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Preparation and Evaluation of In-Situ-Gels for Ocular Drug Delivery

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ABSTRACT

The poor bioavailability and therapeutic response exhibited by conventional ophthalmic solutions due to rapid precorneal elimination of the drug may be overcome by use of in –situ gel forming system that are instilled as a drops into the eye and it undergoes a sol-gel transition in the cul-de-sac. The present work describes the formulation and evaluation of an ophthalmic delivery system of an antibacterial agent, ciprofloxacin, which is used in the treatment of eye infection such as dacrocystitis, bacterial conjunctivitis, corneal ulceration and blepharitis, based on the concepts of pH-triggered in-situ gelation, thermo reversible gelation and Ion activated system. Poly acrylic acid (Carbopol 940) was used as the gelling agent in combination of hydroxy propyl methylcellulose, which acted as a viscosity-enhancing agent. (pH-triggered system). Pluronic F-127 (14%) was used as the thermal reversible gelation in combination of HPMC (1.5%) incorporation of HPMC was to reduce the concentration of pluronic required for in-situ gelling property, with 25% w/w pluronic F-127 reported to form good gels. Gellan gum (Gelrite) is an anionic exocellular polysaccharide by the bacterium pseudo Monas elodea, having the characteristic property cation-induced gelation (0.6%). The developed formulation was therapeutically efficacious, stable, non irritant and provided sustained release of the drug over an 6 hours period, but Gelrite formulation showing long duration of release followed by combination of carbopol, HPMC and pluronic F-127 & HPMC. The developed system is thus a viable alternative to conventional eye drops.

Keywords: Hydroxy propyl methyl cellulose, in-situ, gelation, Ciprofloxacin Hydrochloride

INTRODUCTION

Eye drops that are conventional ophthalmic delivery systems often result in poor bioavailability and therapeutic response because high tear fluid turnover and dynamics cause rapid precorneal elimination of the drug . A high frequency of eye drop instillation is associated with patient non-compliance. Inclusion of excess drug in the formulation in an attempt to overcome bioavailability problem is potentially dangerous if the drug solution drained from the eye is systemically absorbed from the nasolacrimal duct[9, 12]. Various ophthalmic vehicles such as inserts, ointments, Suspensions, and aqueous gels, have been developed in order to lengthen the residence time of instilled dose and enhance the ophthalmic bioavailability[3, 4]. These ocular drug delivery systems, however, have not been used extensively because of some drawbacks such as blurred vision from ointments or low patient compliance from inserts. [8, 9]

Several insitu gel forming system have been developed to prolong the precorneal residence time of a drug and improve ocular bioavailability. These systems consist of polymers that exhibit sol-to-gel phase tansititions due to change in specific physico chemical parameter (pH, temperature), in their environment, the cul-de-sac in this case[4, 6]. Depending on the method employed to cause sol-to-gel phase transition on the eye surface, the following three types of systems are recognized. PH triggered system, temperature dependant system[18] and ion activated system[5]. Using these three methods above in-situ gelling ophthalmic delivery system is developed. However most of the systems require the use of high concentration of polymers. For instance, it needs 25% (w/v) pluronics and 30% (w/v) CAP, respectively, to from stiff gel upon instillation in the eye. As the concentration of carbopol increases in the vehicle, its acidic nature may cause stimulation to the eye tissue[19, 20, 23]. The present study aim was to develop the in-situ gelling ophthalmic delivery system of ciprofloxacin hydrochloride, a second-generation fluoro quinoline derivative used in external infections of eye such as acute and sub acute conjunctivitis, bacterial keratitis and keratoconjunctivitis [1, 2, 9].

