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FORMULATION AND EVALUATION OF *IN SITU* GEL AS OPHTHALMIC DRUG DELIVERY SYSTEM

Madhu Kumari, Nilesh Gupta, Umesh Kumar Jain

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Madhu Kumari, Nilesh Gupta and Umesh Kumar Jain
Bhopal Institute of Science & Technology – Pharmacy, Bhopal, M.P.

Correspondence

Madhu Kumari
Bhopal Institute of Science & Technology – Pharmacy, Bhopal, M.P.

Email: madhu.ku0509@gmail.com

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ABSTRACT

Levofloxacin *in situ* gel is developed to overcome issues associated with traditional eye drops and to enhance their bioavailability. The low bioavailability of standard eye drops is primarily due to various precorneal loss factors. Additionally, this gel offers improved patient compliance through easier application and reduces the need for frequent instillations.

Key words: Levofloxacin, *In situ* gel, Ophthalmic drug delivery, *In vitro* Drug Release.

1 INTRODUCTION

The low ocular bioavailability of drugs from traditional eye drops, often less than 1%, is mainly caused by factors such as rapid tear turnover, poor absorption, limited residence time in the eye's cul-de-sac, and the relatively impermeable nature of the corneal epithelial membrane. Additionally, when topically applied drugs are eliminated from the pre-corneal area, they can also be lost through the nasal cavity, which has a larger surface area and a more permeable mucosal membrane than the cornea. Effective ophthalmic drug delivery should be capable of providing a sustained release of medication and maintaining its presence for an extended period.[1,2]

1.1 *In Situ* Gel System

Preformed hydrogels still have some limitations that can reduce their usefulness for eye drug delivery or as tear substitutes. They often make it difficult to accurately and consistently administer specific amounts of medication, and after use, they can cause blurred vision, crusting around the eyelids, and tearing. A newer approach aims to combine the benefits of both solutions and gels—such as the ease and precision of application from solutions, along with the longer retention time of gels. This has led to the development of *in situ* hydrogels, which undergo gelation directly in the eye. The transition from liquid to semi-solid can be triggered by factors like increased temperature, pH changes, or the ionic strength of the tear film.[3-5]

1.2 Advantages of I*n Situ F*orming Gel

Generally more comfortable than insoluble or soluble insertion. Less blurred vision as compared to ointment. Increased bioavailability due to –Increased precorneal residence time. Decreased nasolacrimal drainage of the drug. Drug effect is prolonged hence frequent instillation of drug is not required.[6-9]

2 METHODOLOGY

2.1 Preparation of I*n Situ* Gelling System

The gel was prepared using a cold method. Poloxamer-407 was mixed into 15 mL of

distilled water and stirred at 500–600 rpm for 2 hours at 42°C. Afterwards, the mixture was refrigerated.The poloxamer dispersion was then combined with HPMC K-100, carbopol-940, and 0.1% propyl paraben, with continuous stirring. Once cooled, Tween 80 and ethanol in a 1:2 ratio were used to dissolve the specified amount of medication. Finally, the poloxamer dispersion was added to the medication solution.[10-13]

3 EVALUATION OF FORMULATION

3.1 Gelling Time

The glass plate was tilted at the same angle as in the ear, and the temperature was maintained at 37°C ± 0.5°C. The timing was measured after dropping separate formulations (100–200 mL) onto plate. It was possible to observe the liquid solution gradually transforming into a thick gel.[14-17]

3.2 Gelling Strength

The gel was poured into a 100 ml measuring cylinder, and a probe was positioned on top of it with a weight placed on the probe. The probe was allowed to penetrate to a depth of 5 cm, and the time taken for this penetration was recorded as a measure of the gel's strength.[18,19]

3.3 Zeta Potential

The stability of a colloidal dispersion is influenced by its zeta potential. The value of the zeta potential reflects how stable the formulations are.[20]

