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Evaluation of Novel Ion Sensitive *In situ* Gelling Polymer in the Development of Ophthalmic Drug Delivery System

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ABSTRACT

The attempt has been made in the present work to formulate an ion sensitive *in situ* gel of an antibacterial agent, Ciprofloxacin HCl employing a novel *in situ* gelling low methoxy pectin (obtained from the heads of *Helianthus annuus* Linn) as bioadhesive polymer. The drug loaded *in situ* gelling formulation was developed employing the cold method. The prepared formulations were evaluated for appearance, clarity, pH, gelling capacity, viscosity, drug content, mucoadhesive force, gelling strength, *in vitro* drug release, isotonicity study, sterility test and stability study. The results of various physicochemical evaluation shows that the formulation comprising of 2.5% w/v low methoxy pectin to be considered as an optimized in terms of gelling capacity, viscosity, gelling strength, the drug release study giving sustained release behavior over period of 11 h. Thus we claim that ion sensitive *in situ* gel of Ciprofloxacin HCl was successfully formulated using low methoxy pectin obtained from heads of *Helianthus annuus* L as a natural ion sensitive, bioadhesive polymer. Thus, it can be concluded that formulation containing low methoxy pectin (2.5% w/v) showed better potential for sustained topical ocular delivery as supported by *ex- vivo* test studies.

Keywords: Ciprofloxacin HCl, *Helianthus annuus* L, *in situ* gel, Low methoxy pectin, Ophthalmic drug deliver

INTRODUTION

The most common route of ocular drug delivery is topical delivery into cul-de-sac. To deliver drug in ocular therapeutics is a challenging task for the formulator and there are various ocular diseases like glaucoma, conjunctivitis, dry eye syndrome, etc. that require frequent drug administration. The attainment of an optimum drug concentration at the site of action is the major problem encountered in drug delivery to eyes [1]. Although external eye structures are readily accessible, the corneal epithelium, the outermost biological barriers mainly limit ocular drug absorption. Consequently after instillation of eye drop, typically less than 5% of an applied dose reaches to the intraocular tissues [2]. Rapid tear turnover, nonproductive absorption, rapid solution drainage by gravity, induced lachrymation, blinking reflex, transient residence time in the cul-de-sac and the relative impermeability of the drugs to corneal epithelial membrane are the major factors responsible for precorneal drug loss. Sometimes undesirable systemic side effects are observed due to systemic absorption of the drug through the nasolachrymal duct [3]. These factors force the clinician to recommend a frequent

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dosing of ophthalmic products at an extremely high concentration and pulse-type dosing leads to several side effects. Some improvements are offered by novel ocular drug delivery systems over a conventional liquid dosage form, however, blurring of vision (e.g., ointments) or lack of patient compliance (e.g., inserts), these formulations are not accepted universally [3].

Problems associated with the above-mentioned formulations suggest that a desirable ocular dosage form would be one that could be delivered in the form of drops, creates little or no problem for vision and needs to be dosed no more frequently than once or twice daily [1]. *In situ* gel-forming systems is such a drug delivery system that can these problems as these formulations would be in the form of drops which on instillation into the eye undergo a sol-gel transition in the cul-de-sac. Different types of *in situ* gel-forming systems based on different mechanisms (temperature, pH, or ion activated) using different polymers have been explored for sustained ocular drug delivery [4].

Low Methoxy Pectin (LMP) has an ability to undergo gelation in the presence of divalent cations, usually calcium. In these polymers gelation takes place due to the formation of intermolecular junction zones between homogalacturonic smooth regions of different chains [5]. The structure of such a junction zone is generally described as 'egg box' binding process, in this process, initial strong association of two polymers into a dimer is followed by the formation of weak interdimer aggregation, mainly governed by electrostatic interactions. The ability of LMP to form gel increases with decreasing degree of methylation. The LMP with a block wise distribution of free carboxyl group is very sensitive to low calcium levels [5].

