



JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Formulation and Development pH induced *in-situ* gelling system of an anti infective drug for sustained ocular drug delivery

Jayant Madhukar Deshpande 1*, Dr. Paresh B. Shah²

¹Research Scholar, Jodhpur National University, Rajasthan

²Principal and HOD Pharmaceutics Dept, Shri B.M.C.P.E.R, Modasa

ABSTRACT:

The aim of the present investigation is to develop an insitu gelling system for ocular drug delivery system by using Lomefloxacin as a model drug, now Conventional ophthalmic solution are quickly eliminate after administration, which is not provide and maintain an adequate concentration of the drug in the precorneal area. One of the major problems in ocular therapeutics is the attainment of optimal drug concentration at the site of action, which is compromised mainly due to precorneal due to loss factor resulting in only a small fraction of the drug being ocularly absorbed. Criteria of this work is to prepare and evaluate an ophthalmic delivery system of an antibacterial drug 'Lomefloxacin HCL', based on the concept of pH – induced in situ gellation. Carbopol 940 (0.1% to 0.5% w/v) was used as the gelling agent in combination with HPMC E50LV (0.5% to 2% w/v) and HPMC E4M (0.2% to 0.6% w/v) as viscosity enhancing agent. Suitable concentration of sodium chloride and benzalkonium chloride were used as an isotonicity adjusting agent and a preservative respectively. All the formulations were sterilized in an autoclave at 121° C and 15 psi for 20 minutes. The aforementioned formulations were evaluated for in vitro gelling capacity, rheological study and percentage drug release. which in vitro gelling capacity was carried out using simulated tear fluid showing a higher gelling capacity for Carbopol 940 (0.2% and 0.3% w/v) formulation containing optimum concentration of HPMC E50LV (1.5% w/v) & HPMC E4M (0.4% w/v).

Key words: pH induced insitu gel, Lomefloxacin HCL, Carbopol 940, HPMC E50LV, HPMC E4M

Article history:

Received 11 Sept 2012

Revised 14 Oct 2012

Accepted 25 Dec 2012

Available online 13 Dec 2012

For Correspondence:

Prof. Jayant Deshpande

L. J Institute of Pharmacy,

Ahmedabad

Email: jayantdeshpandein@yahoo.com

(www.jpsbr.org)

INTRODUCTION:

Today, topical ophthalmic application is preferred way to achieve therapeutic levels of drug agents which is used to treat ocular diseases. These preparations for this route fall in to several categories: solutions, suspensions, semisolids, and others. From a biopharmaceutical stand- point, their use has met some criticism over their efficiency as drug delivery systems. Bioavailability, particularly for ocular solutions, ranges from 1 to 10 % of the total administered dose. This is due in part to the rapid precorneal clearance kinetics resulting from reflex tearing and blinking, where half-life times of instilled isotonic solutions approximate only 15 seconds in the human.^{1, 2}

The eye drop dosage form is easy to instill but suffers from the inherent drawback that the majority of the medication it contains is immediately diluted in the tear film as soon as the eye drop solution is instilled into the cul- de-sac and is rapidly drained away from the precorneal cavity by constant tear flow, a process that proceeds more intensively in inflamed than in the normal eyes, and lacrimal – nasal drainage. Therefore, only a very small fraction of the instilled dose is absorbed into the target tissues, and relatively concen- trated solution is required for instillation to achieve an adequate level of therapeutic effect.

