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FORMULATION AND EVALUATION OF OPHTHALMIC DELIVERY SYSTEM OF LOTEPREDNOL ETABONATE

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ABSTRACT

The objective of this study was to formulate and evaluate an ophthalmic delivery system for Loteprednol Etabonate (LE) to enhance its therapeutic efficacy in treating ocular conditions. Various formulations were developed and characterized for pH stability, drug content, sol-gel transition temperature, viscosity, and release profiles. Results indicated that formulations maintained a physiologically compatible pH, with drug content ranging from 77.06% to 83.82%. The optimized formulation (F10) exhibited a controlled in vitro release profile, achieving 68.906% cumulative drug release over 12 hours. Stability studies revealed consistent pH and viscosity over 60 days, confirming the formulation's robustness. The findings suggest that the developed system could improve patient compliance and therapeutic outcomes in ocular therapy.

Keywords: Loteprednol Etabonate, ophthalmic delivery system, pH stability, drug release, formulation evaluation, ocular therapy, in situ gel, viscosity, stability studies.

INTRODUCTION

Ophthalmic drug delivery systems play a critical role in the treatment of various eye conditions, including inflammation, allergies, and infections. Among the range of therapeutic agents used in ophthalmology, Loteprednol Etabonate (LE) is a corticosteroid that has garnered attention due to its anti-inflammatory properties and reduced side effects compared to traditional corticosteroids (Harris *et al.,* 2017). LE is primarily indicated for the treatment of ocular inflammatory conditions and postoperative inflammation, making effective delivery systems essential for maximizing its therapeutic potential while minimizing adverse effects.

The conventional methods of ophthalmic drug delivery, such as eye drops and ointments, often face challenges, including low bioavailability, rapid drainage from the eye surface, and limited penetration into ocular tissues (Huang *et al.,* 2018). As a result, there is a growing interest in developing novel drug delivery systems that can enhance the efficacy of ocular therapies. Various formulations, such as gels, nanoparticles, and microemulsions, have been explored to improve drug residence time, ocular penetration, and therapeutic efficacy (Ghosh *et al.,* 2020).

Loteprednol Etabonate has been formulated in different dosage forms, including suspensions and gels, to optimize its delivery to ocular tissues. Research has demonstrated that formulating LE in mucoadhesive systems can significantly prolong contact time on the ocular surface, enhancing drug absorption and therapeutic effects (Batra *et al.,* 2019). Moreover, the incorporation of permeation enhancers and nanocarriers has been shown to

facilitate the penetration of LE across the corneal barrier, improving its bioavailability and therapeutic outcomes (Patel *et al.,* 2021).

This study aims to formulate and evaluate an ophthalmic delivery system of Loteprednol Etabonate, focusing on enhancing its stability, bioavailability, and therapeutic efficacy. The use of advanced formulation techniques, including the development of hydrogels and liposomal systems, is anticipated to address the limitations of conventional ophthalmic formulations.

MATERIALS AND METHODS

Preparation of in situ gelling system

The gel was made using a cold technique. Poloxamer-407 was added to 15 mL of distilled water in a beaker with a magnetic stirrer at 500–600 rpm for 2 h at a temperature of 42°C with continuous stirring. Refrigeration was carried out overnight. When the poloxamer dispersion was mixed with HPMC K-100, carbopol-940, and propyl paraben (0.1%), the mixture was stirred constantly. Solubilizing the preservative in hot water yielded the preservative solution. After cooling, it was included in the aforesaid dispersion. Tween 80 and ethanol (1:2) were used to dissolve the weighed quantity of medication. Poloxamer dispersion was then added to the medication solution. Carbopol-containing dispersion was adjusted to pH 5.8 using triethanolamine, and the poloxamer-containing dispersion to pH 7 using triethanolamine (Qian *et al.,* 1987)

Evaluation of formulation

Determination of visual appearance, clarity, pH and Drug Content:

The appearance and clarity were determined visually. The pH of the formulations was measured by using pH meter. The drug content was determined by diluting 1 ml of the formulation to 50 ml freshly prepared simulated tear fluid. The formed gel was completely crushed with the help of a glass rod, followed by vigorous shaking until the formed gel got completely dispersed to give a clear solution. The volume was adjusted to 100 ml with simulated tear fluid. The solution was filtered through a 0.45-mm filter membrane and Loteprednol etabonate concentration was then determined at 230 nm by using UV- Vis spectrophotometer (Nayak *et al.,* 2021).

