ORIGINAL ARTICLE

In situ gelling systems of ofloxacin: Comparative performance of *in vivo* precorneal drainage and pharmacokinetic study

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Our present work describes the formulation and evaluation of an ocular deliver system of ofloxacin based on the concept of temperature-and ion-activated *in situ* gelling system. A combination of Pluronic F-127 and Pluronic F-68 along with chitosan, (pH-sensitive polymer also acts as a permeation enhancer) was used in temperature and pH-triggered *in situ* gelling systems while gellan alone was used in ion-activated *in situ* gelling system. The formulation allows its easy instillation into the eye as a liquid (drops), forms transparent gel, and spreads over the corneal surface. At the formulation pH, transcorneal permeation profile of ofloxacin was comparable to that of *in vitro* release profile. *In situ* gel-forming ability of the developed systems significantly controls precorneal drainage as studied by gamma scintigraphy. Thus, increased residence time in the eye would help to increase the ocular bioavailability. The formulation was also found to be nonirritant and well tolerable. C_{max} of *in situ* gelling formulation was found to be 1.5 times higher than marketed eye drops solution at the similar T_{max} of 1 h.

Key words: *Gamma scintigraphy and pharmacokinetic study, in situ gelling system, ofloxacin*

INTRODUCTION

Ophthalmic drug delivery is one of the most interesting and challenging endeavors being faced by the pharmaceutical scientist. The anatomy, physiology, and biochemistry of the eye render this organ highly impervious to foreign substances. The goal of pharmacotherapeutics is to treat a disease in a consistent and predictable fashion. An assumption is made that a correlation exists between the concentration of a drug at its intended site of action and the resulting pharmacological effect.[1] Topical application is the preferred route of administration for bacterial conjunctivitis and keratitis because the drops provide therapeutically effective concentrations; the drops wash away bacteria and bacterial antigens; adverse systemic effects of the drugs are decreased or eliminated. The factors that contribute to achieving effective therapeutic concentrations of the drug in the cornea include the frequency of administration, the concentration of the drug, the lipophilic nature of the drug where the epithelium is intact, the length of contact time of the drug with the cornea, and the lack of an intact corneal epithelium.[2] Whenever an ophthalmic drug is applied topically to the anterior segment of the eye, only a small amount (5%) actually penetrates the cornea and reaches the internal anterior tissue of the eyes. Rapid and efficient drainage by the nasolacrimal apparatus, noncorneal absorption, and the relative impermeability of the cornea to both hydrophilic and hydrophobic molecules, all account for such poor ocular bioavailability.[3,4] A significant challenge to the formulator is to circumvent (bypass) the protective barriers of the eye without causing permanent tissue damage. Thus, to increase the ocular bioavailability of drug, we need to increase the ocular residence time of the drug. Several *in situ* gelling systems have been developed to prolong the precorneal residence time of a drug, improve patient compliance, and consequently enhance ocular bioavailability.[5] *In situ* forming gels are formulations, conveniently dropped in the eye as a solution, where they undergo transition into a gel. These systems exhibit sol-to-gel phase transitions due

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to a change in a specific physicochemical parameter (e.g., pH, temperature, and ions) in the *cul-de-sac*[6] and thus, prolong the precorneal residence time. Gamma scintigraphy is a non-invasive technique that allows monitoring of the corneal residence without disturbing the normal physiological functions.[7] It was first described by Rossomondo[8] and has since been widely used, i.e., to assess the precorneal drainage of artificial tear products,[9] ophthalmic ointments,[10] liposomal formulation of tropicamide,[11] water in oil microemulsions,[12] thermosetting gels,[13] alginate, and Hydroxy Propyl Methyl Cellulose (HPMC) based on ion-activated *in situ* gelling system[14] and an ion-and pH-activated *in situ* gelling system based on gellan gum and chitosan.[15]

The objective of the present work was to develop thermosensitive and ion-activated *in situ* gelling systems of ofloxacin, a fluoroquinolone derivative used in external infections of the eye. One of the main advantages of the fluoroquinolone is their high intrinsic solubility and low rates of adverse effects. To perform a comparative performance study of *in vivo* precorneal drainage of both the systems and pharmacokinetic study of optimized system, a combination of Pluronic F-127 and Pluronic F-68 along with chitosan, (pH-sensitive polymer also acts as permeation enhancer) was used in temperature-and pH-triggered *in situ* gelling systems while gellan alone was used in ion-activated *in situ* gelling system.

