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FORMULATION AND EVALUATION OF OPHTHALMIC *IN-SITU* GEL FOR THE TREATMENT OF OCULAR INFLAMMATION AND BACTERIAL INFECTION

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ABSTRACT

In this present work describes the formulation and evaluation of ocular drug delivery system of Moxifloxacin Hydrochloride and Dexamethasone Sodium Phosphate based on the concept of pH triggered *in-situ* gelling system. A combination of Moxifloxacin Hydrochloride and Dexamethasone Sodium Phosphate along with carbomer as pH sensitive polymer was used to formulate pH triggered *in-situ* gel. The developed formulation was alternative to conventional ophthalmic dosage form to improve the contact time of the drug in eyes. Moxifloxacin as an antibacterial agent and Dexamethasone as corticosteroids, this two drugs combination *in-situ* gel dosage form is used to treat bacterial infection and ocular inflammation. The developed formulation was effective in the treatments of bacterial infection and ocular inflammation. The formulation which follows sol gel transition system i.e. eye drops instilled into eye which undergo gel form therefore increase the residence time of the drug into the eye. In these formulations carbomer is used as gelling agent which exhibit sol gel phase transitions due to change in physicochemical parameter (pH) & HPMC used as viscosity enhancer. The formulations were evaluated for the clarity, pH, gelling capacity, drug content, rheological study, in vitro drug release study, stability study.

KEYWORDS: Moxifloxacin Hydrochloride, Dexamethasone Sodium Phosphate, Cabomer In situ gelling system, pH triggered method.

INTRODUCTION

Eye is very important organ of body. The eye shows protective mechanism such as reflex lachrymation blinking and drainage. The commonly used route of administration in treatment of eye is topical administration/ application of drug. *In-situ* gel which persists solution form before instillation into eye after when instilled into ophthalmic cavity (Eye) which get convert in to gel form by sol-gel phase transition system which reduce drainage. The most conventional ophthalmic delivery such as eye drops, ointment, suspension which results in poor bioavailability and therapeutic response.

A high frequency of eye drops instillation is associated with patient incompliance. The conventional ophthalmic delivery system drawbacks can be overcome by the use of *in-situ* gelling system. Several *in-situ* gelling system have been developed to prolong the precorneal residence time of a drug. These systems consist of polymer that exhibit sol to gel phase transitions due to change in specific physico-chemical parameter.

There are three method of preparation of *in-situ* gel:

1. pH triggered
2. Temperature dependent
3. Ion-activated induced.

In this current work pH triggered *in situ* gel of Moxifloxacin Hydrochloride & Dexamethasone Sodium Phosphate combination is using carbomer as a gelling agent and HPMC as a viscosity enhancing agent.

Moxifloxacin is broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell replication. Dexamethasone is a glucocorticoid agonist.

MATERIAL AND METHODS

MATERIALS

Moxifloxacin Hydrochloride (Entatec labs Pvt.Ltd.), Dexamethasone Sodium Phosphate (General Importer company India Pvt), Carbomer (Shree Chem.), Benzalkonium Chloride Solution (Merck, India) were obtained from approved sources.

METHODS

- A weighed amount of carbomer was solubilized in Water for Injections at ambient temperature with different concentration of polymer dissolved in Water with continuous stirring.
- Weighed quantity of Moxifloxacin Hydrochloride 0.5% W/V in Water for Injections & dissolved & also same Dexamethasone Sodium Phosphate dissolve in Water for Injections, the prepared drug solution. This drugs solution was further added to polymer solution with constant stirring for 10 min. to gain homogenous mixture.
- Add the Benzalkonium Chloride Solution 0.002%W/V act as preservative for i*n-situ* gels preparation.
- The pH of resultant solution was adjusted by using 0.1 N HCL.
- The prepared *in-situ* gels were filled in LDPE dropper bottles with nozzle.

The different compositions of developed in-situ gel were given in Table 1:

Table No. 1: Composition of in situ gelling system by pH sensitive system.

