	++++	445

* + poor, ++ good, +++ very good, ++++ excellent

Table 7 %CDR of batches containing Carbopol 940P(n=3)

TIME (hrs)	%CDR									
	F1		F2		F3		F4		F5	
	Cx	Cy	Cx	Cy	Cx	Cy	Cx	Cy	Cx	Cy
1	36.4	38.7	26.3	25.7	38.6	28.6	28.6	30.6	27.4	31.5
2	42.9	46.5	41.7	39.4	46.2	43.7	43.7	41.6	40.3	47.8
3	63.6	68.4	58.9	53.7	65.9	59.9	59.9	57.8	52.5	56.4
4	71.5	81.1	64.3	69.4	79.5	73.2	73.2	71.1	67.3	71.9
5	83.7	90.6	79.5	84.6	87.4	83.6	85.6	84.6	79.6	84.3
6	95.6	97.3	92.4	93.2	96.5	95.2	92.2	91.2	90.4	93.8
7			96.6	97.1	98.2	98.1	95.3	96.2	94.3	95.6



DISCUSSION

From the observations, batches F2, F3,F4 and F5 give sustained release for longest duration. But the viscosity of the formulations F4 and F5 are above 400 cps, which is not acceptable. Thus, batch F3 is the optimized concentration of Carbopol 940P.

Observations of batches containing Sodium alginate

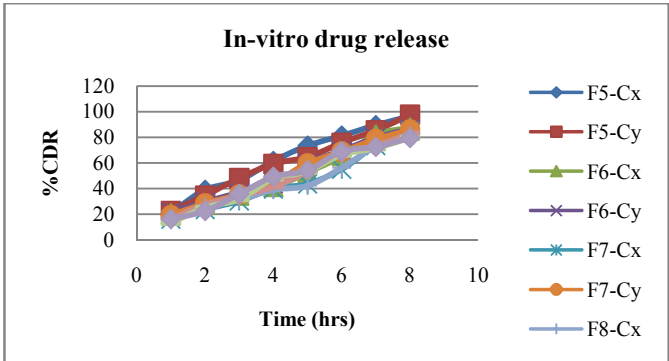
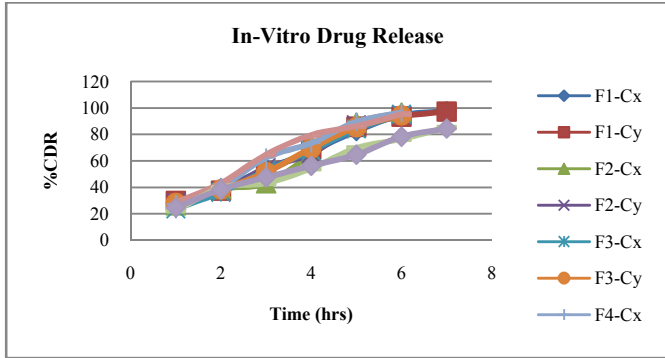
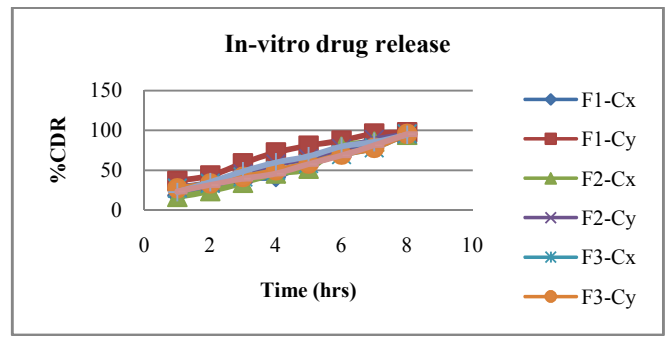
The batches containing sodium alginate in the concentration ranging from 0.6 to 1.8%w/v were evaluated and the results are summarized in table 8 and table 9

Table 8 Evaluation of batches containing Sodium alginate (n=3)