The objective of the present work was to develop an ion sensitive *in situ* gelling system of Ciprofloxacin HCl using LMP obtained from heads of *Helianthus annuus* L. The LMP acts as an *in situ* gelling polymer by undergoing sol-gel phase transitions in response to physiological stimuli (calcium ions) present in the tear fluid [6]. Thus the basic objective was to develop an ophthalmic system that shows prolonged contact time with corneal epithelium, simplicity and installation for patient, non-irritable and comfortable form with appropriate rheological considerations [7]. Gel formulations have found to be successful in achieving much better drug product effectiveness, reliability and safety [8]. Ciprofloxacin HCl commonly used antibacterial drug in the treatment of ocular infections was used as model drug. This drug shows its Pharmacological action by Inhibition of DNA gyrase (Topoisomerase II) which mediate the formation of supercoils of DNA [9].

MATERIALS AND METHODS

The drug Ciprofloxacin HCl was procured from IPCA lab, Silvasa, India. Low Methoxy Pectin (obtained from heads of *Helianthus Annuus* L) was received as a gift sample from Krishna Pectins, Jalgaon, Maharashtra, India. All other chemicals used were of analytical grade.

Preparation of *in-situ* gelling system

The cold method as described by Bhoyar et al. was used to prepare different formulations [8]. Known amount of LMP was added slowly to the cold aqueous buffer solution with continuous stirring. The dispersions were stored in a refrigerator at 4°C overnight to get a clear solution. 0.3% of Ciprofloxacin HCl (CFX) was added to the polymeric solutions with continuous stirring until thoroughly mixed. To the above solution, Benzalkonium chloride (BKC) was added as preservative and Sodium Chloride (NaCl) as tonicity modifier (Table 1). Finally volume was adjusted with aqueous buffer solution and filled in amber colored vials, sealed with aluminium cap and filled vials were terminally sterilized using moist heat sterilization.

Table 1: Formulation table

Ingredients	F1	F2	F3	F4	F5
Ciprofloxacin HCl (% w/v)	0.3	0.3	0.3	0.3	0.3
Low methoxy pectin (% w/v)	2.2	2.25	2.3	2.5	2.75
NaCl (% w/v)	0.9	0.9	0.9	0.9	0.9
Benzalkonium Chloride (% v/v)	0.01	0.01	0.01	0.01	0.01
Aqueous buffer vehicle	q.s.	q.s.	q.s.	q.s.	q.s.

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Physicochemical evaluations

The prepared formulations were evaluated for various physicochemical properties like appearance, clarity, pH, gelling capacity, viscosity, drug content, mucoadhesive force, gelling strength, *in vitro* drug release, isotonicity, sterility and stability.

Appearance and clarity

Visual inspection of the developed formulations was carried out against black and white background to assess the color and clarity and absence of the particulate matter if any [10].

pH

pH was measured by dissolving 1 ml formulation in 25 ml distilled water using digital pH meter (CL- 180 made by Chemiline).

Gelling capacity

A drop of the each sample (about 100 µl) was put up into a test tube containing 2 ml of simulated tear fluid (STF) equilibrated at 35 ± 1°C to determine the gelling capacity of the representative formulations. The composition of STF was sodium chloride 0.67 g, sodium bicarbonate 0.2 g, dihydrate calcium chloride 0.008 g and purified water added to 100 g. The visual assessment of gel formation and dissolution with time was recorded in triplicate [11].

Viscosity

Viscosity of formulation plays an important role in determining residence time of drug in the ocular cavity. The determination of viscosity of prepared formulations was carried out before and after gelation using Brookfield's Viscometer (GT- 21089-1512-T_3, Brookfield) with spindle no.3. The developed sol formulation was allowed to gel in the STF and then viscosity was measured. Viscosity of samples was measured at different angular velocities from 10 to 100 rpm. The hierarchy of angular velocity was reversed (100 to 10 rpm) with similar weight. The average of two readings (ascending and descending angular velocity) was used to calculate the viscosity [12].

Drug content

The vials containing formulation were shaken well to ensure uniform distribution of the drug and then 1ml of the formulation was transferred into volumetric flask using 1ml calibrated pipette. 50 ml of STF was added to it. The developed gel was then completely crushed with glass rod to give clear solution. Final volume was adjusted up to 100 ml with STF. Ciprofloxacin HCl concentration was determined at 272.4 nm by using UV spectrophotometer (Jasco, V-630) [13].

