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# CONTROLLED RELEASE *IN SITU* GEL OF NORFLOXACIN FOR OCULAR DRUG DELIVERY

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**ABSTRACT:** The poor bioavailability and therapeutic response exhibited by conventional ophthalmic solutions due to rapid precorneal elimination of the drug may be overcome by the use of in situ gel-forming systems that are instilled as drops into the eye and undergo a sol–gel transition in the cul-de-sac. Norfloxacin ophthalmic solution has been shown to be effective ocular infections and may be used in patients with chronic conjunctivitis or ocular irritation. Norfloxacin in-situ gel was prepared using various concentrations of polymers such as Carbopol-934 and HPMC K4M by pH triggered gelling system with objectives of increasing contact time, achieving controlled release, reduction in frequency of administration and greater therapeutic efficacy of drug. The prepared in-situ gels were then evaluated for their visual appearance, clarity, pH, drug content analysis, in-vitro gelation (Gelling capacity), rheological studies, sterility testing and *in-vitro* drug release studies. It is evident from these studies that, formed polymeric in-situ gels had transparent, clear possessing satisfactory gelling capacity. The developed formulation was light yellow in colour, therapeutically efficacious, stable, non-irritant with sustained release of drug.

**INTRODUCTION:** 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. The *in situ* gelling polymers undergo sol-to-gel phase transition on exposure to the physiological conditions present in the eye. *Insitu* gels are viscous polymer-based liquids that exhibit *sol-to-gel* phase transition on the ocular surface due to change in a specific physico-chemical parameter (ionic strength, temperature or pH) [1].

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This interest has been sparked by the advantages shown by *in situ* forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort [2].

Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition, once administered [3].

*In situ* gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. From the early 1970's natural and synthetic polymers began to be investigated for controlled release formulations. Various natural and synthetic polymers are used for formulation development of *in situ* forming drug delivery systems.

Poor ocular bioavailability of drugs (< 1%) from conventional eye drops is due mainly to the precorneal loss factors that include rapid tear turnover, nonproductive absorption, transient residence time in the cul-de-sac, and the relative impermeability of the drugs to corneal epithelial membrane.

Another serious concomitant of the elimination of topically applied drugs from the precorneal area is the nasal cavity, with its greater surface area and higher permeability of the nasal mucosal membrane compared to that of the cornea [4]. The development of new products for the treatment of ophthalmic diseases is facing a double challenge *viz* pharmacological and formulation factors. In addition, other problems are tolerability and comfort requirements of the eye [5]. Normal dropper used with conventional ophthalmic solution delivers about 50-75µl per drop and portion of these drops quickly drain until the eye is back to normal resident volume of 7µl. Because of this drug loss in front of the eye, very little drug is available to enter the cornea and inner tissue of the eye.

Actual corneal permeability of the drug is quite low and very small corneal contact time of the about 1-2 min in humans for instilled solution commonly less than 10%. Consequently only small amount actually penetrates the cornea and reaches intraocular tissue [6]. Controlled drug delivery to the eye is restricted due to these limitation imposed by the efficient protective mechanism [7].

Most of ophthalmic drugs are administered topically in the form of eye drops, a dosage form consisting of buffered, isotonic, aqueous solution or suspensions of the drug. Ophthalmic CDDS have been mainly prepared as gels, ointments, liposomes, micro and nanoparticles, micro spheres and ocular minitablets (MT) or films or inserts [8].

Ideal ophthalmic drug delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolong period of time. Consequently it is imperative to optimize ophthalmic drug delivery, one of the way to do so is by addition of polymers of various grades, development of viscous gel, development of colloidal suspension or using erodible or non-erodible insert to prolong the precorneal drug retention [9]. Bioadhesive systems utilized microparticle suspension or polymeric solution [10].

Problems may be overcome by the use of *in situ* gel-forming systems that are instilled as drops into the eye and undergo a sol-gel transition in the *cul-de-sac*. The developed formulation will be characterized for various in vitro parameters e.g., clarity, gelation temperature and pH, isotonicity, sterility, rheological behavior, drug release profile and ocular irritation. The developed system will be a viable alternative to conventional eye drops for the treatment of Bacterial infection and various other ocular diseases [11].

The aim of the present work is to study the pH-triggered in situ gelling system of Norfloxacin, a first generation fluoroquinolone derivative used in conjunctival infections caused by susceptible bacteria [12].