Batch code	Apperance & Clarity	pH	Gelling time (sec)	In-vitro gelling Capacity	Viscosity in cps at 12 RPM
F1	Clear	5.63	17	+	86
F2	Clear	5.69	14	++	194
F3	Clear	5.74	10	++	245
F4	Clear	5.66	9	++++	280
F5	Clear	5.93	7	++++	360

Table 9 %CDR of batches containing sodium alginate(n=3)

TIME (hrs)	% CDR									
	F1		F2		F3		F4		F5	
	Cx	Cy	Cx	Cy	Cx	Cy	Cx	Cy	Cx	Cy
1	27.8	29.7	26.3	28.5	23.7	28.2	27.3	28.5	22.5	24.7
2	39.4	37.4	38.6	36.5	36.3	38.4	40.1	43.2	39.6	38.4
3	53.7	51.7	42.9	54.9	52.7	51.3	62.3	64.8	43.1	47.6
4	66.9	68.6	64.8	65.4	67.8	69.5	73.4	79.6	54.3	56.3
5	82.6	85.7	88.7	87.3	84.1	85.4	89.5	86.3	69.7	64.7
6	94.3	93.5	96.4	94.7	95.2	94.3	96.5	95.4	76.4	78.3
7	97.4	97.2							85.3	84.4



DISCUSSION

The batches F1 and F5 give release upto 7 hrs. There is no significant difference between F3 and F4, thus the batch with suitable viscosity is selected. And therefore, batch F4 is the optimized batch.

Observations of full factorial design batches

The batches containing combination of both the polymers were evaluated and the results are summarized in table 10 and table 11

Table 10 Evaluation of factorial design batches F1 to F9(n=3)

Batch	Apperance & clarity	Ph	Gelling time (sec)	Gelling capacity	Viscosity in cps at 12 rpm
F1	Clear	5.55	12	++	190
F2	Clear	5.63	10	+++	210
F3	Clear	5.78	9	+++	260
F4	Clear	5.58	8	+++++	320
F5	Clear	5.72	6	+++++	385
F6	Clear	5.84	4	+++++	420
F7	Clear	5.92	3	+++++	450
F8	Clear	5.77	3	+++++	515
F9	Clear	5.89	2	+++++	620

Table 11 %CDR of factorial design batches F1 to F5(n=3)

TIME (hrs)	% CDR									
	F1		F2		F3		F4		F5	
	Cx	Cy	Cx	Cy	Cx	Cy	Cx	Cy	Cx	Cy
1	18.40	36.51	16.52	28.21	29.40	27.21	22.39	23.20	21.06	22.40
2	27.23	43.23	23.61	34.53	39.98	33.23	34.92	31.41	39.01	34.43
3	39.68	58.74	34.15	45.22	47.63	41.51	48.43	39.41	46.30	48.02
4	41.53	72.33	45.70	57.68	58.52	49.62	59.60	45.62	61.43	59.22
5	59.32	80.91	51.85	64.59	67.18	58.40	67.34	57.63	73.42	64.43
6	71.23	87.32	79.60	77.09	74.58	69.43	79.62	68.40	81.06	75.69
7	88.04	96.02	86.03	88.43	81.04	78.20	85.33	81.32	89.42	85.29
8	95.20	97.64	94.40	95.42	84.22	95.71	94.31	95.24	96.32	97.63

Table 12 %CDR of factorial design batches F5 to F9(n=3)

TIME (hrs)	% CDR							
	F6		F7		F8		F9	
	Cx	Cy	Cx	Cy	Cx	Cy	Cx	Cy
1	20.53	21.64	16.1	19.20	15.43	16.32	13.02	16.30
2	27.20	29.43	23.51	28.32	25.39	27.43	25.16	22.46
3	34.56	36.68	30.22	35.33	31.02	34.33	31.54	35.74
4	41.28	43.52	39.66	44.32	38.93	41.29	47.69	49.20
5	52.33	59.66	43.56	59.62	42.12	53.43	53.37	54.30
6	65.34	69.43	54.96	68.72	56.05	67.43	66.34	68.92
7	81.92	79.47	73.51	78.43	72.66	73.23	71.32	72.49
8	87.59	86.32	84.59	86.02	81.09	83.20	79.60	79.46

Isotonicity study

The isotonicity test of the formulation was conducted to confirm the isotonicity of the formulation using RBC cells observation before Eye Irritation test. The RBCs were intact on mixing Blood drop and Heparin with formulation.