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MATERIALS AND METHODS

Materials:

Ciprofloxacin Hcl was obtained from Smruthi Organics Pvt ltd, Solapur. Carbopol 940 and Hydroxypropylmethyalcellulose were obtained from Orchid Pharmaceutical Ltd, Chennai. Pluronic F-127 was obtained form sigma labs Pvt ltd. Mumbai, India. Sodium chloride, sodium hydrogen carbonate, calcium chloride dihydrate and sodium hydroxide pellets were purchased from E. Merck Ltd, Mumbai, India.

Estimation of Ciprofloxacin hydrochloride using spectrophotometer method:

Simple, easy and reproducible method for estimation of ciprofloxacin hydrochloride was developed in simulated artificial tear fluid of pH 7.4 buffer. However official method available for ciprofloxacin hydrochloride in 0.1N Hcl showing the l max at 278 nm Beers range of

2-20 mcg/ml. Ciprofloxacin hydrochloride in stimulated artificial tear fluid of pH 7.4 shows l max at 272 nm in a beer's range of 5-40 mcg/ml[1].

Preparation of formulation

P^H-triggered system:

Aqueous solution of varying concentration of carbopol 940 and Hydroxypropylmethyalcellulose of different grades formulation code (Hcl, Hc2 —— Hc7) were prepare and evaluated for gelling capacity and viscosity in order to identify the composition suitable for use as in-situ gelling system. The gelling capacity was determined by placing a drop of the system in a vial containing 2ml of artificial tear fluid freshly prepared and equilibrated at 37°c and visually assessing the gel formulation and noting the time for gelation and the time taken for the gel formed to dissolve. The composition of artificial tear fluid used was sodium chloride 0.670g, Sodium bicarbonate0.200g, calcium chloride2H_2O 0.008g, Purified water q.s 100.0g. The viscosity was measured using a brook field's synochroelectric viscometer (RVT model) in the small volume adaptor. The viscosity measured at 20 rpm used for purposes of comparative evaluation[17, 24].

Formulation 1(F1)

The detailed procedure for preparing the in-situ gel forming system of Ciprofloxacin hydrochloride by pH-triggered system is outlined below (Table 1). The buffer salts were dissolved in 75ml of purified water, methocel E-50lv was added and allowed to hydrate, carbopol was sprinkled over this solution and allowed to hydrate overnight. The solution was stirred with an overhead stirrer, Ciprofloxacin Hcl was dissolved in small quantity of water, benzylkonium chloride (BKC) was added to this solution, the drug solution was added to the polymer solution was obtained. Purified water was then added to make up the volume to 100ml of this solution was filtered through 0-2mm filter paper. When the drug solution and polymer solution were mixed, immediate precipitation of carbopol occurred due to decrease in pH brought about by carbopol. Therefore the drug was incorporated in a sufficient quantity of 0.5M NaoH and then added to the polymer solution to get a clear solution of drug and polymer.

Temperature dependent system:

These hydro gels are liquid at room temperature (20-25°c) and undergo gelation when in contact with body fluids (35-37°c), due to an increase in temperature. Pluronic are the most commonly used thermal setting polymers in ophthalmology. They are formed by a central hydrophobic part (poly oxy propylene) surrounded by hydrophilic part (ethylene oxide)[25]. Pluronic F-127 gives colorless and transparent gels [18]. Sol to gel phase transition after an increase in temperature, including the gradual desolvation of the polymer, increased entanglement of polymeric network and also intra molecular hydrogen bonds might promote gelation[15].

1.5 gm of HPMC was dispersed in 12 beakers each containing 100 m of purified water and these solutions are stirred for 1 hour. After stirring different concentration of Pluronic F-127 ranging form 3 to 17 was dispersed in the HPMC solutions, these solutions were stirred for 1 hour. The partially dissolved Pluronic solutions were stored in the refrigerator until the entire polymer was completely dissolved (approximately 24 hours). These polymer solutions of different concentrations of HPMC and Pluronic F-127 were evaluated for gelling capacity and viscosity in order to identify optimum concentration suitable for use as in-situ gelling system by using Brook Field Viscometer (Model D-III + programmable Rheometer). A concentration of 15% of Pluronic and HPMC E50 LV was selected as it had satisfactory attributes of viscosity and gelling capacity.[27, 15]