The recommended dosage of Norfloxacin for the treatment of bacterial conjunctivitis is 1 or 2 drops of 0.3% solution in the affected eyes for every 2 hours up to 8 times for 2 days, then 1 or 2 drops every 4 hours up to 4 times for next 5 days. A combination of carbopol and HPMC was investigated as a vehicle for the formulation of eye drops of Norfloxacin (0.3%) to form gel when instilled into the eye to provide sustained release of the drug to improve the patient compliance by reducing the frequency of administration [13].

## MATERIALS AND METHODS

**Materials:** Norfloxacin was obtained as gift sample from ICPA, Ankleshwer, India. Carbopol-934 (Hi-Media labs India), HPMC K4 M from Yarrow Chemicals, India, and all other reagents were of analytical grade.

**Preparation of formulations: Table 1** shows the composition of all the formulations. Take 70 ml of Distilled water in 100 ml glass beaker. Heat for 10 min until it boils. Then Add HPMC K4 M in a small part wise with full stirring with an overhead stirrer. After complete addition of HPMC K4 M, the solution was allowed to cool in cold water.

It was clean, colorless and viscous solution. Now add and dissolve citric acid and Di- sodium hydrogen phosphate. Then Norfloxacin was dissolved in 0.1 N NaOH and dissolve it separately. The drug solution was then added to the polymeric solution under constant stirring until a uniform solution was obtained. Now add carbopol 934 small part wise and stir for dissolution and then add Tween 20 and heat it. Then after complete dissolution add Edetate disodium and benzalkonium Chloride as per calculation. Now Distilled water was added to make up the volume up to 100 ml of solution. Then solution was filtered through filter paper by applying the vacuum. The formulations were filled in vials under aseptic conditions, sterilized in the autoclave (121$^{o}$C and 15 psi) for 20 minutes and further evaluations were carried out [14].

**TABLE 1: FORMULATION DESIGNS OF NORFLOXACIN *IN SITU* GELS**

| Ingredients (%W/V) | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| Norfloxacin | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| CARBOPOL-934 | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 |
| HPMC K4 M | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 |
| Edetate disodium | - | - | - | 0.01 | 0.01 |
| Di- sodium hydrogen phosphate I.P. | 1.125 | 1.125 | 1.125 | 1.125 | 1.125 |
| Citric Acid I.P. | 0.407 | 0.407 | 0.407 | 0.407 | 0.407 |
| Tween 20 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Benzalkonium Chloride | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| Distilled water | 100ml | 100ml | 100ml | 100ml | 100ml |

**Evaluation of norfloxacin *in situ* gels:**

1. **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 of *in situ* gel was determined by taking sample (2ml) of *in-situ* gel in a 100 ml volumetric flask and diluted with simulated tear fluid of pH 7.4 to get the concentration of 10g/ml (approximately).Then the absorbance was measured at max (277nm) using UV-spectrophotometer (Simadzu UV 1800) to calculate the percentage of drug content [15].

2. **Gelling capacity:** The prepared *in situ* gelling system was evaluated for gelling capacity in order to identify the composition suitable for use as *in situ* gelling system. The *in situ* gelling system was mixed with simulated tear fluid (in the proportion of 25:7 *i.e.* application volume 25µl and normal volume of tear fluid in the eye is 7µl) to find out the gelling capacity of the ophthalmic product. The gelation was then assessed visually by noting the time for the gelation and the time taken for dissolution of the formed gel [16].

3. **Rheological studies:** The relationship between contact time and the rheology was easily understood for viscosity enhanced ophthalmic solutions. It was noted from various literature that the formulations before gelling should have a viscosity of 5 to1000 cps and after gelling in the eye will have a viscosity from about 50-50,000 cps. Rheological studies of the prepared formulations were carried out by Brookfield synchroelectric viscometer (LVDV III U) .The viscosity of the formulations were determined at different speed conditions (1,1.5, 2,2.5,3, and 4 RPM) [17].

4. ***In vitro* release studies:** The drug release from the prepared formulation was studied by bichambered donor receiver compartment model (Franz diffusion cell) using cellophane membrane soaked overnight in the receptor medium (simulated tear fluid, pH 7.4). The diffusion medium was 100 ml of simulated tear fluid stirred at 50 rpm at 37°C±0.5°C. One end of the diffusion tube was covered by a cellophane membrane. The 2 ml formulation were spread on the cellophane membrane and membrane was placed such that it just touches the diffusion medium (STF) present in receptor compartment.