MATERIALS AND METHODS

Materials

Ofloxacin (NuLife Pharmaceuticals, Pimpri, Pune, India), Gellan gum (Applied Biosciences, Mumbai, India), Pluronic F-127, Pluronic F-68, and HPMC K4M (ICPA Ankaleshwar, Gujarat, India), Chitosan, practical grade, 75-85% deacetylated, molecular weight 150 kDa (Indian Sea Industries, Thiruvananthapuram, India). All solvents used were of analytical grade, unless mentioned.

Methods

Preparation of temperature and pH-triggered in situ gelling systems

Different combinations of placebo formulations were developed and evaluated for gelation temperature and gelling capacity to identify the composition suitable for use as *in situ* gelling system [Table 1]. Chitosan was dissolved in a mixture of glacial acetic acid and distilled water. Mucoadhesive polymer, namely HPMC K4M was dispersed in chitosan solution. Pluronic F-127 and Pluronic F-68 were slowly added to above cold mixture with continuous mixing using a thermostatically controlled magnetic stirrer. The partially dissolved poloxamer solutions were stored in a refrigerator and stirred periodically until clear homogenous solutions were obtained (approximately 24 h). The developed formulations were evaluated for gelation temperature[16,17] and gelling capacity.[18] Drug solution was prepared by dissolving the appropriate amount of ofloxacin, 0.3% (w/v), in the calculated amount of distilled water. 0.1 N hydrochloric acid was added during the mixing step to get a clear solution and mixed with the previously optimized *in situ* gelling system. The formulations were sterilized by terminal autoclaving at 121°C for 20 min at 15 psi. Mannitol and benzalkonium chloride were added as isotonicity agent and preservative respectively. All glassware used during the preparation of the *in situ* forming gels was sterilized by autoclaving and the entire procedure was carried out in a laminar flow hood.

Preparation of the ion-activated in situ gelling system

Different combinations of placebo formulations were developed and evaluated for clarity and gelling capacity to identify the composition suitable for use as *in situ* gelling system [Table 2]. Gellan gum was dispersed in deionized water. Further dispersions were heated to 90°C for 20 min while stirring. Ofloxacin solution was prepared in water with the aid of 0.1 M Sodium hydroxide to get a clear solution. This solution was added to gellan dispersion to obtain a drug concentration of 0.3% w/v. The pH was adjusted to 7.0 ± 0.1 using drops of 0.5 M NaOH, and the dispersion was equilibrated at 4°C overnight. Mannitol and methyl paraben were added as isotonicity agent and preservative respectively. The formulations were sterilized by terminal autoclaving at 121°C for 20 min at 15 psi. All glassware used during the preparation of the *in situ* forming gels was sterilized by autoclaving and the entire procedure was carried out in a laminar flow hood.

Table 1: Composition and studies of an Pluronic F-127/PluronicF-68/HPMC/chitosan-based *in situ* gelling systems

Poloxamer F-127 (% w/v)	Poloxamer F-188 (% w/v)	Chitosan (% w/v)	HPMC K4M (% w/v)	Gelation temperature (°C)	Gelling capacity	pH
15	4	-	-	55.0±0.58	+	6
16	4	-	-	48.3±0.40	+	6
17	4	-	-	42.0±0.50	++	6
18	4	-	-	38.24±0.36	++	6
18	4	-	0.2	36.50±0.25	+++	6
18	4	-	0.4	36.0±0.58	+++	6
18	4	0.25	0.2	33.0±0.5	+++	6

+: Phase transition within 60 s, collapse of gel structure within 1-2 h, ++: Phase transition within 60 s, collapse of gel structure within 3-4 h; +++: Phase transition within 60 s and gel structure stable for more than 6 h, HPMC: Hydroxy propyl methyl cellulose

Medicated in situ gelling systems

For preparing *in situ* gelling medicated formulations, ofloxacin, equivalent to 0.3% w/v was dissolved in sterile water with the aid of 0.1N HCl to get clear drug solution. Further this drug solution was mixed with previously optimized *in situ* gelling systems [Table 3].