Formulation 2(F2)

1.5 gm of HPMC was dispersed in 75 ml of purified water with continuous stirring for 1 hr, after stirring 15 gms of pluronic F-127 was dispersed in the HPMC solutions, this solution was stirred for 1hr. The partially dissolved pluronic solutions were stored in the refrigerator until the entire polymer was completely dissolved (approximately 24 hr). 300 mg of Ciprofloxacin hydrochloride and benzalkonium chloride were dissolved in small quantity of water, this solution was added to the polymer solution under constant stirring until a uniform solution was formed. Then purified water was added to make up the volume to 100ml. This solution was filtered through 0.2mm filter paper.

Ion activated system:

Gellan gum is an anionic exocellular polysaccharide which is water soluble, and undergoes cation-induced gelation, Gellan gum commercially available as Gelrite. The sol-gel transition process is induced by the presence of monovalent or divalent ions such as Na^+ and Ca^+,some other parameters influence the phase transition such as the concentration of polysaccharide, the temperature of the preparation, and the nature and the concentration of cations. Gelrite was selected for preparation of in-situ gel [6, 22].

Formulation 3(F3)

0.6 gms of Gelrite were dissolved in a beaker containing purified water, and this solution was heated about 85°C for 15 min, then beaker was cooled with stirring. After cooling benzalkonium chloride and drug solution were added to the polymer solution and volume was made up to 100 ml and this solution was filtered through 0.2mm filter paper.

Formulation ingredients of formulation F1, F2 and F3 are represented in table 1

Sterility studies:

The test for sterility is an important aspect for ophthalmic preparations. The test for sterility is intended for detecting the presence of viable forms of bacteria, fungi and yeast in or on sterilized preparations. The test must be carried out under conditions designed to avoid

Table 1: formulation ingredients of F1, F2 and F3

S. No.	Name of the ingredient Quantity (gm)	F1	F2	F 3
1	Ciprofloxacin hydrochloride	0.3	0.3	0.3
2	Carbopol 940	0.3	-	-
3	Pluronic F-127	-	15	-
4	Gelrite	-	-	0.6
5	Hydroxy propyl methyl cellulose	1.5	1.5	-
6	Citric acid IP	0.407	-	-
7	Disodium hydrogen phosphate IP	1.125	-	-
8	Benzalkonium chloride (BKC)	0.02	0.02	0.02
9	Purified water	100ml	100ml	100ml

Values are in grams

Table 2: Preliminary evaluation studies of In-Situ gel formulations

TESTS	F1	F2	F3
Visual appearance	Transparent	Transparent	Transparent
Clarity	Clear	Clear	Clear
pH	6.4	7.02	7.10
Drug content	98.6 %	99.3 %	99.1 %

Table 3: Comparison of antimicrobial activity of standard and formulations (*S.aureus*)

Conc. (µg/ml)	Standard Zone of inhibition (cm)	Tests Zone of inhibition (cm)		
		F1	F2	F3
20	2.5	2.3	2.5	2.5
40	3.0	2.7	3.0	2.7
60	3.2	3.0	3.1	3.1
80	3.4	3.3	3.3	3.3
100	3.8	3.7	3.8	3.5

Table 4: Comparison of antimicrobial activity of standard and formulations (*P.aeruginosa*)

Conc. (µg/ml)	Standard Zone of inhibition (Cm)	Tests Zone of inhibition (Cm)		
		F1	F2	F3
20	2.4	2.2	2.4	2.4
40	2.9	2.7	2.7	2.8
60	3.3	3.2	3.2	3.2
80	3.6	3.3	3.5	3.5
100	3.9	3.8	3.8	3.7