The frequent periodic instillation of eye drops becomes necessary to maintain a continuous sustained level of medication. This gives the eye a massive and unpredictable dose of medication, and unfortunately, the higher the drug concentration in the eye drop solution, the greater the amount of drug lost through lacrimal-nasal drainage system. Subsequent absorption of this drained drug, if it is high enough, may result in undesirable systemic side effects.^{3,4,5}

Ocular therapy could be significantly improved if the pre-corneal residence time of drugs could be increased; several new preparations have been developed for ophthalmic use not only to prolong the contact time of the vehicle at ocular surface, but also to slow down the elimination of the drugs.³ This problem can be overcome by using in situ gel forming ophthalmic drug delivery systems prepared from polymers that exhibit reversible phase transitions and pseudo-plastic behavior to minimize interference with blinking.⁶

In the present work, an attempt has been made to formulate pH-induced in-situ gel as an ophthalmic drug delivery system. In situ gels are made from polymers that exhibit phase transition due to physicochemical change in the environment. They can be conveniently dropped as a solution into the conjunctival sac in the eye. Upon contact with the lacrimal fluid, the polymer changes its conformation to form a gel. This delivery system has the ease of administration similar to an ophthalmic solution and has a long retention time because of the gel formulation. Different polymers for preparing pH induced in-situ gels have been evaluated.

Such a system can be formulated as liquid dosage form suitable for administration by instillation in to the eye, which upon exposure to physiological pH condition of eye, shifts to gel phase which has a higher viscosity thus increasing the pre-corneal residence. The prolonged residence time of the gel formed in situ along with its ability to release drugs in a sustain manner will assist in enhancing the bioavailability of the instilled drug and improve patient compliance.⁶

The research work envisaged formulating a pH-induced in situ gelling system of an antibacterial drug '**LOMEFLOXACIN HCL**' for the treatment of various infective diseases of the eye to get better patient compliance by increasing residence time and bioavailability. Similar works has been reported for number of anti infective drugs.^{7-17.}

MATERIALS AND METHODS: Materials:

Lomefloxacin HCl was obtained as a gift sample from Ipca Labs. Limited, Ratlam. HPMC E50LV & HPMC E4M were gifted by Color cone Asia Ltd., Verna, Goa. Carbopol 940 was from S.D. Fine Chemicals Ltd., Mumbai. All other chemicals used during the study were of Analytical grade.

Estimation of Lomefloxacin Hydrochloride by Spectrophotometric Method: A simple method for estimation of Lomefloxacin Hydrochloride by Spectrophotometric method was developed in Simulated Tear Fluid

(STF) pH 7.4. Lomefloxacin Hydrochloride in simulated tear fluid of pH 7.4 was scanned in the range of 200 nm – 400 nm shows Max at 281.5 nm. The calibration curve for Lomefloxacin Hydrochloride Simulated Tear Fluid (STF) pH 7.4 was then prepared in the range of 1-12 /ml and was found to obey Beer's Law.

Preparation of pH Induced In-Situ Gelling System:

The pH sensitive polymers like Carbomer derivatives, Carbopol, forms aqueous solution in the unionized form. These polymers undergo reversible ionization at pH 7.4, physiological condition, to form a stiff gel network, which swells and forms large aqueous pores. Hence, Carbopol 940 was selected for preparation of pH induced in-situ gelling system. For this, optimization of polymer ratio is necessary, so intended work was divided into the two parts. Optimization of polymer ratio Incorporation of active ingredients in optimized polymer ratio. *Optimization of Polymer Ratio for Preparation of In-Situ Gelling System:*

Method 1:

By taking the benefit of polymer like, Carbopol 940, formulations containing different concentration of Carbopol 940 (0.1-0.5 %) were prepared in different nonphysiological condition (like, pH 4 & pH 5), in order to identify the pH, clarity and Gelling capacity.

Procedure:

Firstly, the Acetate buffer of pH 4 and 5 were prepared¹⁷. Two sets of, each with five beakers was filled with acetate buffer of pH 4 and 5, respectively. Different concentration of Carbopol 940 from 0.1 % to 0.5 % was sprinkled to the beakers containing buffer solution of respective pH and allows hydrating overnight. Later the solution containing in the beakers were stirred with an overhead stirrer. These polymers were evaluated for clarity, gelling capacity and viscosity at physiological (pH 7.4) as well as non physiological (pH 4

& 5) condition by using Brook Field Viscometer (DV-E Rheometer). These were carried out to get optimum polymer concentration. See Table 1.