Evaluation of formulations

Drug–polymer interaction studies

The infrared (IR) and ultraviolet (UV) spectrum of pure drug solution and optimized formulation was taken before and after autoclaving. Thin layer chromatogram of pure drug and optimized formulation was obtained using a solvent system which consists of *n*-butanol, methanol, and ammonia in the ratio of 5:1:1.5. Interaction studies investigated any interaction between the drug and excipients and studied the effect of method of sterilization.

In vitro drug release studies

In vitro release of ofloxacin was studied using a modified dissolution testing apparatus.[6] The dissolution medium used was freshly prepared simulated tear fluid pH 7.4 maintained at a temperature of 37 ± 1°C. Cellulose membrane (Spectra/Por dialysis membrane, 12,000-14,000 molecular weight cut-off), previously soaked overnight in the dissolution medium, was tied to one end of specifically designed glass cylinder (open at both ends and of 2.0 cm diameter) and allowed to rotate at 50 rpm. The drug content in the withdrawn samples was determined at 293 nm using UV–visible double-beam spectrophotometer. The results were the means of three runs [Figure 1].

In vitro transcorneal permeation study

In vitro transcorneal permeation study was performed using modified Franz diffusion chamber.[19] Simulated tear fluid was used as the diffusion medium. Fresh goat corneal membrane was separated, soaked in simulated tear fluid, and mounted on by sandwiching between the clamped donor and receptor compartment. Prior to the application of formulations, the membrane was allowed to equilibrate for 30 min. One millilitre of sample was withdrawn and replaced with fresh simulated tear fluid in order to maintain sink conditions. The samples were appropriately diluted and the absorbance was measured at 293 nm using a Shimadzu ultraviolet-Visible spectrophotometer. The results were the means of three runs [Figure 2].

Ocular irritation studies

The ocular irritation was performed according to Draize

Table 2: Physico-chemical properties of ion activated *in situ* gelling systems

Gellan gum (% w/v)	pH	Clarity	Gelling capacity
0.1	7.0±0.2	Transparent	+
0.2	7.0±0.2	Transparent	++
0.3	7.1±0.2	Transparent	+++
0.4	6.90±0.2	Transparent	+++
0.5	6.90±0.2	Transparent	+++

(+) slightly turbid, (++) clear solution, (+++) clear and transparent

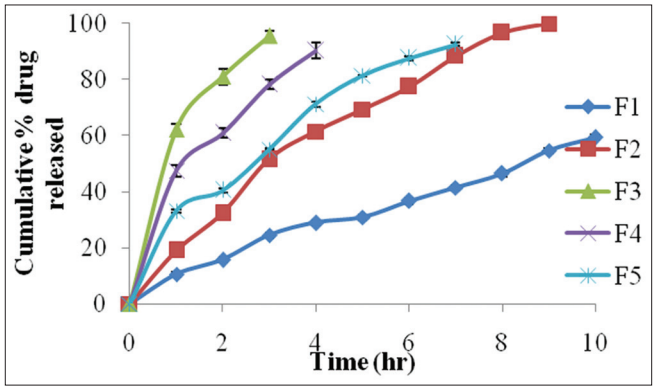

Figure 1: *In vitro* drug release profile of *in situ* gelling system (mean±SD; *n*=3)

