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# FORMULATION AND EVALUATION OF *IN-SITU* GEL FOR OCULAR DRUG DELIVERY SYSTEM

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**Abstract:** *In-situ* gel based ocular drug delivery system was formulated to Improve the bioavailability, Reduce dosing frequency, Increase contact time, Increase precorneal residence time and Prolong the effect of the drug. In preformulation studies all physical and chemical properties have been performed. It was found to be that drug color was yellow, solid in state and amorphous in nature. While identifying in UV spectroscopy it shows maximum peak on the wavelength ƛmax 285.6.nm.and absorbance 0.314. While determining the melting point in melting point apparatus the Moxifloxacin drug shows the melting on temperature 241.°c. The appearances of all formulations were light yellow in color and were clear except the formulation F-2. Formulations F-1, F-3, F-5 prepared from Carbopol 940 (0.5%)/HPMC (K4M), Carbopol 940 (0.5%)/HPMC (K15M) respectively showed better gelling capacity. The rheological study of the formulations exhibited decrease in viscosity on increase in shear rate because of the pseudoplastic behavior of the Formulations. This formulation is an alternate to conventional eye drops to improve the bioavailability through its longer precorneal residence time and ability to sustain drug release. The patient compliance may be improved due to the decrease in frequency of drug administration.

**Keyword:** *In-situ*, Gel, Ocular, Drug, Delivery

## INTRODUCTION

*In-situ* gelation is a process of gel formation at the site of application after the composition or formulation has been applied to the site[1]. In the field of human and animal medicine, the sites of application refer to various injection sites, topical application sites, surgical sites, and others where the agents are brought into contact with tissues or body fluids[2]. As a drug delivery agent, the *in-situ* gel has an advantage related to the gel or polymer network being formed *in-situ* providing sustained release of the drug[3]. At the same time, it permits the drug to be delivered in a liquid form. *In-situ* is a Latin phrase meaning in the place[4].

Various other synthetic and natural polymers have also been used in drug delivery formulations that may or may not have formed cross linked gels, including starches and modified celluloses, gelatin, chitosan, hyaluronic acids, pectin's, etc[5]. Moxifloxacin is a fourth-generation synthetic fluoroquinolone anti-bacterial agent[6,7]. The poor bioavailability and therapeutic response exhibited by conventional ophthalmic solutions due to rapid precorneal elimination of the drug System that are instilled as drops into the eye and undergo a sol dose[8].

*In-situ* gel based ocular drug delivery system was formulated to Improve the bioavailability, Reduce dosing frequency, Increase contact time, Increase precorneal residence time and Prolong the effect of the drug.

## EXPERIMENTAL WORK

### Preformulation Studies:

**Collection of Material:** Moxifloxcin hydrochloride was a kind gift sample to Zee laboratory, Konta. Himachal Pradesh. HPMC K-15 and Eudragid RS 100 were purchased from Ranchem Laboratory, Delhi. PEG00 and Methanol was purchased from Ranchem Lab, Delhi. All other chemicals used in our work were of analytical grade.

**Identification of drug by UV:** Infrared (IR) light is electromagnetic radiation with longer wavelengths than those of visible light, extending from the nominal red edge of the visible spectrum at 0.74 micrometres to, an of wavelengths 100 down to 1 THz, and includes most of the thermal radiation emitted by objects near room temperature.

**Procedure:** Determination of λ max mix of Moxifloxacin hydrochloride in Distilled water 10ang of drug was taken in a test tube then dissolved in small quantity of water, then transferred 3 10ml volumetric flask and the volume was made up to 10ml then from this solution 10ppm solution was prepared. The spectrophotometric method of analysis of Moxifloxacin hydrochloride at Amax 292.0 nm was found to be reproducible and highly sensitive.