Method 2:

As observed during practical work that Carbopol solution with lower concentration of it, viscosity of gels formed after gellation at pH 7.4 was very low and at higher concentration of it, viscosity of gels formed was very high. One more problem were found that as Carbopol concentration increase, the pH of the formulation became acidic. Another problem was observed that as Carbopol concentration increases, the solution became translucent at pH 4 but at pH 5 it was clear. Hence for further procedure, formulation pH was selected as pH 5.

From the above observations; Carbopol cannot be used alone

for preparation of in-situ gels. Hence it was decided to take the help of polymer, which increases the viscosity without compromising the gelling capacity of Carbopol 940.

Procedure:

Firstly, the Acetate buffer of pH 5 was prepared¹⁷, and 100 ml of it was distributed in each of 16 beakers. Different concentration of HPMC E50LV ranging from 0.5 % to 2 % was added to the beakers containing buffer solution for hydration. Different concentration of Carbopol 940 ranging from 0.1 % to 0.4 % was sprinkled over these solutions and allows for hydrating over- night. Later the solutions were stirred with an overhead stirrer until to get uniform solution. These different solutions were observed for clarity, gelling capacity and viscosity at physiological (pH 7.4) as well as nonphysiological (pH 5) conditions by using Brook Field Viscometer (model DV-E Rheometer). See Table 2.

Method 3:

In this method the high viscosity grade was taken to reduce the concentration of HPMC without compromising the viscosity increasing capacity. So that, that the HPMC E50LV (40-60 cps) was replaced by the HPMC E4M (4000-5600 cps).

Procedure:

Firstly, the Acetate buffer of pH 5 was prepared¹⁷, and 100 ml of it was distributed in each of 9 beakers. Different concentration of HPMC E4M (0.2%, 0.4 %, and 0.6 %) was added to the beakers containing buffer solution for hydration. Different concentration of Carbopol 940 ranging from 0.1 % to 0.3 % was sprinkled over these solutions and allows for hydrating over- night. Later the solutions were stirred with an overhead stirrer until to get uniform solution. These different solutions were observed for clarity, gelling capacity and viscosity at physiological (pH 7.4) as well as nonphysiological (pH 5) conditions by using Brook Field Viscometer (model DV-E Rheometer). See Table 3.

Results from method 2 reveals that the formulations CH 11 (0.3 % Carbopol 940 and 1.5 % HPMC E50LV) and CH 15 (0.4 % Carbopol 940 and 1.5 % HPMC E50LV) showed good gelling capacity and desire viscosity. Results from method 3 reveals that the formulations CH 21 (0.2 % Carbopol 940 and 0.4 % HPMC E4M) and CH 24 (0.3 % Carbopol 940 and 0.4 % HPMC E4M) showed good gelling capacity and desire viscosity.

These four formulations were selected as those had satisfactory attributes of gelling capacity and desired viscosity at physiological (pH 7.4) as well as non- physiological (pH 5) conditions. The detail data of the prepared formulations for pH induced in-situ gelling system of Lomefloxacin HCL are given in Table 4.

Procedure:

The buffer salts were dissolved in 50 ml of purified water; HPMC (E50LV / E4M) was added to hydrate. Carbopol 940 was sprinkled over this solution and allowed to hydrate overnight. The solution was stirred with an overhead stirrer. Lomefloxacin Hydrochloride was dissolved in small quantity of water, Benzalkonium Chloride (Preservative) and Sodium chloride (Isotonocity ad- justing agent) was added to this solution; the drug solution was added to the polymer solution under constant stirring until a uniform solution was obtained. Purified water was then added to make up the volume to 100ml. Formulation pH was adjusted to pH 5 with the help of 0.5 M Sodium Hydrox- ide. This solution was filtered through 0.2 m filter paper.