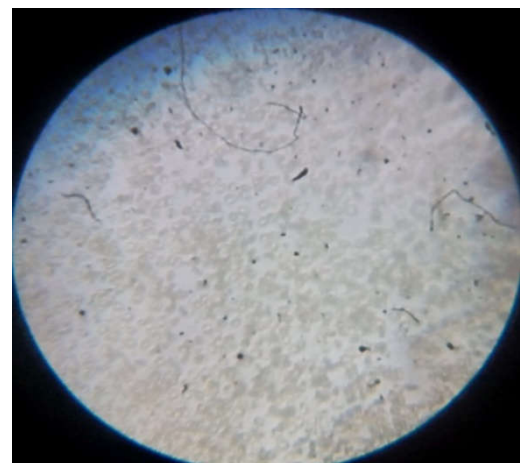
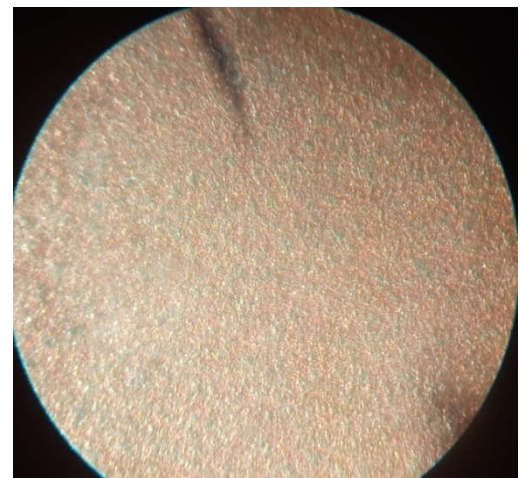


Figure 1 (A)RBCs without formulation (B) RBC with formulation

Sterility test

Results were made for two weeks in fluid thioglycolate and soya been casein medium. In results the growth of aerobic, anaerobic, and fungi were checked for 14 days. After 14 days, there was no sign of bacterial or fungal growth; turbidity in solution was observed in test control sample.

Table 13 Sterility testing

Bacterial growth					
Time days	1	4	8	12	14
Negative control					
Soya been casein	No growth	No growth	No growth	No growth	No growth
Fluid thioglycolate	No growth	No growth	No growth	No growth	No growth
Positive control					
Soya been casein	No growth	No growth	No growth	No growth	No growth
Fluid thioglycolate	No growth	No growth	No growth	No growth	No growth
Test control					
Soya been casein	No growth	No growth	No growth	No growth	No growth
Fluid thioglycolate	No growth	No growth	No growth	No growth	No growth

Ocular Irritation (Het-Cam Test)

Ocular irritancy test of optimized formulation was checked by Hen’s egg chorioallamtoic membrane and the scores were given. The average score was taken to decide the formulation is irritant or not.