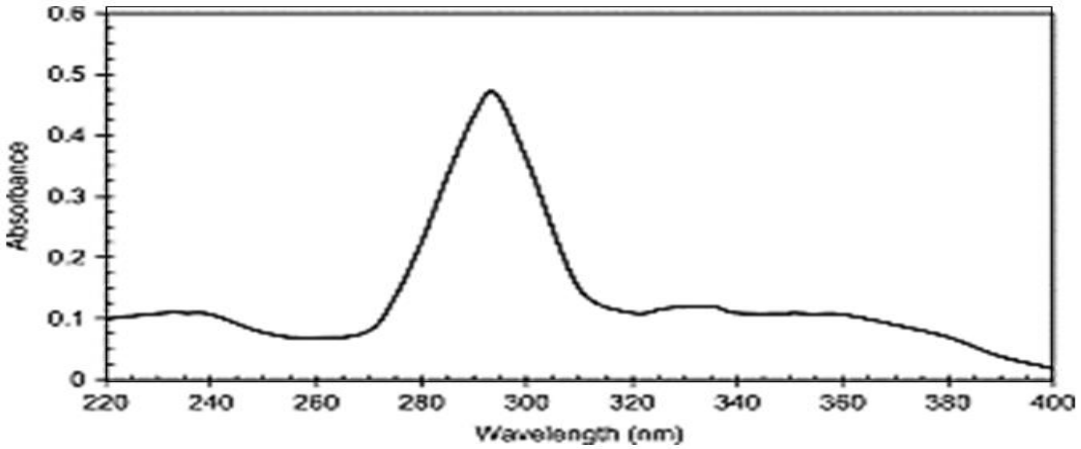


**Figure 1: Determination of λmax of Moxifloxacin in D. water**

**Identification of drug by FTIR:** Infrared (IR) light is electromagnetic radiation with longer wavelength of light, extending from the nominal red edge of Use visible span74) 83 nm. This range of wavelengths corresponds to a frequency range of approximately 800 down to 1 THz, and includes most of the thermal radiation emitted by objects near Infrared light is emitted or absorbed by molecules when they change their rotational vibration movements.

Initially, a FTIR transmittance spectrum of Moxifloxacin HCl was obtained from a KBr pellet and interpreted following characteristic absorption bands FTIR spectra of Moxifloxacin HCl showed aromatic C-C stretching at 1621, 1515 and 1454 $cm^{-1}$ and C-H bending for substituted benzene at 873 $cm^{-1}$. Besides, spectra also showed carboxylic acid C-O stretching at 1705 $cm^{-1}$, C-N stretching at 1350 $cm^{-1}$, stretching of Monofluoro benzene at 1183 $cm^{-1}$.

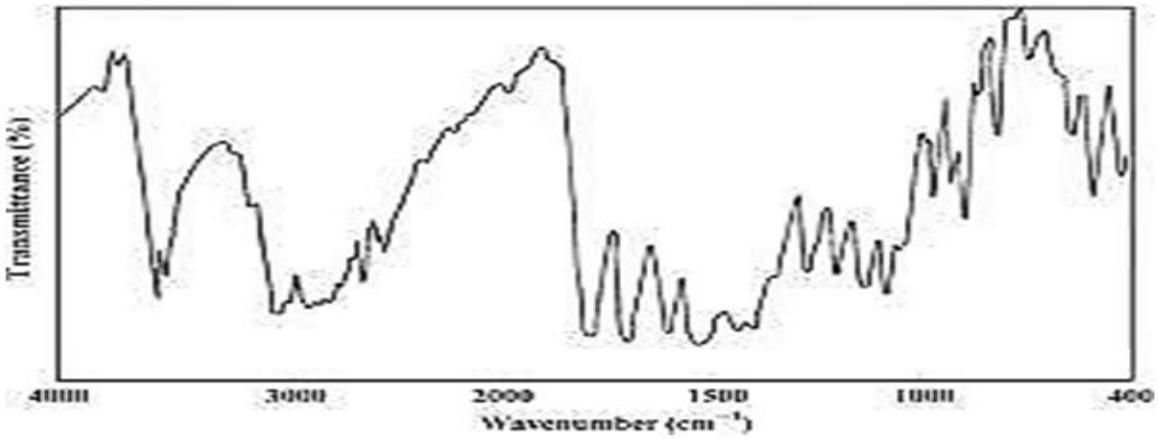


**Figure 2: FT-IR spectroscopy of moxifloxacin HCl**

**Solubility Study:** Solubility study should be performed for Moxifloxacin to determine in which solvent it is soluble, for that various solvents like water, ethanol, methanol, methylene chloride, ethyl acetate, cyclohexane was used, for determining the solubility the drug should be dissolved in individual solvent in 1:10 ratio (Drug: Solvent) and visually observed for its solubility.

**Table No. 1: Solubility Profile of Moxifloxacin HCl**

| S. No. | Medium | Solubility Profile | Parts of Solvent |
|---|---|---|---|
| 1 | Water | Freely Soluble | <1 |
| 2 | Ethanol | Very slightly soluble | 1000 – 10,000 |
| 3 | 0.1 N Hydrochloric Acid | soluble | 1-10 |
| 4 | 0.1 N Sodium Hydroxide | Soluble | 1-10 |
| 5 | Propanol | Insoluble | >10,000 |
| 6 | Chloroform | Insoluble | >10,000 |

Where Mean of three determination, freely soluble - 1-10 parts of solvent, soluble= 10-30 pats of solvent, sparingly soluble = 30-10 parts of solvents, slightly soluble - 100-1000 parts vent, very slightly soluble - 1000-10000 parts of solvent.