Preliminary Evaluation Studies on Prepared In situ Gel Formulations:

Visual Appearance and Clarity: Visual appearance and Clarity was done under fluorescent light against a white and black back ground for presence of any particulate matter.

*pH:*The pH of the prepared in-situ gelling system after addition of all the ingredients was measured using pH meter.

*Drug Content Analysis:*Drug content analysis of prepared in-situ gelling systems was carried out using

Spectrophotometric method. The assay of these formulations was carried out by pipetting 0.1 ml of all four optimized formulations, and it was diluted up to 100 ml of Simulated Tear Fluid (pH 7.4). The absorbance was measured at 281.5 nm using UV-Visible spectrophotometer.

In-Vitro Gellation Study:

The Gelling capacity of the formulations containing different ratio of Carbopol 940 and HPMC (E50LV / E4M) was evaluated. It was performed by placing a drop of polymeric solution in vials containing 1 ml of Simulated Tear Fluid, freshly prepared and equilibrated at 34 C, and visually assessed the gel formed and time for gellation as well as time taken for the gel formed to dissolve. See Table 5.

The Composition of Simulated Tear Fluid was Sodium chloride (0.670 g), Sodium Bi Carbonate (0.2 g), Calcium Chloride dihydrate and bi-distilled water quantity sufficient up to 100 g. Physiological pH (7.4 0.2) was adjusted by adding the required amount of 0.1 N HCL 18.

Interaction studies:

Compatibility study of drug with the excipients was determined by I.R. Spec- troscopy (FTIR) using Perkin Elmer spectrum RX1 FT-IR spectrometer model. The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100.The pellets thus prepare were examined and the spectra of drug and other ingredients in the formulations were compared with that of the original spectra.

Sterility Testing:

Sterility testing were intended for detecting the presence of viable form of microorganisms and were performed for Aerobic and Anaerobic bacteria and fungi by using Fluid Thioglycolate Medium and Soyaban Casein Digest medium, respectively as per the Indian Pharmacopoeia¹⁷.

Rheological Studies: Rheological properties of the prepared in-situ gelling systems under the different Shear rates (2, 4, 6, 10, 20, and 30 rpm) were measured at non physiological (pH 5 and 25 C) and physiological condition (pH 7.4 and 34 C), respectively. The hierarchy of the shear rate was reversed, and the average of two reading was used to calculate the viscosity.

In-Vitro Release Studies: In-vitro drug release from the formulations was studied by the diffusion process. Here the pH of the Lacrimal fluid and the blinking rate of the eye were taken into consideration and were simulated.

Procedure: The in-vitro release of Lomefloxacin HCL as pure drug well as from the prepared formulations was studied through cellophane membrane using diffusion cell. The cellophane membrane was soaked over night in the receptor medium (Simulated Tear Fluid, pH 7.4). It was tied to one end of a glass

diffusion cell. 100 ml of receptor medium was taken in the 200 ml beaker. The diffusion cell was filled with 2 ml of the formulation and suspended in 100 ml of receptor containing beaker by assuring that the membrane was just touched the receptor medium surface. The whole assembly was transferred on magnetic stirrer and was maintained at 34 C 1 C and 22 rpm. The drug samples were withdrawn at the interval of 30 minutes from receptor medium and replaced by equal volumes of the receptor medium. The samples were diluted with appropriate receptor medium and analyzed by a UV-Visible spectrophotometer at 281.5 nm using receptor medium as a blank. The in-vitro release of marketed formulation was also studied in a similar way and compared.

Pharmacokinetic Release Studies:

All the optimized formulations were subjected to study the release kinetics of it. So the best fit kinetic model was determined for the optimized formulations using analysis software PCP – Disso V2.