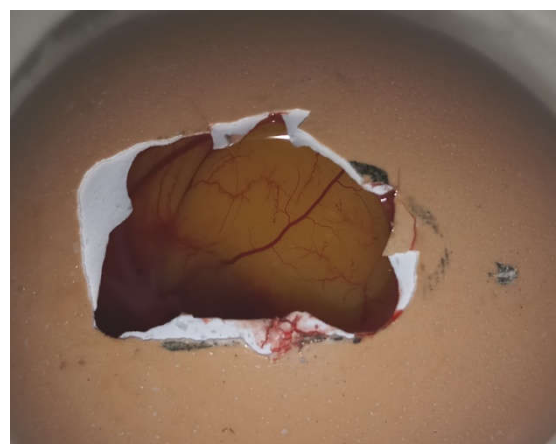
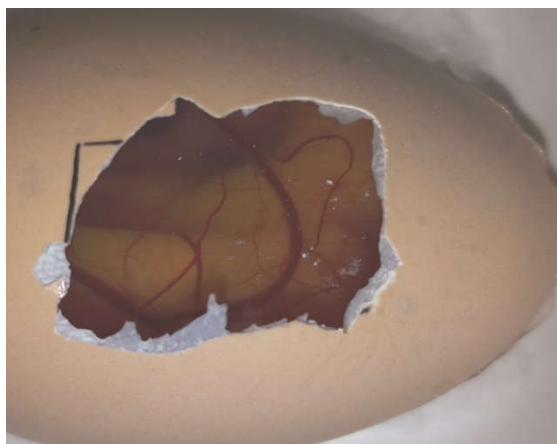
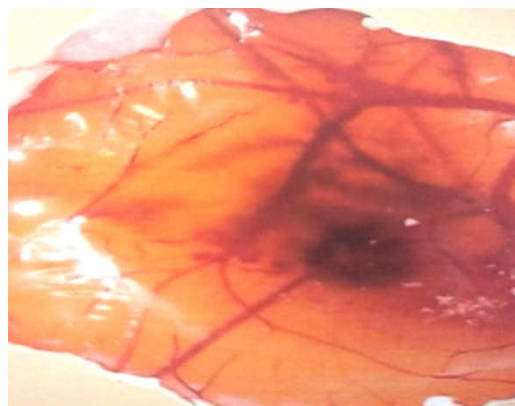


Figure 5.13 (A) With In-situ gel
(B) With NaCl



(C) With irritant SDS
(SDS=Sodium Dodecyl Sulphate)

Table 14 Scores of HET-CAM TEST

Formulation		Scores								
		Time (minutes)								
		0	5	15	30	60	120	240	480	1440
Normal saline	Egg	0	0	0	0	0	0	0	0	0
	Egg	0	0	0	0	0	0	0	0	0
	Egg	0	0	0	0	0	0	0	0	0
	Mean	0	0	0	0	0	0	0	0	0
Optimized formulation	Egg	0	0	0	0	0	0	0	0	0
	Egg	0	0	0	0	0	0	0	0	0
	Egg	0	0	0	0	0	0	0	0	0
	Mean	0	0	0	0	0	0	0	0	0

Stability study

The formulation F5 was found to be clear after 1 month of storage. No significant change in drug content and pH was observed. Gelling was compatible to initial gelling. Solution viscosity was slight higher due to hydration of polymers.

Table 15 Stability study

Stability study at 40 °C ±2 °C and 75% ±5% RH					
Time interval	Appearance	pH	Gelling capacity	Viscosity	Drug content
Before (1 month)	Clear	5.84	+++++	385	
After (1 month)	Clear	5.93	+++++	387	

CONCLUSION

In situ ophthalmic gel of Loteprednol etabonate and Tobramycin was successfully formulated and evaluated to give a formulation with improved patient compliance and release profile of up to 8hr. The formulations F1 to F5 all showed drug release for up to 8hr, but only the batches F2, F3, F4 and F5 showed suitable viscosity. Out of these four batches, considering the gelling time and gelling capacity, batch F5 was considered as the optimized batch. Release mechanism of Loteprednol etabonate and Tobramycin from the in situ ophthalmic gel followed Higuchi model. The optimized batch F5 was found to be stable after one month of stability study. Thus, by formulating the in situ ophthalmic gel of Loteprednol etabonate and Tobramycin, the advantages of solutions like ease of administration can be combined with the advantages of gels like sustained release for longer duration.

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