**Melting point determination:** The melting point of a solid is the temperature at which it changes state from solid to liquid. The melting point of a substance depends (usually slightly) on pressure and is usually specified at standard pressure. When considered as the temperature of the reverse change from liquid to solid, it is referred to as the freezing point or crystallization point. Melting point of Moxifloxacin was found at 241$^{O}$C Melting point of Moxifloxacin.

**Determination of Partition coefficient:**

In the physical sciences, a partition (P) or distribution (D) coefficient is the ratio of concentrations of a compound in a mixture of two immiscible phases at equilibrium. These coefficients are a measure of the differencein solubility of the compound in these two phases. In medical practice, partition coefficients are useful for example in estimating distribution of drugs within the body. Hydrophobic drugs with high octanol/water partition coefficients are preferentially distributed to hydrophobic compartments such as lipid bilayers of cells while hydrophilic drugs (low octanol/water partition coefficients) preferentially are found in hydrophilic compartments such as blood serum.

**Table No. 2: Partition Coefficient Value of Drug**

| S. No. | Medium | Abs | Conc. | Partition Coefficient (Log P) |
|---|---|---|---|---|
| 1 | Water | 3.626 | 3.478941 | 0.999138 |
| 2 | n- octanol | 3.623 | 3.475941 | |

**Preparation of *In-Situ* Gel:**

Different concentrations of polymers were used to prepare ophthalmic solutions as per the composition shown in Table-1. The polymers were dissolved in citrophosphate buffer and allowed to hydrate. To this buffered polymeric solution tween 20 was added. Moxifloxacin hydrochloride was dissolved in sodium hydroxide solution (0.1N) separately and after adjusting the pH, benzalkonium chloride was added and filtered. The drug solution was then added to the polymeric solution under constant stirring until a uniform solution was obtained. Distilled water was then added to make up the final volume. The formulations were filled in vials under aseptic conditions, sterilized in the autoclave (121 C and 15 psi) for 20 minutes and further evaluations were carried out.

**Table No. 3: Formulation configuration of *in-situ* gel**

| Ingredients | Ingredients (gm) | | | | | |
|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 |
| Drug | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| Carbopol 940 | 0.2 | 0.3 | 0.4 | 0.2 | 0.3 | 0.4 |
| HPMC-K4M | 0.3 | 0.3 | 0.3 | ……. | ……. | …… |
| HPMC-KISM | ….. | …… | ….. | 0.3 | 0.3 | 0.3 |
| Sodium hydroxide | 0.16 | 0.16 | 0.16 | 0.16 | 0.16 | 0.16 |
| Di-sodium Hydrogen phosphate | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 |
| Tween 20 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Benzalkonium chloride | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| Purified water | 50 ml | 50 ml | 50 ml | 50 ml | 50 ml | 50 ml |

**Determination of visual appearance, clarity, pH and drug content:** The appearance and clarity were determined visually. The pH of the formulations was adjusted by using pH meter. The drug content of in situ gel was determined by taking sample (2ml) of in-situ get in a 100ml Volumetric Mask, and diluted with simulated tear fluid of pH 7.4 to get t concentration of 10g/ml approx): Then absorbance was measured at max (28) calculate the 12 percentage of drug content.

The appearances of all formulations were light yellow in colour and were clear except the formulation F-2. Terminal sterilization by autoclaving had no effect on the formulations. The business observed during autoclaving due to precipitation of HPMC at elevated temperature was found to disappear and the clarity was regained after overnight standing the top the formulations was found to be within the range of 6.0 to 6.4, which is desirable for the ophthalmic formulations. The drug content of all the formulations was within the range of 98.35% 100.13%, shown the uniform distribution of drug in the ophthalmic formulations.

**Table No. 4: Evaluation of *in-situ* gels**

| Formulations | Appearance | Clarity | PH | Gelling capacity | Percentage Drug content ± SD |
|---|---|---|---|---|---|
| F1 | White | Clear | 6.1 | ++ | 98.72±0.770 |
| F2 | White | Clear | 6.0 | +++ | 97.35±0.551 |
| F3 | White | Clear | 6.1 | ++ | 98.04±0.675 |
| F4 | White | Clear | 6.2 | ++ | 99.34±0.348 |
| F5 | White | Clear | 6.0 | +++ | 98.84±0.563 |
| F6 | white | Clear | 6.1 | + | 99.36±0.569 |

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. Formulations F-1, F-3, F-5 prepared from Carbopol 940 (0.5%) / HPMC (K4M), Carbopol 940 (0.5%)/HPMC (K15M) respectively showed better gelling capacity. The other formulations were not having desirable gelling capacity.