Antimicrobial Efficacy Studies:

The Antimicrobial efficacy studies were carried out to ascertain the biological

Activity of the optimized formulations. Staphylococcus Aureus, Pseudomonas Aeruginosa and E.coli were used as the test organisms. These were determined by Agar diffusion test employing Cup-Plate method¹⁷. A layer of nutrient agar (20 ml) seeded with the test microorganisms (0.2 ml) were

allowed to solidify in the petri dishes. Cups were made on the solidified agar layer with the help of sterile borer. Then the volume of the formulations containing equivalent amount of drug was poured into the cups. After keeping the Petri dishes at room temperature for 4 hours, the plates were incubated at 37 C for 24 hours. The zones of inhibitions were measured around the cups¹⁹. The entire operation except the incubation was carried out in a laminar airflow unit.

Ocular Irritancy Studies:

In developing a novel ophthalmic delivery system, an injury to the eye was taken into consideration. Since, eye being a sensitive, most delicate and yet most valuable of the sense organs, the injuries to the Cornea, Conjunctiva, and Iris were measured according to Draize test. According to the Draize test, the amount of the test substance applied to the eye is normally 100 μ l placed into the lower cul-de-sac with observation of the various criteria made at a designated required time interval of 1hr, 24 hrs, 48 hrs, 72 hrs, and 1 week after administration. A total four albino rabbits (male) weighing 1.5-2 kg were used for the present study. The sterile formulations were instilled twice a day for a period of 7 days. Rabbits were observed periodically for redness, swelling, watering of the eye. The evaluation was made according to the Draize test protocol.

Accelerated Stabilities Studies:

Stability is defined as the extent, to which a product retains with in specified

limits and through out its period of storage and use i.e., shelf life. Stability studies were carried out on optimized formulations according to International Conference on Harmonization (ICH) guidelines. A sufficient quantity of formulations in previously sterilized vials was stored in desiccators containing a saturated solution of sodium chloride, which gives a relative humidity of 75 %. The desiccators were placed in a hot air oven maintained at a temperature 40 C 0.5 C and at room temperature. Samples were withdrawn at 7 days interval for 42 Days. The logarithms of percent drug remaining were calculated and plotted against time in days. It was also analyzed for visual appearance, clarity, and pH.

RESULTS:

Preliminary Evaluation Studies on Prepared In situ Gel Formulations:

All the prepared in-situ gelling systems were evaluated for preliminary steps such as Visual appearance, Clarity, pH, and Drug content. These formulations were transparent and clear. The pHs of the formulations were found to be 5.0-5.5, and drug content was in between 99.38 % to 99.71%. See Table 5.

In – Vitro Gellation:

Prepared in-situ gelling systems were evaluated for In – Vitro Gellation capacity. All the formulations were given satisfactory results. See Table 6

Interaction Studies:

The prepared in-situ gelling systems were evaluated for interaction studies to ensure that there is no interaction between drug and polymers. For conformation of the stability of drug in the prepared formulations, the IR spectra were taken and compared with that of pure drug. The result of this study reveals that there was no definite change obtained

In-Vitro Release Studies:

The in-vitro release of Lomefloxacin HCL as pure drug well as from the prepared formulations and marketed eye drops was studied through cellophane membrane using diffusion cell. The release studies of prepared in-situ gelling systems were carried out up to 8 hours, and that of pure drug was up to 2.5 hours and that of marketed eye drops for 3 hours.

Pharmacokinetic Release Studies:

The best fit kinetic model for the optimized formulation were the zero order and peppas model (shown in Table 11), which suggest that the drug release was independent of the concentration and occurred by diffusion mechanism. The polymer can absorb a significant amount of water to form to elastic gel and at the same time, release the dissolved entrapped drug by diffusion through swollen regions of the gel. With a hydrophilic carbopol-HPMC gel, tear fluid would except to diffuse into the gel interior and leach out water soluble drug such as lomefloxacin HCL

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 the case of all Formulations. The diameter of zone of inhibition produced by formulations against all test microorganisms is given

Ocular Irritancy Studies:

Prepared in-situ gelling systems subjected for ocular irritancy studies were found to be non-irritating with no ocular damage or abnormal clinical signs to the cornea, iris, and conjunctiva observed.