3.4 Spreadability

An excess amount of sample was placed between two glass slides and then compressed to a uniform thickness by applying a 100-gram weight on the top slide for five minutes. A 50-gram weight was added to the pan. The time taken for the upper glass slide to move over the lower plate, from the moment pressure was applied until separation, was recorded as the measure of spreadability. [21-24]

3.5 *Ex-Vivo* Permeation Study

The ex-vivo permeation study was conducted using a Franz diffusion cell. Porcine oral mucosa served as the biological membrane. The receptor chamber contained PBS at pH 7.4 and was stirred with a stirring bead. The membrane was positioned between the donor and receptor compartments. About 500 mg of gel was placed in the donor chamber. Samples were collected at intervals of 15, 30, 45, 60, 75, 90, 120, 180, and 360 minutes. These samples were then analysed.25-27

3.6 *In-Vitro* Drug Release Studies

The in vitro release experiments were conducted on formulations labeled F1 to F10 using a modified USP dissolution apparatus. The dissolution medium was kept at a temperature of 37±1°C. The shafts rotated steadily at 50 rpm. Samples were collected at set time points over an 8-hour period, and an equal volume of fresh medium was added to replace each sample. The amount of drug in the samples was measured using a UV-visible double beam spectrophotometer. The formulations were selected based on their viscosity and their in vitro release performance.[28]

4 RESULT

4.1 Evaluation of Gel

4.1.1 Appearance/clarity

White and dark colours were used to visually examine the mixtures that were made. All of the formulations appeared to be clear and see-through.

4.1.2 Temperature of sol-gel transition in formulations

Temperature of *sol-gel* transitions in formulations shown in table no. 2

4.1.3 Rheological Investigations

The parameters of the formulations(F10) is optimum as compared to others. However, based on the data provided, formulation F10 appears to be a good candidate for further development shown table no. 3.

4.1.4 Zeta potential determination

The zeta potential of the dispersion influences its stability as a colloidal system. The ideal zeta potential values, which suggest stability and prevent the formation of aggregates, are approximately around -35.6 mV.

4.1.5 Cumulative drug release

The percentage cumulative drug release (%CDR) of pure Levofloxacin and the optimized formulation (F10) at different time points, shown in table no.4.

4.1.6 Ex-vivo release of different formulations

Ex-vivo release of different formulation shown in table no. 5

5 CONCLUSION

Most eye conditions are commonly treated with eye drops or ointments applied directly to the surface. When a drop is

Table 1: Composition of formulations

Tim	Drug %(w/v)	Tween80+ Ethanol	P407% (w/v)	C-940 %(w/v)	HPMC %(w/v)	Propyl Paraben	D/W (mL)
F1	0.3	8	5.5	0.2	0.06	0.005	40
F2	0.3	8	5.6	0.2	0.06	0.005	40
F3	0.3	8	5.7	0.2	0.06	0.005	40
F4	0.3	8	5.8	0.3	0.06	0.005	40
F5	0.3	8	5.9	0.3	0.06	0.005	40
F6	0.3	8	6.0	0.3	0.06	0.005	40
F7	0.3	8	6.1	0.4	0.06	0.005	40
F8	0.3	8	6.2	0.4	0.06	0.005	40
F9	0.3	8	6.3	0.4	0.06	0.005	40
F10	0.3	8	6.4	0.4	0.06	0.005	40

Table 2: Temperature of sol–gel transition in formulations

M	Formulation	Transition Temperature	Gelling Time(sec)
1	F_1	36 ± 0.42 ˚C	89 ± 0.43
2	F_2	35 ± 0.51˚C	121 ± 0.65
3	F_3	35 ± 0.21 ˚C	79 ± 0.54
4	F_4	36 ± 0.76 ˚C	49 ± 0.54
5	F_5	37 ± 0.65 ˚C	89 ± 0.43
6	F_6	35 ± 0.43 ˚C	36 ± 0.21
7	F_7	37 ± 0.65 ˚C	79 ± 0.51
8	F_8	36 ± 0.87 ˚C	89 ± 0.31
9	F_9	35 ± 0.63 ˚C	63 ± 0.58
10	F_{10}	33 ± 0.43 ˚C	39 ± 0.41