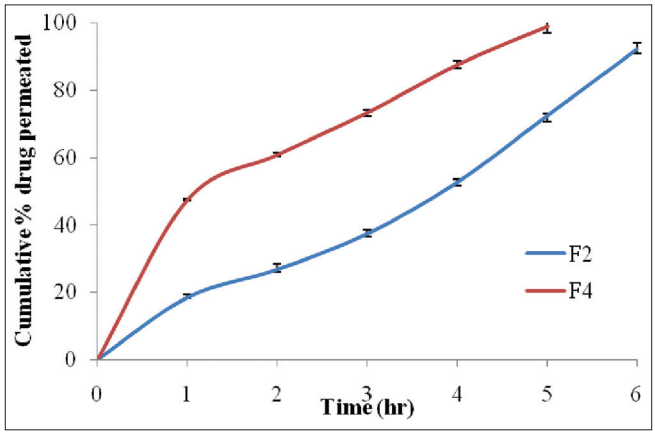

Figure 2: *In vitro* drug transcorneal permeation profile from optimized *in situ* gelling system (mean±SD; *n*=3)

Table 3: Developed medicated *in situ* gelling systems

Formulation code	Ofloxacin (% w/v)	Poloxamer F-127 (% w/v)	Poloxamer F-188 (% w/v)	Chitosan (% w/v)	HPMC K4M (% w/v)	Gellan gum (% w/v)
F1	0.3	18	4	-	0.2	-
F2	0.3	18	4	0.25	0.2	-
F3	0.3	-	-	-	-	0.3
F4	0.3	-	-	-	-	0.4
F5	0.3	-	-	-	-	0.5

technique on New Zealand white albino rabbits, each weighing 2-3 kg. 50 µl of each selected formulation was instilled into the lower *cul-de-sac* the left eye of the rabbit. The right eye, which remained untreated, served as a control. To prevent the loss of test material, the lower eye lid was gently held together for approximately 5 s. The sterile formulations were instilled twice a day and the rabbits were observed after 1 h, 24 h, 48 h, and 72 h for redness, excessive tearing, and inflammation of the eye.

Gamma scintigraphy

In vivo precorneal drainage of radionuclide was studied using single photon emission computing tomography (SPECT) (SPECT LAB, Pune, India), autotuned to detect the 140 KeV 99m radiation of technetium (Tc). Each selected formulation F2 and F4, was assessed on a group of four rabbits with a minimum washout period of 3 days. The solution of ofloxacin was placed in an amber-colored bottle and radiolabeled with Tc-99m by direct labeling method using stannous chloride as the reducing agent. This radiolabeled drug solution was then mixed with other ingredients in such a way that the final solution would contain 0.3% w/v ofloxacin and required concentration of polymers. Rabbits were anesthetized using ketamine HCl injection given intramuscularly at a dose of 15 mg/kg body weight. The rabbits were positioned 5 cm in front of the probe and 25 µl of the radio-labeled formulation (equivalent to ~100 µCi) was instilled onto the left corneal surface of the rabbits. Recording was started immediately after instillation and continued for 10 min. Region of interest was selected on the one frame of the image and time activity curve was plotted to calculate the rate of drainage from eye [Figure 3].

Ocular pharmacokinetic study

New Zealand white rabbits of about 5-6 months age and weighing about 2-3 kg were selected. Eyes of the rabbits were examined to ensure that they did not have abnormality in any ocular structures. All the animal experiments were done in accordance with the Organization for Economic Co-operation and Development principles of good laboratory practice. All the experiments were approved and conducted as per guidelines of Institutional Animal Committee (Reg. No. 1036/A/07/CPCSEA). Optimized *in situ* gelling medicated formulation containing ofloxacin F2 was assessed on a group of four rabbits with a minimum washout period of 3 days. The right eye, which remained untreated, served as the control. 50 µl of medicated formulation was instilled into the lower *cul-de-sac* of left eye of the rabbit. The conjunctival sac was held for 30 s. with the help of fingers. The rabbits were anesthetized using ketamine HCl injection given intramuscularly at a dose of 15 mg/kg body weight and aqueous humor was sampled with the help of 28 G needle after 30 min, 1 h, 2 h, 3 h, 4 h, 5 h, and 6 h from the left eye. Aqueous humor samples (100 µl) were mixed with methanol and kept in a refrigerator for 1 h. The mixture was then centrifuged at 3000 rpm for 15 min and 20 µl of the supernatant, thus obtained, was analyzed for drug content by high performance liquid chromatography HPLC [Figure 4].