Name of Ingredient	F1	F2	F3	F4	F5
Moxifloxacin Hydrochloride	0.5% W/V	0.5% W/V	0.5% W/V	0.5% W/V	0.5% W/V
Dexametasone Sodium Phosphate	0.2% W/V	0.2% W/V	0.2% W/V	0.2% W/V	0.2% W/V
Carbomer	0.1% W/V	0.2% W/V	0.3% W/V	0.4% W/V	0.5% W/V
HPMC	1.5% W/V	1.5% W/V	1.5% W/V	1.5% W/V	1.5% W/V
Benzalkonium Chloride Solution	0.02% W/V	0.02% W/V	0.02% W/V	0.02% W/V	0.02% W/V
Water for Injections	100 ml	100 ml	100 ml	100 ml	100 ml

RESULT AND DISCUSSION

1. Physiological characteristics

a) Clarity and Appearance

Clarity of the formulation was found to be satisfactory. The formulations were pale yellow in color. Terminal sterilization with autoclaving had no effect on the physicochemical properties of the formulation. Prepared formulation clarity was found satisfactory.

b) pH

The formulation was prepared with different concentration of polymer. The pH of all formulations from F1 to F5 was within the range of 6.0 to 6.8 pH values of formulation shown in Table No: 2 and hence would not cause not cause any irritation upon instillation to eye.

Table No. 2: pH values of formulations.

Sr. No.	Formulation Code	Observed pH
1	F1	6.42
2	F2	6.43
3	F3	6.45
4	F4	6.38
5	F5	6.43

2. Drug Content

The drug content was found to be in acceptable range (98%-102%) indicating uniform distribution of drug. The drug content of formulation is shown in Table No: 3.

Table No. 3: Drug Content of formulations.

Sr. No.	Formulation Code	Drug Content (%)
1	F1	100.07
2	F2	98.05
3	F3	99.43
4	F4	101.13
5	F5	102.00

The percentage drug content of all prepared ophthalmic formulation was found to be in the range of 98-102%. Therefore uniformity of drug was maintained in all formulation.

3. In vitro gelling Capacity

The results of in vitro gelling capacity revealed that gel formed in situ preservative its integrity without dissolving for a sufficient period of time.

4. Rheological Study

The viscosity of formulation at room temperature is shown in Table No. 4. The viscosity profile of formulation at room temperature is shown in figure no. 1.

Table No. 4: Rheological studies of formulations.

RPM	Viscosity in cps. (Before gelling at room temperature.)				
	F1	F2	F3	F4	F5
1	125	236	235	533.8	752
1.5	124	217	230	532	710
2	121	212	229	530	671
2.5	121	203	227	530	650
3	116	204	226	526	630
4	115	187	235	519	625