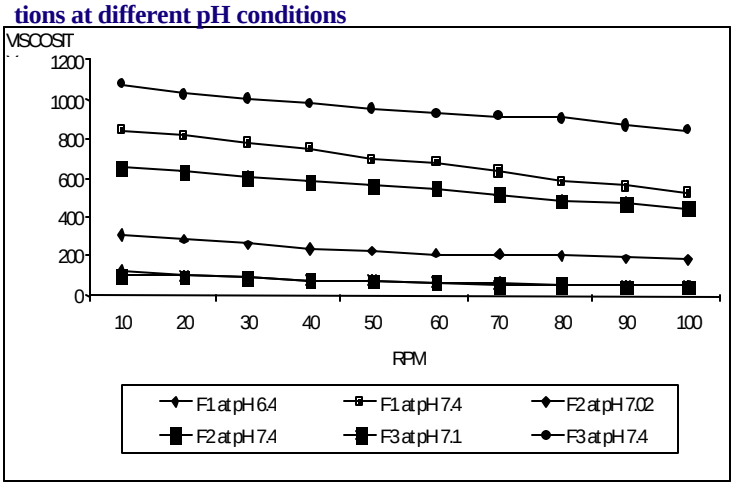
Table 5: Stability studies of Ciprofloxacin Hcl In-situ gels (F1, F2 & F3) room temperature

S. No.	No. of Weeks	% Drug remaining		
		F1	F2	F3
1	0	99.89	99.92	99.98
2	1	99.76	99.90	99.95
3	2	99.68	99.86	99.92
4	3	99.56	99.82	99.90
5	4	99.10	99.76	99.88
6	5	98.85	99.70	99.80
7	6	98.82	99.68	99.78
8	7	98.79	99.61	99.72

Table No. 6: Stability studies of Ciprofloxacin Hcl In-situ gels (F1, F2 & F3) at 40°C

S. No.	No. of Weeks	% Drug remaining		
		F1	F2	F3
1	0	99.89	99.92	99.97
2	1	99.76	99.90	99.94
3	2	99.72	99.80	99.90
4	3	99.68	99.75	99.89
5	4	99.65	99.72	99.86
6	5	98.60	99.70	99.84
7	6	98.58	99.65	99.70
8	7	98.49	99.41	99.67

Figure 1: Comparative rheological properties of in-gel formulations at different pH conditions



Values are in CPs

Figure 2: Comparative *In-Vitro* release profile of pure drug and in-situ gel formulation

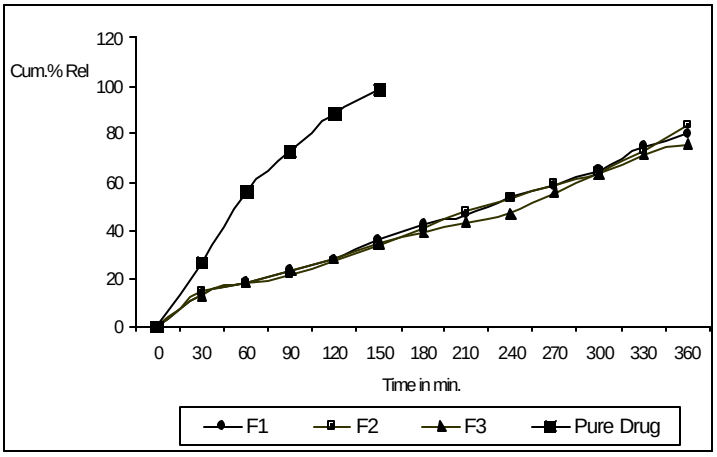
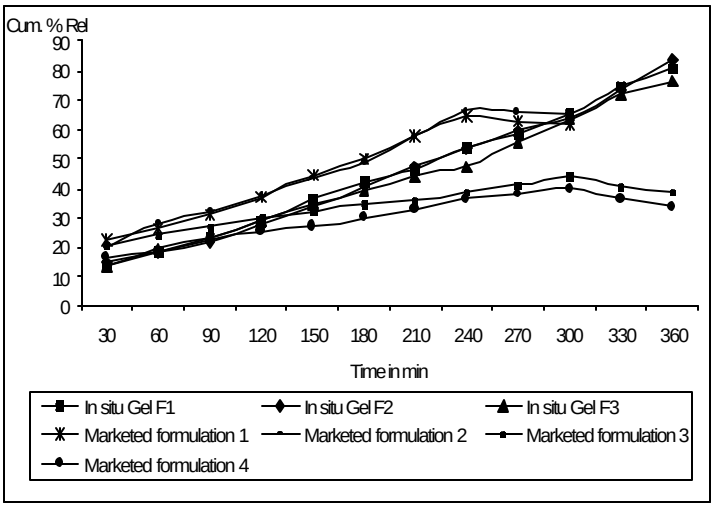