Mucoadhesive force

Excised goat cornea was used to determine the Mucoadhesive force of all the batches. A section of corneal membrane obtained from eye of a goat was instantly fixed using rubber band with its mucosal side out on to each glass vial. The vial with membrane was then connected to the balance in inverted position whereas first vial was placed on a height adjustable pan (modified balance method). Before applying the ocular gel onto the ocular membrane, 150 µl of STF was evenly spread on the surface of the test membrane. The height of the second vial was then so adjusted that the mucosal surfaces of both vials come in intimate contact and remain in that position for 2 min. Then weights were added in ascending order on the other side of pan until vials get detached. Mucoadhesive force was the minimum weight required to detach two vials. The ocular mucosa was changed for each measurement [12].

$$\text{Detachment stress (dynes/cm}^2\text{)} = mg/A$$

Where, m is the weight added to the balance in grams,

g is the acceleration due to gravity,

A is the area of tissue exposed, i.e. 2.5 cm^2.

Gelling strength

Formulated gels were placed in the test tubes in a thermostat at 37°C. The apparatus for measuring gel strength (Weight: 27 gm.) was then placed on to the gel as described by Patel et al. [14]. The time taken by the apparatus to go downwards to a depth of 5 cm through the prepared gel was measured for each formulation.

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***In vitro* drug release: membrane less method**

The test solution (2 ml) was taken in a circular plastic cup (2.5 cm internal diameter and 1.2 cm depth) and was placed on an inverted USP basket kept inside a 250 ml beaker. Dissolution medium (200 ml of STF) maintained at 37 ± 1°C was added and stirred with a magnetic bead. At regular time intervals samples (5 ml) were withdrawn and replaced with an equal volume of pre warmed medium. The samples were analyzed by UV Spectrophotometer at 274.2 nm [15].

***In vitro* drug release: (through dialysis membrane)**

Dialysis membrane previously soaked overnight in STF was taken, washed and tied on to one end of the glass cylinder (2.5 cm diameter, open at both ends). One end of cylinder was attached to the shaft of USP dissolution apparatus and then suspended in 200 ml of dissolution medium in such a way that membrane just touches the STF, maintained at 37 ± 1°C. The dissolution medium was stirred using magnetic stirrer at 50 rpm. 1 ml of the formulation was added on the other side of the cylinder which acts as a donor compartment. Aliquots were withdrawn at intervals of 1 h and replaced by equal volumes of dissolution medium. Aliquots were analyzed by UV spectrophotometer at 274.2 nm [16].

Isotonicity study

Isotonicity is one of the important characteristics of the ophthalmic formulations and it has to be maintained to prevent tissue damage or irritation to the eye. Isotonicity testing of all developed formulations was carried out as per the method reported by Verma et al. [13]. The shape of red blood cell (bulging or shrinkage) was compared with standard marketed ophthalmic formulation containing Ciprofloxacin HCl.

***Ex-vivo* permeation study**

Excised goat cornea was utilized for determining the permeation across the corneal membrane. Whole eyeball of goat was obtained from a slaughter house and transported to laboratory in cold condition (4ºC) in normal saline. The cornea was carefully removed along with a 5-6 mm of surrounding scleral tissue and washed with cold saline. The washed cornea was then kept in cold freshly prepared STF [3]. Corneal membrane previously soaked overnight in STF was taken and same procedure was followed for studying permeation of the drug as that for dialysis membrane.

Sterility test

All ophthalmic preparations need to be sterile and therefore the test for sterility is most important evaluation parameter. With the help of a sterile pipette or with a sterile syringe or a needle 2 ml of the formulation was removed from test container and was aseptically transferred to sterilized fluid thioglycolate medium (20 ml). The inoculated media were then incubated for not less than 14 days at 30 to 35°C and observed for bacterial growth, if any [12].

***In vitro* antimicrobial efficacy**

Antimicrobial efficacy study was carried out to ascertain the biological activity of sol-to-gel systems against micro-organisms. Agar diffusion test employing "cup plate technique" was used to determine antimicrobial efficacy. Sterile solution of Ciprofloxacin HCl (as a standard) and the developed formulations (test solutions) were poured into cups bored into sterile nutrient agar gel previously seeded with test organisms (*Staphylococcus aureus*). The plates were incubated for 24 h at 37°C after allowing diffusion of solutions for 2 h. The zone of inhibition (ZOI) measured around each cup and was then compared with that of standard. Both positive and negative controls were maintained throughout the study [17].