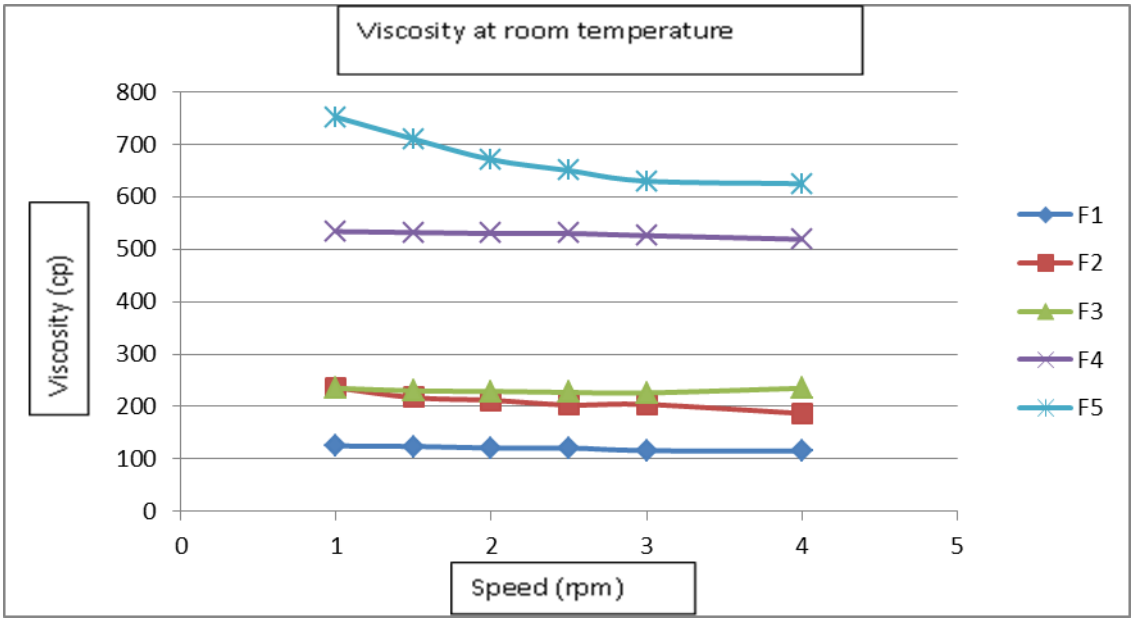

Figure No. 1: Viscosity profile of formulation at room temperature.

To assess the rheological behavior, the viscosity of F3 formulation was determined before gelation and after gelation was evaluated using brook field viscometer, with varying RPM. The Rheological behavior formulation viscosity studies before gelation and after gelation as shown in Table no 5.

Table No. 5: Viscosity studies before gelation and after gelation.

RPM	Viscosity (cp)	
	Before gelation (25 ^{0}C)	After gelation (37 ^{0}C)
10	304	1028
20	276	1000
30	217	882
50	194	655
100	147	542

5. Isotonicity study

All prepared formulations iso-tonicity compared with marketed samples and which were found satisfactory.

6. Measurement of the gel Strength

The gel strength of ophthalmic *in –situ* gel formulation at room temperature and 37 ^{0}C are shown in table no.6 and 7 respectively.

Table No. 6: Gel strength of formulation at room temperature.

Sr. No.	Formulation Code	Gel Strength (sec) (+ S.D.)
1	**F1**	**0.59±0.015**
2	**F2**	**0.65±0.051**
3	**F3**	**0.78±0.042**
4	**F4**	**0.89±0.021**
5	**F5**	**1.12±0.022**

Table No. 7: Gel strength of formulation at 37 ^{0}C.

Sr. No.	Formulation Code	Gel Strength (sec) (+ S.D.)
1	F1	0.68±0.011
2	F2	0.66±0.078
3	F3	0.79±0.053
4	F4	0.89±0.018
5	F5	1.12±0.052

7. In Vitro Drug Release Study

The in vitro drug release study of formulation is shown in Table No.8 and Figure no.2.

Table No 8: Cumulative drug release of formulations.

Cumulative Drug Release (%) (+ S.D.)					
Time in (Hrs)	**F1**	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0
30 min	40.44±0.011	35.64 ±0.005	28.04±0.007	14.92±0.014	14.92±0.014
1	47.04±0.028	37.41± 0.007	49.59±0.005	18.66±0.011	26.17 ±0.018
2	49.86± 0.007	44.11±0.007	58.96±0.005	34..60±0.011	37.44±0.025
3	58.23±0.021	48.79± 0.005	65.55±0.007	37.44±0.025	43.06±0.025
4	67.63 ± 0.002	54.43 ± 0.007	71.18±0.005	43.06±0.025	49.61±0.007
5	68.61 ± 0.014	66.62 ±0.002	75.87±0.005	65.56±0.014	64.63±0.014
6	72.35 ± 0.007	77.88±0.007	83.39±0.007	68.37±0.011	71.20±0.014
7	76.06 ± 0.014	81.63±0.005	93.72±0.014	74.94±0.007	84.33±0.018
8	78.93 ± 0.007	86.33± 0.007	96.53±0.007	77.77±0.005	85.28±0.014