Figure 3: Comparative *In-Vitro* release profile of In-Situ gel formulations and marketed preparations



accidental contamination of the product during the test.

Rheological studies:

The rheological properties of solutions and gels were measured using a Brookfield synchroelectric viscometer. The developed formulation was poured into the small adaptor of the brook field synchroelectric viscometer and the angular velocity increased gradually from 10 to 100 rpm. The hierarchy of the angular velocity was reversed. The average of the two reading was used to calculate the viscosity. The formulation was then poured into an ointment jar and the pH rise to 7.4 by adding simulated lachrymal fluid [11, 12].

In-Vitro release studies of Ciprofloxacin Hydrochloride *In-Situ* gels:

The in-vitro release of Ciprofloxacin hydrochloride from the prepared formulations was studied through cellophane membrane using a modified USP XXIII dissolution testing apparatus[10].

The dissolution medium used was artificial tear fluid freshly prepared of pH 7.4.buffer Cellophane membrane previously soaked over night in the dissolution medium was tied to one end of a specifically designed glass cylinder (open at both ends of 5 cm diameter) a 2 ml volume of the formulation was accurately pipetted in to this assembly. The cylinder was attached to the metallic drive shaft and suspended in 100 ml of dissolution medium maintained at 37±1°c so that the membrane just touched the receptor medium surface. The shaft was rotated at 50-rpm aliquots each of 1 ml volume, were with drawn at hourly intervals and replaced by an equal volumes of the receptor medium. The aliquots were diluted with receptor medium and absorbance was measured at 272 nm[10].

Anti microbial efficacy studies:

This was determined by the agar diffusion test employing "cup plate technique". Sterile solutions of Ciprofloxacin hydrochloride (standard solution) and the developed formulations were diluted at different concentration (test solutions) these solutions were poured in to cups bored into sterile nutrient agar previously seeded with test organisms (Pseudomonas aeruginosa and Staphylococcus aureus). After allowing diffusion of the solutions for 2 hours, the agar plates were incubated at 37°C for 24hrs. The zone of inhibition (ZOI) measured around each cup was compared with that of control. The entire operation except the incubation was carried out in a laminar airflow unit. Both positive and negative controls were maintained the study[9].

Accelerated stability studies:

Accelerated temperature stability studies, are generally conducted at 40^0 C, 50^0 C and 60^0 C, as well as at room temperature and freezing temperature. The samples were stored at different storage conditions of elevated temperature such as 40°c and room temperature at RH of 75%. The samples were withdrawn at weekly intervals and estimated for the drug content spectrophotometerically at 272 nm using UV-visible spectrophotometer under fluorescent light.

Comparative evaluation of *In-Vitro* drug release from marketed preparations with *In-Situ* gel formulations

In-situ gels of different formulations and marketed products of eye drops and eye ointments were taken for the preliminary studies and in-vitro release studies. Using modified dissolution testing apparatus did the in-vitro release study. The release study performed using 100 ml of pH 7.4 buffer (simulated artificial tear fluid). All the selected formulations were subjected to preliminary evaluation studies, such as visual appearance, clarity, pH, and drug content.