In vitro Gelation Studies

Determination of temperature of the Sol–Gel Transition

The temperature of the water bath was adjusted by 1◦C every five minutes from 33 to 40◦C for the sol–gel transition temperature test in many test tubes (Huang *et al.,* 2010).

Gelling Time

The gelling periods of the formulation were determined using a glass plate with the same slope as the ear, and the temperature was kept at 37 ◦C ± 0.5 ◦C. The gelling time was measured after the separate otic formulations (100–200 mL) were dropped on the glass plate. It was possible to see the transformation of a liquid solution into a thick gel. The -ve symbol is used to indicate preparations that did not gel. Those solutions with a phase transition after 90 s received the lowest score of +ve. The solutions that produced the gels in between 30 and 90 s received the maximum score of ++. The solutions that transitioned within 30 s and created stable gels for more than 30 min received the maximum score of +++ (Garala *et al.,* 2013).

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 (Madan *et al.,* 2015).

Zeta Potential

The zeta potential of the dispersion determines the stability of colloidal dispersion. The zeta potential value indicates the stability of the formulations (Gabal *et al.,* 2014).

Rheological studies

The rheological properties of solutions and gels were measured using a Brookfield synchroelectric viscometer. The developed formulation was poured into the small adaptor of the brook field synchroelectric viscometer and the angular velocity increased gradually from 10 to 100 rpm. The hierarchy of the angular velocity was reversed. The average of the two reading was used to calculate the viscosity. The formulation was then poured into an ointment jar and the pH rise to 7.4 by adding simulated lachrymal fluid (Manjappa *et al.,* 2009).

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 (Patil *et al.,* 2015).

Ex-Vivo Permeation Study

The ex-vivo permeation investigation was undertaken using the Franz diffusion cell. Porcine oral mucosa was used as a biological membrane in the investigation. Porcine oral mucosa was obtained from a slaughterhouse in the area and stored at 4◦C in phosphate buffer (pH 7) from the time of acquisition. Within three hours after purchasing it, it was put to use. The receptor compartment had phosphate buffer put into it (pH-7.4). This chamber also contains a stirring bead that is powered by a magnet. An appropriately sized membrane was placed between the donor and receptor compartments. A magnetic stirrer was used to keep the cell at 37 ± 1 ◦C while it was being swirled at 600 rpm. A gel sample of about 500 mg was placed in the donor compartment. Samples were taken at 15, 30, 45, 60, 75, 90, 120, 180, and 360 min. It was necessary to replenish the receptor compartment with an equal volume of fresh, hot phosphate buffer (pH 7.4) to maintain sink conditions. Before being evaluated for absorbance at 230 nm, the samples were filtered and diluted (Baloglu *et al.,* 2011).

***In vitro* drug release studies**

The *in vitro* release studies were carried out on formulation codes F1 to F10 using a modified USP dissolution testing apparatus. The dissolution medium maintained at temperature of 37±1°C. The shafts were allowed to rotate at a constant speed (50 rpm). At predetermined time intervals for 8 hrs, aliquots were withdrawn and replaced by an equal volume of the receptor medium. The drug content in the withdrawn samples was determined at 230 nm using UV-visible double beam spectrophotometer. The results were the means of three runs. The results of

in vitro data were analyzed. The formulations were optimized on the basis of viscosity and in vitro release studies (Rani *et al.,* 2022).

Kinetic Modeling and Mechanism of Drug Release:

Data obtained from in vitro drug release study were fitted to following kinetic models. Zero order release kinetics, First order release kinetics, Higuchi Release Model, Peppas & Koresmeyer Model (Power Law).