RESULTS AND DISCUSSION

An effective approach to improve the ocular delivery of topically applied drugs and diminishing of adverse effects is the use of polymer vehicles. Poloxamers were previously proven to undergo thermal gelation. Gelation temperature of poloxamer 407 can be adjusted to the temperature of the eye (33-34°C) by modifying cross-linking agents, by mixing the different series of poloxamers.[4] Below the transition temperature, poloxamer solutions allow a comfortable and precise delivery by the patient to the *cul-de-sac*, where thermogelation occurs. Gels containing poloxamer 407 had good gelation properties, in that, the gelation temperature of the gel decreased as the concentration of poloxamer increased [Table 1]. Combination of 18% w/v Poloxamer 407 and 4% w/v Poloxamer 188 was found to be forming gels quickly within 60 s. and gel structure stable for more than 3 h. When HPMC K4M was incorporated in poloxamer combination, the gel formulation was quick and gel structure retained for longer time, i.e., more than 6 h. This finding suggests an increase in gel strength with addition of this mucoadhesive

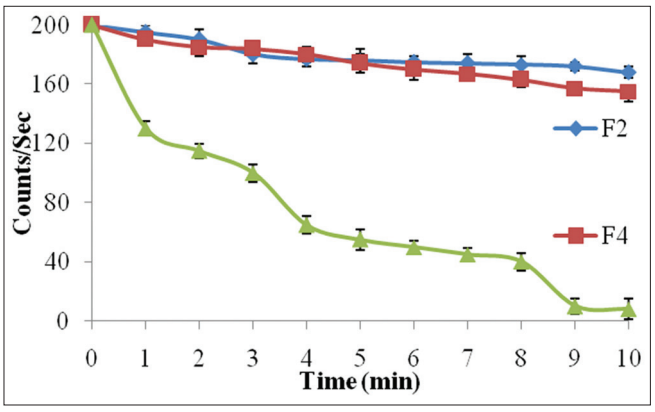

Figure 3: Time activity curve shows precorneal drainage of selected formulations (F2 and F4) and marketed eye drop solution (mean±SD; *n*=3)

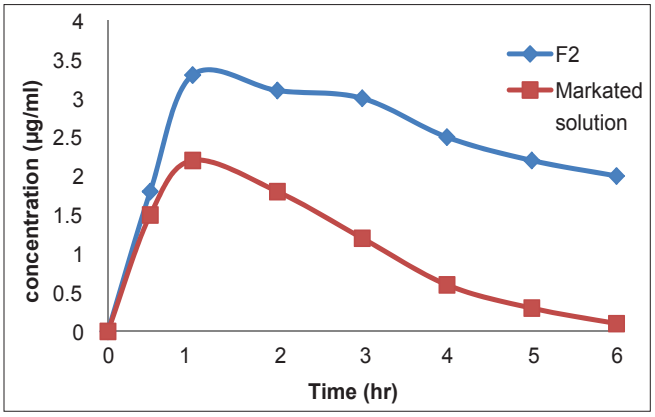

Figure 4: Concentration of drug in aqueous humor versus time for optimized formulation (F2) and marketed eye drops solution

polymer. Also, addition of mucoadhesive polymers viz. HPMC and chitosan lowered the gelation temperature of the *in situ* forming gels. The gelation temperature-lowering effect of such mucoadhesive polymers could be explained by their ability to bind to polyoxyethylene chains present in the poloxamer molecules. This will promote dehydration, causing an increase in entanglement of adjacent molecules and extensively increasing intermolecular hydrogen bonding which will lead to gelation at lower temperature.

All the formulations containing different concentrations of gellan gum (0.1-0.5% w/v) showed the gelling ability in the presence of simulated tear fluid [Table 2]. It is attributed to the formation of a three-dimensional network by its complex formation with Ca^{2+} ions and hydrogen bonding with water. Interaction studies, before and after autoclaving were carried out by Ultraviolet-Visible and Infrared spectroscopy revealed that the ingredients were compatible to each other and no physicochemical reactions took place. It also demonstrated that the formulation ingredients were stable to heat and the final formulation could be terminally sterilized by autoclaving.