DISCUSSION:

Ocular therapy could be significantly improved if the pre-corneal residence time of drugs could be increased; several new preparations have been developed for ophthalmic use not only to prolong the contact time of the vehicle at ocular surface, but also to slow down the elimination of the drugs.

Conventional ophthalmic solution dosage forms have advantage such as, ease of instillation and proper dosage administration. Beside ophthalmic ointments have the advantages of increased contact time. By utilizing these advantages of different dosage forms, the newer approach, In-Situ Gelling System was developed. These gels exhibit a unique property of sol-to-gel transition when a change in their physicochemical property takes places. This type of novel ocular drug delivery can provide increased bioavailability by increasing residence time of gel formed and better patient compliance due to ease of administration.

The aim of the present work envisaged formulating a “pH Induced In-Situ Gelling System of Antibacterial agent, Lomefloxacin HCL” for the treatment of various bacterial diseases of eye, by providing comfortness, compliance to the patients and improved therapeutic performance of the drug over conventional ocular dosage forms.

In the present work the in-situ gelling systems were prepared by pH triggering method with the help of gelling agent, Carbopol 940 and viscosity increasing agent, HPMC E50LV & HPMC E4M.

Firstly the formulation containing Carbopol 940 (0.1-0.5 %) alone was prepared. As observed during practical work that Carbopol solution with lower concentration of it, viscosity of gels formed after gellation at pH 7.4 was very low and at higher concentration of it, viscosity of gels formed was very high. One more problem were found that as Carbopol concentration increase, the pH of the formulation became acidic. So to decrease the concentration of Carbopol 940 without compromising gelling capacity of it, it was decided to use the viscosity-increasing agent, HPMC. Different viscosity grades of HPMC (E50LV / E4M) were used in combination with Carbopol 940 to optimize the concentration of them for desired viscosity and gelling capacity.

From the 25 prepared formulation best 4 formulations were selected on the bases of Viscosity and Gelling capacity. Drug was incorporated in these optimized formulations with other excipients. Results from method 2 reveals that the formulations **CH 11 (0.3 %**

Carbopol 940 and 1.5 % HPMC E50LV) and **CH 15 (0.4 % Carbopol 940 and 1.5 % HPMC E50LV)** showed good gelling capacity and desired viscosity. Results from method 3 reveals that the formulations **CH 21 (0.2 % Carbopol 940 and 0.4 % HPMC E4M)** and **CH 24 (0.3 % Carbopol 940 and 0.4 % HPMC E4M)** showed good gelling capacity and desired viscosity

Using Simulated Tear Fluid developed a simple Spectrophotometric method for estimation of Lomefloxacin HCL. The absorption maxima by UV spectrophotometer were obtained at 281.5 nm in Beer's range of 1-12 g/ml.

Optimized in-situ gels were subjected for preliminary evaluation such as, Visual appearance, Clarity, pH and Drug content. All formulations were found transparent and clear. pH of the formulations was within 5-0.5. Drug content was found within 99.38-99.71 % in all optimized in-situ gelling systems.

During blinking the shearing force on the preparation is large. If the viscosity at high shear rate is too high, this will result in irritation. On the other hand, if the viscosity is too low, it will give rise to increased drainage. So, the formulation should have optimum viscosity for easy instillation into the eye as liquid, which will undergo a rapid sol-to-gel transition, hence the good gelling capacity. But administration of the formulation should influence the pseudoplastic character of precorneal film. In order to evaluate the Rheological behavior, viscosity of the formulations before and after addition of STF was evaluated using Brook Field viscometer. It showed that viscosity of all formulations decreased as the shear rate increased, which showed the character of pseudoplastic fluid.