Stability Studies

The stability of the optimized formulation (F10) was evaluated over a period of 60 days at 4 ˚C and 25˚C. Parameters like pH, gelling capacity, and viscosity were evaluated at various time intervals. The pH of the formulation was measured using a pH meter. The gelling capacity of the formulation was assessed visually by observing whether it formed a gel when it was placed in the refrigerator. The viscosity of the sol and gel phases of the formulation was measured using a viscometer.

RESULTS AND DISCUSSION

The formulation and evaluation of an ophthalmic delivery system for Loteprednol Etabonate (LE) were carried out to enhance the therapeutic efficacy and patient compliance of this important corticosteroid. Several key parameters, including pH stability, drug content, sol-gel transition characteristics, viscosity, in vitro and ex vivo drug release profiles, and stability over time, were assessed to optimize the formulations.

The pH values of the formulations, as shown in Table 2, indicate that the majority of the formulations maintained a pH close to physiological levels (around 7.0), which is crucial for ocular formulations to avoid irritation and ensure comfort upon administration. Formulations F1, F3, and F5 exhibited stable pH values over 48 hours, suggesting their suitability for ocular applications.

Table 3 highlights the drug content of the formulations, with values ranging from 77.06% to 83.82%. The consistency in drug content across the formulations indicates reliable formulation techniques and assures adequate dosing upon administration. Such levels are essential for ensuring therapeutic efficacy.

The sol-gel transition temperatures and gelling times presented in Table 4 suggest that formulations like F6, which had a lower transition temperature and faster gelling time, may be particularly advantageous for in situ gel systems. This rapid transition could enhance drug residence time on the ocular surface, providing prolonged therapeutic action.

Formulations demonstrated varying viscosities in both solution and gel states, as shown in Table 5. Higher viscosities in gel form suggest a better retention capability on the ocular surface, reducing drainage and enhancing drug absorption. Formulations F8 and F10 exhibited superior spreadability and gel strength, critical attributes for effective ocular delivery.

The in vitro release studies (Table 6) show that the optimized formulation F10 released LE gradually, with a cumulative drug release (CDR) of 68.906% by 12 hours. This controlled release profile is advantageous for maintaining therapeutic drug levels over extended periods. The ex vivo release data in Table 7 further reinforces this, showing that F10 maintained a consistent release pattern,

suggesting effective permeation through ocular tissues.

Table 8 outlines the stability of formulation F10 over a 60-day period. The stability of pH and viscosity, alongside its consistent gelling capacity, indicates that the formulation is likely to remain effective throughout its shelf life. This stability is crucial for ensuring patient safety and therapeutic efficacy over time.

Table 1: Composition of formulations

F. Code	Drug %(w/v)	Tween 80+ Ethanol	P407% (w/v)	C-940 %(w/v)	HPMC %(w/v)	Propyl Paraben
F1	0.3	6	4.5	0.1	0.05	30
F2	0.3	6	4.6	0.1	0.05	30
F3	0.3	6	4.7	0.1	0.05	30
F4	0.3	6	4.8	0.2	0.05	30
F5	0.3	6	4.9	0.2	0.05	30
F6	0.3	6	5.0	0.2	0.05	30
F7	0.3	6	5.1	0.3	0.05	30
F8	0.3	6	5.2	0.3	0.05	30
F9	0.3	6	5.3	0.3	0.05	30
F10	0.3	6	5.4	0.3	0.05	30

Table 2: pH determination at 37 °C

Formulation	At the Time of Preparation	After 24 h	After 48 h
F1	7.23 ± 1.32	7.00 ± 2.43	7.00 ± 2.34
F2	6.34 ± 2.56	6.22 ± 1.34	6.21 ± 1.34
F3	7.45 ± 3.67	7.53 ± 4.34	7.52 ± 0.89
F4	7.67 ± 2.89	7.00 ± 3.23	7.00 ± 0.56
F5	7.49 ± 2.12	7.83 ± 1.23	7.84 ± 1.67
F6	7.89 ± 3.56	7.29 ± 2.56	7.25 ± 2.89
F7	7.60 ± 3.45	7.43 ± 2.67	7.46 ± 1.45
F8	7.00 ± 2.67	7.12 ± 4.56	7.49 ± 4.34
F9	6.57 ± 1.78	7.00 ± 2.34	7.00 ± 5.46
F10	7.45 ± 1.23	7.47 ± 1.32	7.43 ± 6.45