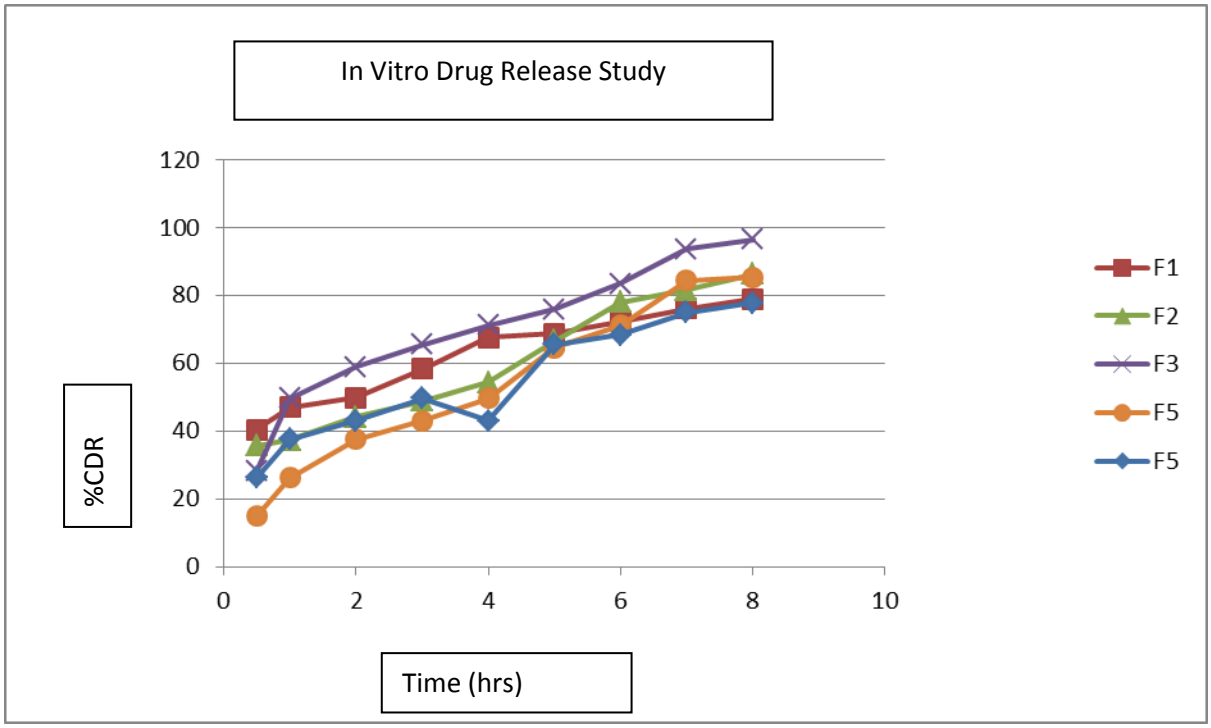

Figure No. 2: In-vitro Drug release profile of formulations.

8. Stability Study

Accelerated stability study of F3 formulation at 25 ^{0}C ±2^{0}C/60%RH±5%RH. There were no signs of drug degradation and the drug was present uniformity distributed throughout the storage period as indicated in Table No.9 As observed no attributes showed any significant changes over the study period, it is apparent the drug product will renaming well within the acceptance criteria during the proposed shelf life.

Table No. 9: Stability data of formulation at ^{0}C ±2^{0}C/60%RH±5%RH.

Parameters		Initial	1 month	2 Month	3 Month
Appearance		Clear	Clear	Clear	Clear
pH		6.41	6.40	6.36	6.35
Gelling capacity		+++	+++	+++	+++
Viscosity in cps at 5 rpm	**Before gelling**	172.3	169.9	164.5	160.5
	After gelling	379.5	366.9	371.8	364.2
Drug content		100.25%	100.20%	99.12%	98.32%

CONCLUSION

The development of in situ gelling pH triggered in situ gelling system for ophthalmic drug delivery overcomes the drawback of conventional ocular drug delivery system and used as alternative for conventional ocular dosage form. *In situ* gelling system of Moxifloxacin Hydrochloride and Dexamethasone Sodium Phosphate using Carbomer and HPMC was

successfully formulated and used for treatment ocular inflammation and bacterial infection and of The prepared formulation were liquid state at the formulated pH and underwent rapid gelation occur upon raising pH. The prepared all formulation (i.e. F1, F2, F3, F4, and F5) pH was found to be satisfactory. Also the clarity and visual appearance of the prepared formulations was found satisfactory. The percentage drug content of all prepared ophthalmic formulation was found to be in the range of 98-102%. Therefore uniformity of drug was maintained in all formulation. The viscosities of all the formulations were greatly affected by concentration of carbomer and HPMC polymers. The developed in situ gel formulations were subjected to stability studies for the period of 3 month and the results of pH, Drug content and clarity, gelling capacity, viscosity was found to be satisfactory results. The developed in situ gelling system was easy to instillation in to eye as a liquid state and form gel when in contact with stimulated tear fluid.

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