Table 3: Viscosity of formulations

Formulation	Solution State Viscosity (cp)	Gel State Viscosity (cp)	Spreadability	Gel Strength
F1	80.3 ± 1.14	1427.56 ± 0.39	5.46 ± 0.97	10.65 ± 0.67
F2	84.6 ± 0.17	1495.32 ± 0.43	4.34 ± 0.46	18.93 ± 0.53
F3	86.1 ± 0.56	1525.78 ± 0.89	5.12 ± 0.78	12.65 ± 0.36
F4	88.2 ± 0.45	1447.57 ± 0.65	4.57 ± 1.27	29.89 ± 0.85
F5	92.4 ± 0.34	1538.28 ± 0.56	4.93 ± 1.56	45.34 ± 0.47
F6	94.1 ± 0.67	1612.45 ± 0.74	5.27 ± 0.34	34.27 ± 1.32
F7	96.5 ± 0.39	1467.76 ± 1.05	4.5 ± 0.64	56.58 ± 1.48
F8	97.1 ± 0.69	1621.85 ± 3.68	5.67 ± 0.67	43.23 ± 0.45
F9	98.5 ± 0.78	1534.43 ± 1.14	5.29 ± 0.59	59.76 ± 0.37
F10	99.5 ± 1.45	1586.67 ± 1.14	6.35 ± 0.37	65.78 ± 0.45

instilled, only a small amount of the drug actually penetrates the cornea, with most being absorbed and entering the bloodstream. To enhance bioavailability, *in situ* gel formulations have been developed. These formulations were tested for various factors such as pH, appearance, gelation properties, rheology, and in vitro drug release. The formulation F10 demonstrated better stability and drug release characteristics. Overall, the study successfully contributed to the development of an *in situ* gelling system for Levofloxacin.

Table: 4 Comparison of percent of *in-vitro* release of formulation (F10) and drug.

Time	% CDR of pure Levofloxacin	% CDR of optimized formulation of levofloxacin
0.5	5.2432 ± 4.19	0.491 ± 7.42
1	8.543 ± 0.04	6.149 ± 8.17
2	8.934 ± 5.32	7.923 ± 2.87
3	11.106 ± 3.10	16.149 ± 1.41
4	12.289 ± 9.45	27.290 ± 4.22
5	14.624 ± 0.87	38.405 ± 3.11
6	17.749 ± 8.17	40.813 ± 8.56
7	30.202 ± 5.74	45.747 ± 4.32
8	43.289 ± 4.16	51.907 ± 7.66
9	45.129 ± 7.87	56.558 ± 4.16
10	46.126 ± 2.56	62.213 ± 3.62
11	50.765 ± 4.312	69.906 ± 1.25
12	55.444 ± 1.15	82.286 ± 1.45

Table 5: Ex vivo release data of different formulations.

Time (min.)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
15	25.22	18.29	22.58	24.29	25.29	24.453	23.29	17	15.55	18.21
30	35.63	32.57	34.40	32.26	30.37	35.109	26.94	24.69	27.23	22.92
45	49.49	45.94	43.56	42.75	47.48	43.489	38.42	37.76	41.68	34.84
60	65.45	63.27	60.67	64.52	57.62	60.526	58.16	57.87	59.35	56.76
75	74.32	72.03	71.24	76.24	69.177	70.73	67.26	68.81	66.19	77.48
90	87.65	85.92	86.37	83.22	80.776	78.99	82.09	76.82	78.42	71.49
120	96.63	89.73	89.73	91.78	89.75	90.18	94.15	87.65	84.87	79.84
180	90.37	90.27	91.16	87.74	90.35	92.27	89.13	88.09	90.16	89.06
360	93.84	92.38	93.78	91.49	93.78	92.05	93.75	90.63	91.63	98.99

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