Stability study

The optimized formulations chosen based on the outcome of various physicochemical evaluations was studied for stability studies as per ICH guidelines. Formulations were kept at 40 ± 1ºC and 75% RH and evaluated at periodic intervals of 30, 60, 90 days for the drug content, clarity, pH, rheology, *in vitro* drug release [10].

RESULTS AND DISCUSSION

The aim of the present work was to enhance the ocular bioavailability of an antibacterial agent, Ciprofloxacin HCl by formulating an *in situ* gelling solution based on LMP. The developed formulations were characterized for the clarity, drug content, viscosity, gelling capacity, mucoadhesive strength, isotonicity study and *in vitro* drug release.

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Drug excipients compatibility studies

From DSC spectrum of individual Ciprofloxacin HCl and LMP it was observed that sharp endothermic peak was obtained at 319°C and 224°C. A sharp endothermic peak obtained at 170°C and 224°C in the DSC spectrum of combination Ciprofloxacin HCl and LMP indicates thermal behavior of drug (Ciprofloxacin HCl) and polymer (LMP). On comparing individual DSC spectra with that of combination it was observed that the drug and polymer are compatible with each other as there was no interaction found between drug and polymer.

Selection of buffer

Buffers play a crucial role in formulating ophthalmic drops. Buffers not only contribute significantly to chemical stability and clinical response but also influence the comfort and safety of the product. The experiments done using various buffer solutions indicated the drug was soluble in acetate buffers of pH 4.6, 4.8 and 5.0 and in citrophosphate buffer of pH 6.8 at the desired dosage level (0.3% w/v). The solutions were stable to elevated temperatures and autoclaving. However, their instability to light as evidenced by discoloration of the exposed solutions necessitated their packing in amber vials. The marketed eye drop was found to have a pH of 6.6. Therefore we selected Citrophosphate buffer, pH 6.8, as a vehicle for the development of eye drops.

Physicochemical evaluations

Appearance, clarity, pH, drug content

All the developed formulations were found to be clear and were light yellow in color. Appearance was found to be transparent for all formulations. Autoclaving done for terminal sterilization had no deleterious effect on the physicochemical properties of the formulations. The pH values for all the formulations have been depicted in Table 2.

Table 2: Physicochemical evaluation

Batch / Parameters		F1	F2	F3	F4	F5
Appearance		Clear	Clear	Clear	Clear	Clear
pH		6.5	6.8	6.7	6.7	6.7
Viscosity (cps)	Sol	30 ± 2	35 ± 3.2	40 ± 3.4	55 ± 3.4	65 ± 5.6
	Gel	500 ± 5.4	510 ± 4.5	530 ± 5.3	550 ± 5.3	560 ± 6.7
Gelling capacity		++	++	++	+++	+++
% Drug Content		95.3 ± 0.05	93.7 ± 0.19	94.15 ± 0.19	95.48 ± 0.023	92.71 ± 0.02
Mucoadhesive force (dynes/cm^2)		2561 ± 34	2654 ± 87	2913 ± 45	3210 ± 56	3452 ± 15
Gelling strength (sec.)		26 ± 4	29 ± 5	30 ± 5	32 ± 4.5	34 ± 3.2

The pH was within acceptable range and hence would not cause any irritation upon administration of the formulation. Table 2 shows the result of percent drug content for all the formulations. The drug content was also found to be in acceptable range (92.00 - 96.00%) for all the formulations confirming to the uniform distribution of drug throughout the

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formulation.