**Spreadability:** For the determination of spreadability, excess of sample was applied between the two glass slides and was compressed to uniform thickness by placing 1000 g weight for 5 min. Weight (50 g) was added to the pan. The time required to separate the two slides, i.e. the time in which the upper glass slide moves over the lower plate was taken as measure of spreadability (S). S-MXL/T,

Where M = weight tide to upper slide, L. length moved on the glass slide, T- time taken.

**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 to 1000 mpa and after gelling in the eye will have a viscosity from about 50-50,000 mpa. The viscosity of the formulations was determined at different speed conditions (10,20,50,75 to 100 rpm).

The pseudo plastic character of precorneal tear film should be disturbed less by the administration of ophthalmic products. The ocular shear rate is about 0.03 s during interred blinking periods and 4250-28500 s during blinking. So, the viscoelastic fluids having high viscosity under low shear rates and low viscosity under high shear rates which is called as pseudoplastic fluid is often preferred the viscosity of the formulations (F-1 to F-6) ranged from 1- 107 cps and it was shown in Figure. 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 staining the release of drug in the conjunctival sac of the eye, and also without blinking difficulty for undergoing shear thinning.

**Table No. 5: Correlation coefficient (1') and constant (K) of different kinetic models for moxifloxacin**

| Ingredients | Zero Order | First Order | Higuchi Equation | Pappas Equation |
|---|---|---|---|---|
| | R2 | R2 | R2 | R2 |
| F1 | 0.941 | 0.941 | 0.990 | 0.554 |
| F2 | 0.943 | 0.943 | 0.989 | 0.621 |
| F3 | 0.979 | 0.979 | 0.965 | 0.745 |
| F4 | 0.982 | 0.982 | 0.960 | 0.670 |
| F5 | 0.983 | 0.983 | 0.979 | 0.663 |
| F6 | 0.983 | 0.989 | 0.973 | 0.675 |

**Accelerated 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.

**RESULT AND DISCUSION**

**Preformulation studies**: In preformulation studies all physical and chemical properties have been performed and observation of result is as follows:

**Physical Evaluation:** While seeing the drug with naked eyes it was found to be that its color was yellow; it is solid in state and amorphous in nature.

**Identification of drug by UV:** While identifying in UV spectroscopy it shows maximum peak on the wavelength ƛ max 285.6.nm.and absorbance 0.314.

**Identification of drug by FTIR:** FTIR observation shows the peak on wave numbers. 1621, 873, 1705, 1350 which shows the presence of-C-C, C-H, C=O, -C-N functional groups. The peak was compared with reference peak of the drug monograph. The drug powder is identified.

**Standard Calibration Curve of Moxifloxacin:** Standard Calibration Curve was plotted for Moxifloxacin the linearity of graph shows that the drug follows the lambert Beers Law.

**Determination of Solubility:** In solubility parameter the drug was freely soluble in water and soluble in 0.1 N HCL and soluble in 0.1 N. NaOH.

**Determination of Melting Point:** While determining the melting point in melting point apparatus the Moxifloxacin drug shows the melting on temperature 241 $^{O}$C.

**Evaluation:** Appearance, clarity, pH and drug content: The appearances of all formulations were light yellow in colour and were clear except the formulation F-2. The drug content of all the formulations was within the range of 98.35% 100.13%, shown the uniform distribution of drug in the ophthalmic formulations.

**Gelling capacity:** Formulations F-1, F-3, F-5 prepared from Carbopol 940 (0.5%) / HPMC (K4M), Carbopol 940 (0.5%) / HPMC (K15M) respectively showed better gelling capacity. The other formulations were not having desirable gelling capacity.

**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.

## CONCLUSION

The novel ophthalmic pH-triggered in situ gelling drug delivery was successfully formulated by using carbopol 940 and HPMC (K4M and K15M). The formulated in situ gelling systems were characterized for appearance, clarity, pH, gelling capacity, theological character, in vitro release in simulated tear fluid. The formulation was liquid at the formulated p11 (6.0) and underwent rapid gelation upon raising the pH to 7.4. The pH- triggered in situ gelling system showed sustained drug release over 8-h period of time. So, this formulation is an alternate to conventional eye drops to improve the bioavailability through its longer precorneal residence time and ability to sustain drug release. The patient compliance may be improved due to the decrease in frequency of drug administration.

## CONFLICTS OF INTERESTS

There are no conflicts of interests.

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