The drug samples were withdrawn at the interval of one hour for the period of 8hrs from diffusion medium and analyzed by a UV spectrophotometer at 277 nm using simulated tear fluid as blank.

5. **Sterility Testing:** The sterility test was performed according to Indian Pharmacopoeia. Direct inoculation method was used. 2 ml of liquid from test container was removed with a sterile pipette or with a sterile syringe or a needle. The test liquid was aseptically transferred to fluid thioglycolate medium (20 ml) and soyabean-casein digest medium (20 ml) separately. The liquid was mixed with the media. The inoculated media were incubated for not less than 14 days at 30°C to 35°C in the case of fluid thioglycolate medium and 20°C to 25°C in the case of soyabean-casein digest medium.

6. **Antimicrobial Efficacy Studies:** The Antimicrobial efficacy studies were carried out to ascertain the biological activity of the optimized formulation. *Staphylococcus aureus, Pseudomonas aeruginosa* and *E. coli* were used as the test organisms. Anti-microbial efficiency was determined by agar diffusion test employing Cup-Plate method. Sterile solutions of Norfloxacin (standard solution) and the developed formulations were diluted at different concentration (test solutions). These solutions were poured in to cups bored into sterile nutrient agar previously seeded with test organisms (*Pseudomonas aeruginosa, E.coli and Staphylococcus aureus*), after allowing diffusion of the solutions for 2 hours, the agar plates were incubated at 37°C for 24hrs. The zone of inhibition (ZOI) measured around each cup and was compared with that of control. The entire operation except the incubation was carried out in a laminar airflow unit. Both positive and negative controls were maintained during the study [18].

7. **Ocular irritancy studies:** Ocular irritation studies were performed on male albino rabbits weighing 1-2 kg. The modified Draize technique was designed for the ocular irritation potential of the ophthalmic product. According to Draize test, the eye drops (100µl) was normally placed in the lower cul-de-sac and irritancy was tested at the time interval of 1hr, 24hrs, 48hrs, 72hrs, and 1 week after administration. The rabbits were observed periodically for redness, swelling and watering of the eye [19].

8. **Accelerated stability studies:** The ophthalmic formulations in amber colored vials were used for a short term accelerated stability studies by storing at 40°±2°C and 75±5% RH as per modified ICH guidelines. Samples were periodically evaluated for appearance, pH, gelling capacity and drug content during the study period.

**RESULTS AND DISCUSSION:** Five formulations of Norfloxacin *in situ* gelling systems were prepared by using various concentrations of carbopol 934 along with different concentration of hydroxy propyl methyl cellulose as given in **Table 1**. All the formulations had fixed drug concentration of (0.3%w/v) Norfloxacin.

**Appearance, clarity, pH and drug content:** The appearances of all formulations were light yellow in color and were clear. Terminal sterilization by autoclaving had no effect on the formulations. The haziness observed during autoclaving due to precipitation of HPMC at elevated temperature was found to disappear and the clarity was regained after overnight standing. The pH of all the formulations was found to be within the range of 6.0 to 6.5, which is desirable for the ophthalmic formulations. The drug content of all the formulations was within the range of 97.45% to100.43%, showed the uniform distribution of drug in the ophthalmic formulations and the results are shown in **Table 2**.

**Gelling capacity:** The viscosity and gelling capacity plays important role for in situ gelling system. The formulation should have an optimum viscosity for easy instillation into the eye as a liquid which undergo sol-to-gel transition. Prepared *in situ* gelling systems were evaluated for the *in vitro* gelation capacity. All the formulations gave satisfactory results (**Table 3**).

**TABLE 2: PRELIMINARY EVALUATIONS OF VISUAL APPEARANCE, CLARITY, PH, AND DRUG CONTENT**

| Formulation Code | Visual Appearance | Clarity | pH | Drug Content |
|---|---|---|---|---|
| F1 | Light Yellow | Clear | 6.0 | 98.33 |
| F2 | Light Yellow | Clear | 6.1 | 97.45 |
| F3 | Light Yellow | Clear | 6.4 | 99.12 |
| F4 | Light Yellow | Clear | 6.3 | 100.43 |
| F5 | Light Yellow | Clear | 6.5 | 99.77 |

**TABLE 3: EVALUATION OF GELLING CAPACITY**

| Formulation | Gelling capacity |
|---|---|
| F1 | + |
| F2 | ++ |
| F3 | ++ |
| F4 | +++ |
| F5 | +++ |

**NOTE:** ++ indicates gelation is immediate and remains for few hours, +++ indicates gelation is immediate and remains for extended period

**Rheological studies:** The rheological study of the formulations exhibited decrease in viscosity on increase in shear rate because of the pseudoplastic behavior of the formulations. Moreover, the pseudoplastic property of these formulations may be in favor of sustaining the release of drug in the conjunctival sac of the eye.