Gelling capacity

LMP, the aqueous solution transforms into stiff gel in presence of cations usually calcium ion was used as excipient in ion sensitive *in situ* gelling system. However, the higher concentration of LMP required for forming stiff gels results in highly turbid solutions which are not clear for eye vision. A selection of appropriate concentration of LMP without disturbing the gelling capacity and rheological properties of the delivery systems could be achieved between 2.2 to 2.75% w/v. The formulation needs to have best possible viscosity that will allow easy instillation into the eye as a liquid which would then undergo a rapid sol-to-gel transition. Additionally, the gel formed *in situ* should preserve its integrity without dissolving or eroding for a prolonged period of time. In order to identify the compositions suitable for use as *in situ* gelling, gelling systems of various concentrations of LMP were prepared and evaluated for gelling capacity. The outcomes of the gelling capacity test of the developed formulations F1-F5 have been depicted in Table 2 as dissolution time of the gel in STF. Although all of them could form gel immediately as they make contact with the STF equilibrated at 35 ± 1°C, the formulations F4 and F5 were eroded by STF about 2 times slower than the formulations F1, F2 and F3. As gelling is due to binding of calcium ions (present in tear fluid) with LMP, the formulation containing more LMP would possess stronger gel structure. Since F4 showed ability to be retained as a gel for more than few hours, it was selected as optimized formulation.

Viscosity

Formulations should have optimum viscosity which allows easy instillation in to eye cavity, and should not hinder the normal eye ball movement after instillation. The developed formulations exhibited shear thinning or pseudoplastic rheology. The viscosity was found to be directly dependent on the polymeric content in each formulation. Table 2 shows the viscosity values obtained before gelation and after gelation for all the formulations using Brookfield's Viscometer. No change in the viscosity of the formulations as observed after autoclaving. F5 showed the maximum viscosity of 65 Cps at 100 rpm whereas the minimum viscosity at 100 rpm was shown by F1. Increased viscosity after gelation proves excellent gelling ability of the formulations.

Mucoadhesive force

Ocular mucoadhesion depends upon the interaction between the polymer and the mucin coat covering the conjunctiva and corneal surfaces of the eye. Structurally, mucin consists of a protein or polypeptide core with carbohydrate side chains branching off the core. The polymer with many hydrophilic functional groups (e.g. carboxyl group, hydroxyl group and sulfate) can establish electrostatic and hydrophobic interactions and hydrogen bond with the underlying surface. The concentration of LMP has shown significant impact onto the mucoadhesive force under physiological condition as depicted in Table 2. The mucoadhesive force of 2.75% w/v LMP was 1.6 times greater than that of the 2.2% w/v. These can be mainly attributed to the hydrogen bonds between the carboxyl groups of the LMP molecule and the carboxyl groups of the carbohydrate side chains of the mucin. Besides, electrostatic, hydrophobic interactions and inter diffusion of the mucin and the polymer also have some contribution. The mucoadhesive force is an important physicochemical parameters for prolonging ocular retention time and there by better therapeutic effects. Detachment stress of F4 was found to be satisfactory in comparison with other formulation. All the formulations showed mucoadhesive force in increasing order i.e. highest mucoadhesive force for F5 and lowest for F1. This could be attributed to the concentration of LMP in the formulations. Table 2 shows mucoadhesive forces of all formulations.

Gelling strength

For sustained release ability of polymer, measurement of gelling strength is an important parameter. All the formulations (F1 to F5) exhibited good gel strength (in the range of 25 to 50 sec).

***In vitro* drug release**

The cumulative percent of Ciprofloxacin HCl released versus time profiles for developed formulation is shown in Figures 1 and 2.

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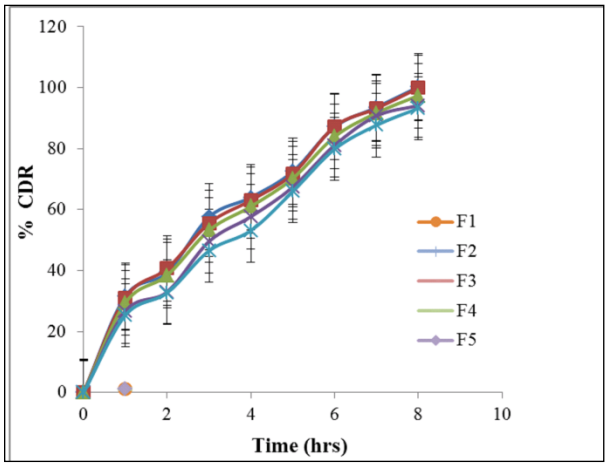

Figure 1: *in- vitro* drug release, %CDR (membrane less method)