So the pseudoplastic property of these formulations is in favor of sustaining drainage of drug from the conjunctival sac of the eye and simultaneously without blinking difficulty for undergoing shear thinning.

In-vitro release of Lomefloxacin HCL from the selected formulations was studied through diffusion cell using cellophane membrane for 8 hours. It was compared with the pure drug as well as marketed eye drop. Results reveal that all formulations exhibited sustained release of the drug (above 88 %) from the Carbopol 940 and HPMC E50LV /E4M network over 8-hours. Cellulose derivatives like, HPMC E50LV / E4M dissolve in water and yield much more viscous solution compared to Carbopol 940 solution. Thus, the increase in viscosity might have contributed to the decrease in rate of drug release from these formulations.

For the conformation of the intactness of the drug in formulations, all formulations were subjected to IR study and compared to IR absorption spectra of pure drug. Studies reveal that there was no definite changes in bands were observed with respect to pure drug. So it was conformed that formulations do not have any drug-polymer interactions.

Further all formulations were subjected for sterility testing using nutrient agar media and incubated for 7 days under daily observation. This study showed that formulations do not having any microbial contamination, and was sterile.

Antimicrobial efficacy study carried out by using Staphylococcus Aureus, Pseudomonas Aeruginosa and E.coli as test microorganisms. After incubation up to 24 hours, it was

found that all formulations were effective as antimicrobial action.

Lastly formulations were evaluated for the stability studies for 42 days. Results reveal that no changes were found in Visual appearance, Clarity and pH. These formulations were also analyzed for % drug remaining. This study showed that there was no definite change observed in the intactness of the drug after accelerated study of 42 days.

CONCLUSION:

Lomefloxacin HCL, a Fluoroquinolone agent (antibacterial), used to treat the

various bacterial disease of eye like, conjunctivitis, was successfully formu-

lated as pH induced in-situ gelling system (0.3 % w/v) using Carbopol 940, as a gelling agent, in combination with HPMC E50LV and HPMC E4M, as a viscosity increasing agent. Optimized formulations **CH 11 (0.3 % Carbopol**

940 and 1.5 % HPMC E50LV), CH 15 (0.4 % Carbopol 940 and 1.5 % HPMC E50LV), CH 21 (0.2 % Carbopol 940 and 0.4 % HPMC E4M) and CH 24 (0.3 % Carbopol 940 and 0.4 % HPMC E4M) were liquid at the formulation pH and underwent rapid gellation upon raising the pH to 7.4. Also, the formulations were found to be clear, having good in-situ gelling capacity and sustained drug release over 8 hours periods as compared to pure drug and marketed eye drop. All optimized formulations were sterile, having good antibacterial efficacy and non-irritant as per the Draize test protocol.

As per the stability study formulations were stable (transparent and clear) at room temperature as well as at 40 C. The developed formulations are a viable alternative to conventional Lomefloxacin HCL eye drop by virtue of its abilities that it can not only be readily administered and decreases the frequency of administration, thus resulting in better patient acceptance, but also prolong the precorneal residence time to get higher bioavailability and reduce the systemic side effects caused by the drainage from the nasolacrimal duct. Hence, "pH Induced In-Situ Gelling System of an Antiinfective drug (Lomefloxacin HCL) for Sustained Ocular Delivery" was successful experiment.

REFERENCES:

- Hill J. M., Callaghan O., Hobden R. J., Kaufman E., and Mitra A. K., Ophthalmic Drug Delivery Systems, volume 58, 1-10, 29-56, 59-72, 83-105, 121-131, 177-188, 203-204, New York, Marcel Dekker Inc., 1993.
- Bourlais C. L., Acar L. Zia H., Sado P. A., Needhan S. Leverage R., Ophthalmic Drug Delivery Systems – Recent Advances, Progress in Retinal and Eye Research, 1998; 17:1; 33-58.