**TABLE 4: RHEOLOGICAL STUDIES OF FORMULATIONS**

| RPM | Viscosity in cps. (Before gelling) (Spindle No.61) | | | | | Viscosity in cps. (After gelling) (Spindle No.61) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F1 | F2 | F3 | F4 | F5 |
| 1 | 140 | 253 | 240 | 760 | 1230 | 197 | 395 | 430 | 1740 | 1901 |
| 1.5 | 135 | 223 | 235 | 750 | 1204 | 190 | 370 | 429 | 1700 | 1729 |
| 2 | 130 | 221 | 239 | 680 | 1136 | 175 | 357 | 421 | 1656 | 1631 |
| 2.5 | 128 | 213 | 236 | 660 | 1080 | 172 | 339 | 420 | 1603 | 1570 |
| 3 | 124 | 203 | 231 | 640 | 1050 | 170 | 320 | 415 | 1561 | 1520 |
| 4 | 123 | 196 | 240 | 635 | 1002 | 165 | 171 | 402 | 1430 | 1450 |

***In vitro* release studies:** The release profile of the formulations shown in **Figure 1**. The results indicated that the formulation F-5 showed better sustaining effect amongst all formulations. This may be due to the presence of higher concentration of carbopol 934 along with HPMC K4 M in the formulation F-5. The *in vitro* release profile of F-5 was then compared with marketed formulation of Norfloxacin (NORFLOX eye Drop). From the release studies, it was found that the drug release was about 49.05% and 12.80% for marketed product and F5 respectively after 1hr. And at the end of three hours the drug release was 98.89% and 38.31% for marketed product and F-5, respectively. The comparative release was shown in **figure 2**.

Results indicated that, the drug release was significantly prolonged by using the *in situ* gelling system due to the addition of the polymers carbopol 934 and HPMC K4 M. For all the formulations, the best fit model was Higuchi matrix equation and suggesting diffusion controlled release may be due to the swelling nature of polymers.

The 'n' value were less than 0.5, which indicated that all the formulations showed drug release by Fickian diffusion mechanism.