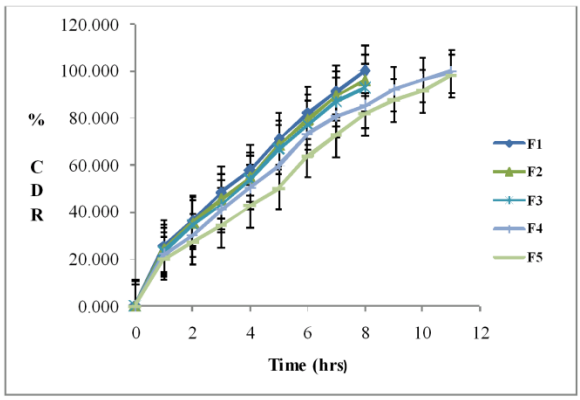

Figure 2: *in - vitro* permeation study, %CDR

Initially drug released study was carried out with membrane-less method. F1 shown drug released around 100.29% in 8 h. While formulations F2, F3, F4, F5 released 99.86%, 97.38%, 94.12%, and 93.22% of drug respectively in 8 h, which indicated slow release of drug with increased concentration of LMP. Further release study was carried out till 100% release of drug through cellophane membrane (Figure 2) and it demonstrated that the formulations F4 and F5 had relatively better sustained-release effect as compared to other formulations. F4 releases 99.84% of drug and F5 releases 98.08% of drug in 11 h. This was indicating that F4 can be used as an ophthalmic sustained release drug delivery system. Hence F4 was selected as optimized formulation on basis of % drug released. Finally optimized formulation shows 27.01% cumulative drug release after 1 h and 98.81% after 11 h by membrane-less method as shown in Figure 3.

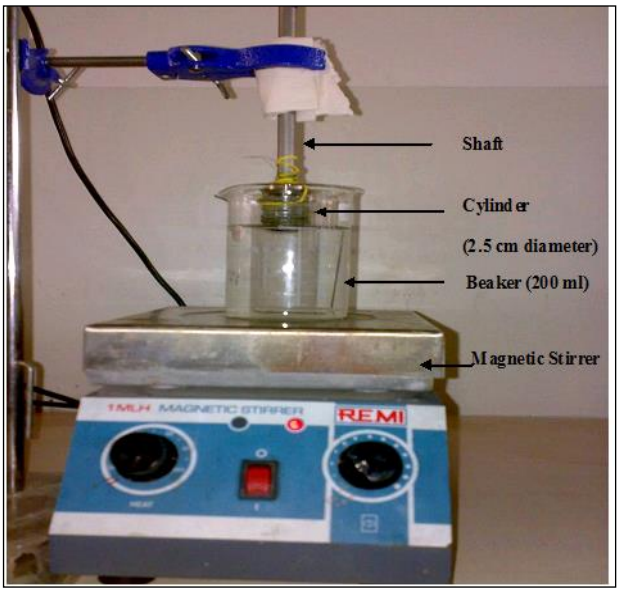

Figure 3: Modified USP dissolution apparatus

Drug release kinetics

In order to investigate drug release mechanism, the release data was analyzed by PCP disso software fitted to models representing Zero order, First order, Higuchi and Korsemeyer Peppas equation. The examination of coefficient of correlation (r^2) values for the formulation F4 indicated that Korsemeyer Peppas equation was more suitable fit to drug release mechanism from developed ion activated *in situ* gelling system.

Korsemeyer Peppas equation:

$Mt/M\infty = Kt^n$

$\text{Log } (Mt/M\infty) = \log K + n \log t$

Where Mt/M is the amount (%) of Ciprofloxacin HCl released at time t,

n is the diffusional exponent,

K is the apparent release rate.

Our data shows that the release index (*n*) of the formulations studied was 0.69 which suggest drug release taking place by combination of diffusion and dissolution from the dosage form. The release mechanism for semisolid vehicles containing dissolved drug was found to be non-fickian or anomalous involving both diffusion and polymer relaxation ($0.5< n< 1$). The value of n suggest that Ciprofloxacin HCl release from formulation was dependent on two simultaneous processes: water migration into the *in situ* gelling system and drug diffusion through continuously swelling gelling system.