Table 3: Drug contents of formulations F1–F10

S. No.	Formulation	% Drug Content
1	F1	80.58 ± 0.14
2	F2	83.11 ± 0.65
3	F3	80.92 ± 0.25
4	F4	77.71 ± 0.44
5	F5	83.82 ± 1.15
6	F6	79.84 ± 0.48
7	F7	78.70 ± 1.15
8	F8	77.06 ± 0.30

Table 4: Temperature of sol–gel transition in formulations

S. No	Formulation	Transition Temperature (°C)	Gelling Time (s)
1	F1	35 ± 0.22	90 ± 0.23
2	F2	34 ± 0.56	120 ± 0.39
3	F3	35 ± 0.67	80 ± 0.67
4	F4	35 ± 0.89	50 ± 0.89
5	F5	36 ± 0.76	90 ± 0.53
6	F6	34 ± 0.12	35 ± 0.34
7	F7	36 ± 0.32	80 ± 0.39
8	F8	35 ± 0.69	90 ± 0.29
9	F9	34 ± 0.56	58 ± 0.47
10	F10	33 ± 0.68	40 ± 0.59

Table 5: Viscosity of formulations F1–F10 in solution and gel form

S. No	Solution State Viscosity (cp)	Gel State Viscosity (cp)	Spreadability	Gel Strength
1	F1	80.3 ± 1.14	1427.56 ± 0.39	5.46 ± 0.97
2	F2	84.6 ± 0.17	1495.32 ± 0.43	4.34 ± 0.46
3	F3	86.1 ± 0.56	1525.78 ± 0.89	5.12 ± 0.78
4	F4	88.2 ± 0.45	1447.57 ± 0.65	4.57 ± 1.27
5	F5	92.4 ± 0.34	1538.28 ± 0.56	4.93 ± 1.56
6	F6	94.1 ± 0.67	1612.45 ± 0.74	5.27 ± 0.34
7	F7	96.5 ± 0.39	1467.76 ± 1.05	4.5 ± 0.64
8	F8	97.1 ± 0.69	1621.85 ± 3.68	5.67 ± 0.67
9	F9	98.5 ± 0.78	1534.43 ± 1.14	5.29 ± 0.59
10	F10	99.5 ± 1.45	1586.67 ± 1.14	6.35 ± 0.37