3. Chein Y.W., Novel Drug Delivery Systems, 2nd edition, volume 29, 269-300, New York, Marcel Dekker Inc., 1993.
4. Lieberman H. A. Rieger M. M. and Banker G. S., Pharmaceutical Dosage Forms : Disperse System, 2nd edition, volume 2, 357-397, New York, Marcel dekker Inc.,
5. Geeta M. P., Madhubhai M. P., Recent Advances and Challenges in Ocular Drug Delivery Systems, *Pharma Times*, 2007; 39:1; 21-25.
6. Thilekkumar M., Bharathi D., Balasubhraniam J., Kant S. and Pandit J. K., pH- induced In Situ Gelling Systems of Indomethacin for Sustained Ocular Delivery, *Indian Journal of Pharmaceutical Sciences*, 2005; 67:3; 327-333.
7. Roizer A., Manzuel C., Grove J., and Planzonnet B., Gelrite: A Novel, Ion-activated, In Situ Gelling Polymer for Ophthalmic Vehicles Effect on Bioavailability of Timolol, *International Journal of Pharmaceutics*, 1989; 57:2; 162-168.
8. Lindell K. and Engstrom S., In Vitro Release of Timolol from An In Situ Gelling Polymer System, *International Journal of Pharmaceutics*, 1993; 95:1-3, 219-228.
9. Kumar S., Haglund B. O., Himmelstein K. J., In Situ Forming Gels for Ophthalmic Drug Delivery, *Journal of Ocular Pharmacology*, 1994; 10:1; 47-56.
10. Kumar S., and Himmelstein K. J., Modification of In Situ Gelling Behavior of Carbopol Solutions by HPMC, *Journal of Pharmaceutical Sciences*, 1995; 84:3; 344-348.
11. Cohen S., Lobel E., Trevoda A. and Peled Y., A Novel In Situ Forming Ophthalmic Drug Delivery System from Alginates Undergoing Gellation in the Eye, *Journal of Controlled Release*, 1997; 44:2-3; 201-208.
12. Ding S., Recent Developments in Ophthalmic Drug Delivery, *Pharmaceutical Sciences and Technology Today*, 1998; 1:8; 328-335.
13. Dimitrova E., Bogdanova Sv., Mitcheva M., Tanev I., Minkov E., Development of Model Aqueous Ophthalmic Solution of Indomethacin, *Drug Development and Industrial Pharmacy*, 2000; 26:12; 1297-1301.
14. Sechoy O., Tissie G., Sebastian C., Maurin F., Driat J., Trinquand C., A New Long Acting Ophthalmic Formulation of Carteolol containing Alginate Acid, *International Journal of Pharmaceutics*, 2000; 207; 109-116.
15. Lin H., and Sung K. C., Carbopol / Pluronic Phase change Solution for Ophthalmic Drug Delivery, *Journal of Controlled Release*, 2000; 69:3, 379-388.
16. Srividya B. Cardoza R. M., and Amin P. D., Sustained Ophthalmic Delivery of Ofloxacin from a pH Triggered in Situ Gelling System. *Journal of Controlled Release*, 2001; 73:2-3; 205-211.
17. Mitan R. G., Jolly R. P., Megha B., Dharmesh M. M., A pH Triggered In Situ Gel Forming Ophthalmic Drug Delivery System for Tropicamide, *Drug Delivery Technology*, 2007, 7:5; 44-49.
18. Qi H., Chen W., Huang C., Li L., Chen C., Li W., and et al, Development of a Poloxamer Analogs / Carbopol based In Situ Gelling and Mucoadhesive Ophthalmic Delivery System for Puerarin, *International Journal of Pharmaceutics*, 2007; 337; 178-187.
19. Charoo N. A., Kohil K. and Ali A. Preparation of In Situ Forming Ophthalmic Gels of Ciprofloxacin HCL for the Treatment of Conjunctivitis: In Vitro and In Vivo Studies, *Journal of Pharmaceutical Science*, 2002, 92:2; 407-413.