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Isotonicity study

In order to be nonirritant to the ocular tissues, formulation must be isotonic in nature. The shape and size of red blood cell was found to be same or nearly same as that of blood cell suspended in the solution of standard marketed formulation. Hence it can be concluded that developed formulations were isotonic.

***Ex-vivo* permeation study**

Ex-vivo trans-corneal permeation studies of Ciprofloxacin HCl formulations were conducted and higher and prolonged permeation across goat cornea was observed with LMP based formulation as compared to marketed eye drop. This might be attributed to the gelling ability of LMP in presence of STF. *Ex-vivo* Trans-corneal permeation shows 22.2% cumulative drug release after 1 h and 73.76% after 11 h as shown in Figure 4.

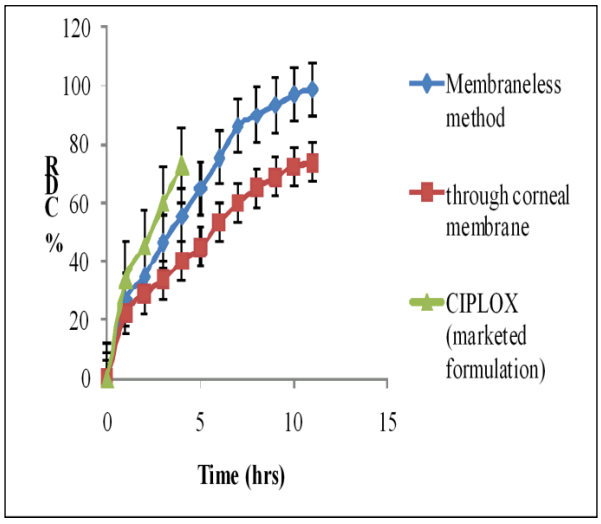

Figure 4: Drug release study (%CDR)*: In-vitro* drug release (membrane less method), *Ex-vivo* permeation study for optimized and marketed formulation

Ex-vivo Trans-corneal permeation study was also carried out for marketed formulation (Ciplox) containing Ciprofloxacin HCl. It releases same % of drug in 4 h. This indicates that LMP based formulation increases the residence time of drug.

Sterility test

The preparations being examined for sterility were found to pass the test for sterility as turbidity was not observed when all the formulations were incubated for not less than 14 days at 30°C to 35°C in case of fluid thioglycolate medium. This was clear evidence suggesting no microbial growth in the formulations.

***In vitro* antimicrobial efficacy**

The result of the antimicrobial efficacy tests shown that the Zone of Inhibition (ZOI) values for the developed formulations were approximately same as that of the ZOI values for the standard antibacterial ophthalmic preparation. The satisfactory ZOI values obtained for the formulations could be attributed to the slow and prolonged diffusion of the drug from the polymeric solution due to its higher viscosity. % inhibition for F4 was found to be 96.10%.

Stability study

Stability studies were performed onto the developed formulation at 40 ± 1°C, 75 ± 5% RH. Formulations were screened at periodic interval for clarity, drug content, pH, gelling capacity, viscosity and *in vitro* drug release. Every formulation at the end of each month was found to be clear. There was insignificant change in the pH of formulation for all three month's batches. Drug content at the end of each month was found to be 92-96% indicating drug content uniformity. Gelling capacity and viscosity was in the acceptable range and finally *in-vitro* drug release after 11 h was approximately (97%) equal for all the batches. Hence optimized formulation containing 2.5% w/v LMP was found to be stable in all aspects.

CONCLUSION

Ciprofloxacin HCl was formulated successfully as *in situ* gelling ocular drug delivery system using novel ion activated bioadhesive polymer obtained from the heads of *Helianthus annuus* L. Very simple and cost effective methodology was adopted for the preparation of *in situ* gelling system was. Polymer used in present research work proved its utility by improving residence time and in turn bioavailability of the Ciprofloxacin HCl by prolonging drug release. The developed formulation could serve as best alternative to the conventional ocular formulations by the virtue of its method of preparation, decreased frequency of administration and better patient compliance. It can be concluded from the outcome that

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formulation containing 2.5% w/v of the novel polymer exhibited better potential for sustained topical ocular drug delivery.

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