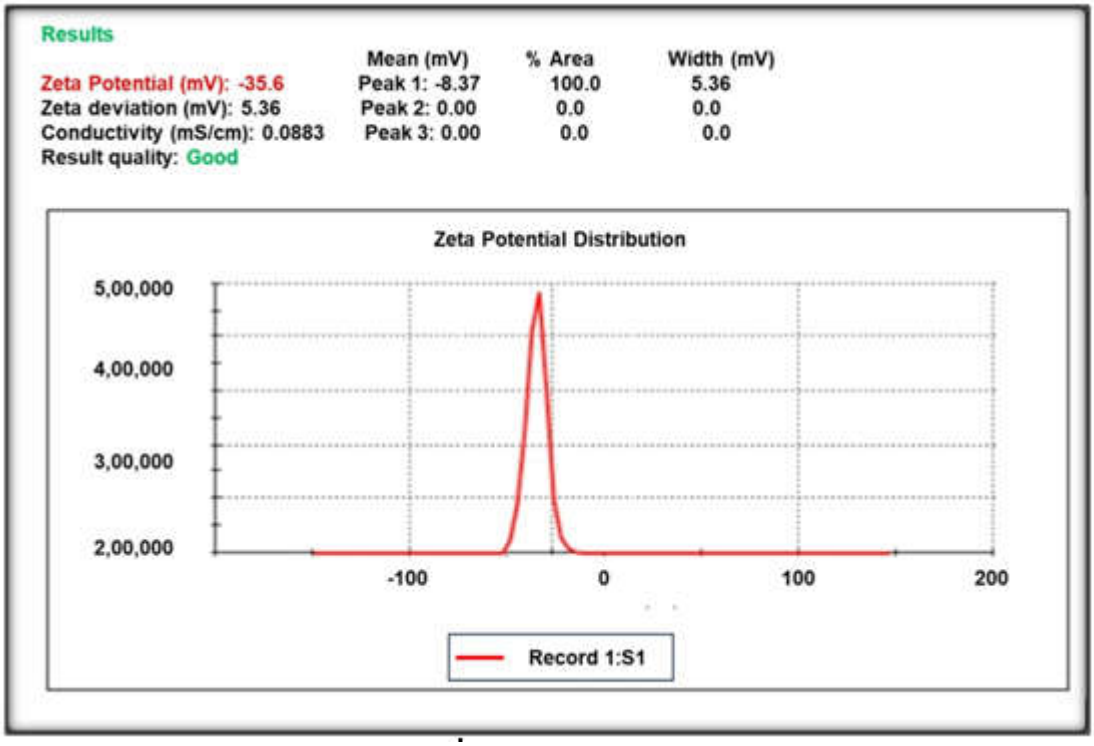

Figure 1: Zeta potential of the optimized formula F10

Table 6: Comparison of percent of in vitro release of formulation (F10) and drug

Time	% CDR of Pure Loteprednol etabonate	% CDR of Optimized Formulation of Loteprednol etabonate
0.5	6.22222 ± 4.19	0.391 ± 8.39
1	8.54547 ± 0.04	5.149 ± 8.17
2	8.936111 ± 6.49	8.388 ± 1.41
3	11.10494 ± 3.10	17.149 ± 2.73
4	12.28364 ± 8.25	26.190 ± 3.21
5	14.62346 ± 0.87	37.405 ± 2.23
6	17.74753 ± 8.17	41.813 ± 8.56
7	31.20926 ± 5.74	46.747 ± 6.19
8	43.28395 ± 4.16	50.907 ± 6.39
9	46.1284 ± 7.87	57.558 ± 4.16
10	46.1284 ± 3.31	61.178 ± 4.06
11	49.86605 ± 5.64	68.906 ± 1.25
12	54.44228 ± 1.15	81.286 ± 1.45

Table 7: Ex vivo release data of different formulations

Time (min.)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
15	25.209	18.203	22.569	24.223	25.203	24.453	23.203	17.000	15.584	18.234
30	35.645	32.549	34.457	32.254	30.3.45	35.109	26.940	24.625	27.125	22.963
45	49.480	45.904	43.554	42.765	47.489	43.489	38.404	37.766	41.667	34.839
60	65.467	63.266	60.687	64.543	57.616	60.526	58.126	57.880	59.337	56.71
75	74.303	72.079	71.224	76.205	69.177	70.778	67.212	68.800	66.151	77.45
90	87.642	85.993	86.343	83.231	80.776	78.923	82.007	76.876	78.470	71.405
120	96.648	89.729	89.709	91.709	89.708	90.129	94.120	87.685	84.825	79.856
180	90.392	90.234	91.105	87.773	90.343	92.221	89.103	88.065	90.132	89.009
360	93.845	92.325	93.715	91.413	93.705	92.098	93.775	90.642	91.654	97.653

Table 8: Stability studies on formulation F10

Parameter	30 Days	45 Days	60 Days
pH	6.8	7	7.2
Gelling capacity	+++	+++	+++
Viscosity sol	15.1	15.3	14.6
Viscosity gel	99.5	99.5	97.1

+++ = Immediate gelation and leftovers for extended duration

CONCLUSION

The comprehensive evaluation of the Loteprednol Etabonate ophthalmic delivery system indicates that the optimized formulation (F10) demonstrates promising characteristics for effective ocular therapy. With favorable pH stability, consistent drug content, advantageous sol-gel properties, and controlled release profiles, F10 stands out as a suitable candidate for clinical applications. Future studies could focus on in vivo evaluations to further validate the therapeutic efficacy of this formulation.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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