The main prerequisites of ocular gelling system are clarity and gelling capacity (speed and extent of gelation). Both the systems allow its easy instillation into the eye as a liquid (drops), which forms transparent gels and spread over the corneal surface. However, the nature of the gel formed depended upon the polymer concentration. Based on this study, *in vitro* drug release of ofloxacin in selected formulation [Table 3] was studied. The ofloxacin release was inversely proportional to the gellan gum concentration [Figure 1], as might be due to a more dense gel structure. A similar release pattern was reported for carteolol, wherein the initial fast release (burst effect) decreased with an increase in polymer concentration.[20] In temperature-and pH-triggered *in situ* gelling systems, chitosan increases the mucoadhesion potential but its penetration-enhancing properties dominate more. Transcorneal permeation profile was comparable to that of *in vitro* release profile. Gellan gum-based ion-sensitive *in situ* gelling system showed comparably more permeation as may be due to the absence of any mucoadhesive polymer [Figure 2].

The results of the ocular irritation studies [Table 4] indicate that the selected formulations were non-irritant and well tolerated. No ocular damage or abnormal clinical signs to the cornea, iris, or conjunctivae were visible.

Table 4: Ocular irritation test of developed *in situ* gelling systems

Parameter	Duration F2				Duration F4			
	1 h	24 h	48 h	72 h	1 h	24 h	48 h	72 h
Redness	0	0	0	0	0	0	0	0
Excessive tearing	0	0	0	0	0	0	0	0
Inflammation	0	0	0	0	0	0	0	0

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

For scintigraphic studies, during prelabeling efficiency, labeling parameters like Stanous chloride concentration and pH were optimized. 50 µg $SnCl_2$ at pH 3.0 was found to give the maximum labeling efficiency (95.4%). *In vitro* stability of the Tc-99m-labeled complex was also tested and the complex was found to be stable for up to 3 h. The observation of the acquired gamma camera images showed that both, developed *in situ* gelling systems form good clear gel over the corneal surface immediately after administration as compared with marketed eye drop solution. Marketed eye drop solution cleared very rapidly from the corneal region whereas, both *in situ* gelling systems were cleared at a slow rate and retained at the corneal surface for a longer duration [Figure 3]. *In situ* gel-forming abilities of the developed systems significantly control the precorneal drainage. Thus, increased residence time in the eye would help to increase the ocular bioavailability. The period of drug absorption is short because the activity gradient decreases rapidly owing to precorneal solution drainage and conjunctival systemic absorption. A minimum of 5-10 min of ocular contact time was determined to be necessary for significantly reducing systemic drug absorption.[21] Reports of superficial cornea1 haze/opacity have been noted in 20% of patients after 8 weeks of administration with gellan based systems.[22,23] A similar corneal change has been noticed with carbomer, contained in ophthalmic gel after the same period of time.[24] Looking toward the data supported, further study was conducted on thermosensitive *in situ* gelling medicated formulation.

The optimized formulation and marketed eye drops of the ofloxacin were subjected to *in vivo* pharmacokinetic studies to estimate drug levels of aqueous humor in the eyes of animals. The reported minimum inhibitory concentration (MIC_{90}) of ofloxacin is ≤2 µg/ml for most of the susceptible microorganisms.[25] As shown in Figure 4, the MIC_{90} of drug in aqueous humor was achieved by *in situ* gelling formulation and was maintained up to the study duration of 6 h. In the marketed eye drops solution, higher drug levels were observed initially and after some time, they drop down. C_{max} of *in situ* gelling formulation was found to be 1.5 times higher than that of the marketed eye drops solution at the similar T_{max} of 1 h.

CONCLUSION

The developed formulation of ofloxacin allows its easy instillation into the eye as a liquid (drops), and forms a transparent gel. The observation of the acquired gamma camera images showed that the developed *in situ* gelling system form a good clear gel over the corneal surface immediately after administration as compared with marketed eye drop solution. *In situ* gel-forming ability of the

developed system significantly controls precorneal drainage. Pharmacokinetic data revealed that, optimized *in situ* gelling system showed increased drug aqueous humor levels as compared to marketed eye drop solution. Further work is needed to establish the therapeutic usefulness.

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