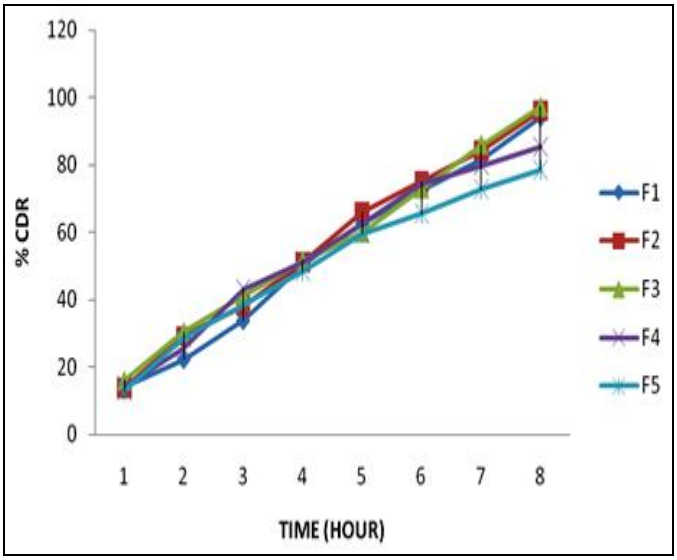


**FIG. 1: COMPARISON OF IN VITRO RELEASE OF IN SITU GEL FORMULATIONS**

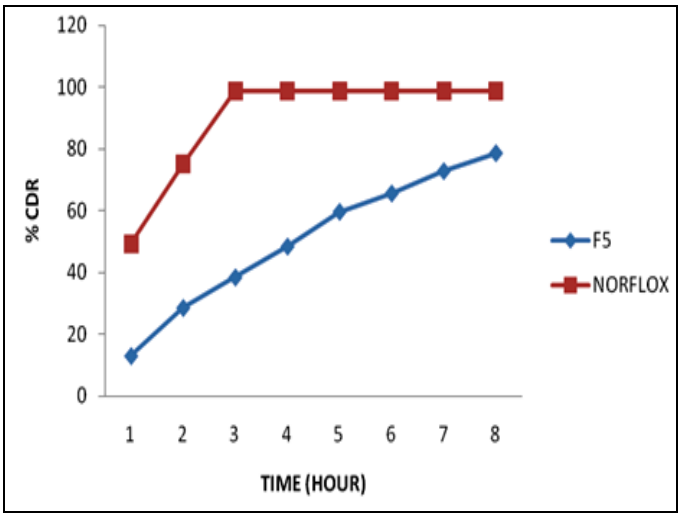


**FIG. 2: COMPARISON OF DRUG RELEASE PROFILE OF MARKETED CONVENTIONAL EYE DROP (NORFLOX) WITH FORMULATION F-5**

**Sterility Testing:** All the prepared *in situ* gelling systems were evaluated for the sterility. After 7 days of incubation the results showed no microbial growth in all formulations (**Table 5**).

**TABLE 5: STERILITY TEST DATA OF PREPARED IN SITU GELS**

| Formulation Code | Incubation Days | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| F1 | - | - | - | - | - | - | - |
| F2 | - | - | - | - | - | - | - |
| F3 | - | - | - | - | - | - | - |
| F4 | - | - | - | - | - | - | - |
| F5 | - | - | - | - | - | - | - |

**NOTE:** '–'sign indicates no Growth.

**Antimicrobial Efficacy Studies:** The optimized *in situ* gelling formulations showed antimicrobial activity when tested microbiologically by the Cup-Plate technique. Clear zones of inhibition were obtained in all the formulations. The diameter of zone of inhibition produced by formulations against all test microorganisms is given in **Table 6**.

**Ocular irritancy studies:** The observations of ocular irritancy are shown in **Table 7**.The results of the ocular studies indicated that the formulation F-5 was non-irritant with excellent ocular tolerance. No ocular damage or abnormal clinical signs to the cornea, iris or conjunctiva were visible.

**TABLE 6: ANTI-MICROBIAL ACTIVITY OF NORFLOXACIN *IN SITU* GELS**

| Sr. No | Formulation | *Pseudomonas aeruginosa* | *Staphylococcus aureus* | *E .coli* |
|---|---|---|---|---|
| | | | Zone of inhibition (mm) | |
| 1. | F1 | 25 | 20 | 26 |
| 2. | F2 | 28 | 20 | 27 |
| 3. | F3 | 28 | 21 | 26 |
| 4. | F4 | 33 | 22 | 27 |
| 5. | F5 | 34 | 22 | 27 |
| 6. | NORFLOX | 24 | 18 | 21 |

**TABLE 7: OCULAR IRRITATION TESTING OF OPTIMIZED FORMULATION F- 5**

| Parameter | Duration | | | | |
|---|---|---|---|---|---|
| | 1hrs. | 24hrs. | 48hrs. | 72hrs. | 1 week |
| Redness | 0 | 0 | 0 | 0 | 0 |
| Excessive Tearing | 0 | 0 | 0 | 0 | 0 |
| Inflammation | 0 | 0 | 0 | 0 | 0 |

(0 - No redness, no inflammation or excessive tearing, 1 - Mild redness with inflammation & slight tearing, 2 - Moderate redness with moderate inflammation and excessive tearing, 3 - Severe redness with severe inflammation and excessive tearing)

**Stability studies:** From the results it has been observed that the formulations showed no change in appearance, clarity and pH. Further it was observed that the gelling capacity of the formulations was least affected.

**CONCLUSION:** Norfloxacin, a broad spectrum antibacterial agent use in the treatment of ocular infections, was successfully formulated as $P^H$-triggered *in situ* gelling system (0.3% w/v) using Carbopol 934.

The formulations were liquid at the formulated pH (6- 6.5) and underwent rapid gelation in contact with STF due to ionic interactions. The formulated system provided sustained release of the drug over 8-hrs *in vitro*, and the developed formulations were devoid of any deleterious effect on the ocular tissues. The formulation demonstrated better therapeutic efficacy as it were successful in inhibiting the growth of the microorganisms for the entire duration of the study (24 hr) when compared with the marketed eye drop, thus developed formulations are viable alternative to conventional eye drops by virtue of its ability to sustain dug release. Also important is the ease of administration afforded and decreased frequency of administration resulting in better patient acceptance.

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