RESULTS AND DISCUSSION

The developed formulations were evaluated for visual appearance, pH and drug content by UV spectrophotometer at 272 nm, clarity by visual observation against a black and white back ground, pH (Digital pH meter), sol- gel transition, sterility, In-vivo release studies, antimicrobial studies and accelerated stability studies and sterility. The obtained results of preliminary evaluation studies are represented in table 2.

Rheological Studies

The two main prerequisites of an in-situ gelling system are viscosity and gelling capacity. Viscoelastic fluid with a viscosity that is high under conditions of low shear rate and low under conditions of high shear rates are preferred. In order to evaluate the rheological behavior viscosity of the formulation before and after addition of simulated lacrimal fluid was evaluated using Brookfield rheometer using increased shear stress by varying the angular velocities. All the selected formulations were shear thinning exhibiting pseudoplastic behavior. All the formulations were liquid at room temperature and underwent rapid gelation upon raising the pH to 7.4 with gelrite formulation showing the optimum variation in viscosity. The Comparative rheological properties of in situ-gel formulations at different pH conditions results are shown in figure 1.

In-vitro release studies

The *in-vitro* release studies were carried out for pure drug Ciprofloxacin hydrochloride and the formulations i.e. (F1, F2 & F3). The studies were carried out by using modified USP XXIII Dissolution apparatus pH 7.4 simulated artificial tear fluid as a medium, for a period of 6 hours at rpm 50 and 37^0 C ± 2^0 C. Samples were withdrawn at the interval of 30 min. The release profile obtained is shown in fig 2 & 3

Antimicrobial studies

Antimicrobial efficacy studies were determined by the agar diffusion test employing “cup plate technique”. Sterile solutions of standard Ciprofloxacin hydrochloride and the in-situ gels of different formulations were (F1, F2, & F3) poured into cups bored into sterile nutrient agar. These formulations are diluted at different concentration (20, 40, 60, 80 & 100) and the test organisms used were (Pseudomonas aeruginosa and Staphylococcus aureus). The zones of inhibition of standard and prepared formulations were found to be similar. The results of the antimicrobial efficacy tests are represented in table 3 & 4.The present study results indicate that Ciprofloxacin hydrochloride retained its antimicrobial efficacy when formulated as an in-situ gelling system.

Accelerated stability studies

Short-term stability studies were carried out for sterilized, packed formulations (F1, F2 & F3) for 45 days, stability studies were carried out as per ICH guidelines at RT and 40^0C ± 2^0C and at 75% RH. Samples were withdrawn at 7 days intervals and analyzed for visual appearance, clarity, pH and drug content. The results are shown in table 5 & 6 respectively. The stability data at the end of the 7 weeks revealed that all the formulation was found to be stable and efficacious.

CONCLUSION

Ciprofloxacin Hcl, a broad spectrum antibacterial against in the treatment of ocular infections, was successfully formulated as pH-triggered in-situ gel forming eye drops (0.3% w/v) using carbopol 940 and methocel E50LV, temperature dependent in-situ gel forming eye drops (0.3% w/v) using pluronic F-127 and methocel E50LV and ion activated in-situ gel forming eye drops (0.3% w/v) using gelrite as gelling agent. The formulations were liquid at the formulated pH use between of (6.4 to 7.1) and underwent rapid gelation up on raising the pH (7.4) and temperature (37^oC). The developed formulation was therapeutically efficacious, stable, non irritant and provided sustained release of the drug over a 6 hours period, but Gelrite formulation showing long duration of release followed by combination of carbopol, HPMC and pluronic F-127 & HPMC. The developed formulations are viable alternative to conventional eye drops by virtue of its stability to enhance bioavailability through its longer precorneal residence time and ability to sustain dug release. Also important is the ease of administration afforded and decreased frequency of administration resulting in better patient acceptance.

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