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Smart drug delivery systems: Thermo - p^H responsive ciprofloxacin ophthalmic gels

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ABSTRACT

In the present study Thermo and P^H responsive smart polymers were utilized to overcome the problems encountered for the ophthalmic formulation which normally get drained,short ocular residence once instilled by formulating the smart ophthalmic gels that shows Newtanion flow easy to administer the same get transformed in to gel on contact with eye site due to lachrymal P^H and physiologic temperature. With such a systems one can increase the contact time of the drug with the localised site and increase bioavailabity which is normally desired for the treatment of ocular infection with ciprofloxacin Hcl.. The prepared formulations where passed all the Physico-Chemical examinations and sterility test and results illustrates that with increase in the polymer concentration increases the viscosity and decreases the drug release. Formulation F3 compounded with Polyacrylic Acid (Carbopol 934) 0.3% and Pluronic F 127 (PF 127) 12% was considered to be the best amongst all the five with 94.5% drug release upon 8^{th} hour diffusion study, 60.5 Cps non-physiologic, 100.2 Cps physiologic condition viscosity respectively and 99.35% drug content with no chemical interaction as per FT-IR spectra.

Key words: Smart polymers, Ocular infection, Drug release ,Viscosity FT-IR study, sterility test.

INTRODUCTION

The most essential field of the health care is drug delivery. Extended lifespan and suffering of patients treated with effective drug delivery system.

In the past few decades, the drug delivery field has grown exponentially. With US market for advance DDS is about $121 billion in 2010.[1]

The reason behind it,the average cost approximately $20–50 million and time is 3–4 years which is sinificntly lower than new drug drug (approximately $500 million and over 10years).

Tremendous research in DDS advent to Stimuli-responsive polymers which shows a sharp change in properties upon a small or modest change in environmental condition,e.g. temperature, light, salt concentration or P^H. This behaviour can be utilised for the preparation of so-called Intelligent or 'smart' drug delivery systems.[2]

Smart DDS are one which is able to release, at the appropriate time and site of action, the entrapped drugs in response to specific physiological triggers.[3]

Hydrogels represent a DDS class that has excelled at smart drug delivery. Hydrogels are high-water content materials prepared from cross-linked polymers that are able to provide sustained, local delivery of a variety of therapeutic agents.[4]

Tear volume is 10-30 µl, therefore application of two drops equal to 100 µl of the preparation, results in expelling more than 70% of the dose from the eye by overflow if drug is instilled by conventional dosage in Eye-drops forms.

The poor bioavailability and less therapeutic response of conventional eye drops occurs mainly due to the gravity induced lacrimal flow and normal tear turnover of the eye.[5]

Ophthalmic drug deliver is one of the foremost attractive and challenging field for the formulator.[6]

Therefore the objective of the present research is to develop smart drug delivery systems of ciprofloxacin HCl a second generation fluroquinolone derivatives used in the ocular infection such as acute conjunctivitis.

The Physico-Chemical behaviour underlying the phase transition of Thermo and P^H responsive polymers will be discussed.

MATERIALS AND METHODS

Materials

Ciprofloxacin Hcl was obtained as gift Sample from Riyadh Pharma, Riyadh, Polyacrylic Acid (Carbopol 934) Purchased from Loba Chemicals India, Pluronic F 127 (PF 127) was received from Drug Delivery Research Lab SAU.

All the other chemicals, including sodium chloride, sodium hydrogen carbonate, calcium chloride and sodium hydroxide pellets were purchased from Loba Chemicals India and were used as received.

Methods

Table:- 1 Composition of Thermo - P^H Responsive Ciprofloxacin Ophthalmic Gels

COMPONENTS % W/V	FORMULATION CODE				
	F1	F2	F3	F4	F5
Ciprofloxacin HCl	0.3	0.3	0.3	0.3	0.3
Polyacrylic Acid (Carbopol 934)	0.1	0.2	0.3	0.4	0.5
Pluronic F 127 (PF 127)	4	8	12	16	20
NaCl	0.9	0.9	0.9	0.9	0.9
Benzalkonium chloride	0.01	0.01	0.01	0.01	0.01
Acetate Buffer P^H 4 Upto	100	100	100	100	100

Preparation of Thermo - P^H Responsive Ciprofloxacin Ophthalmic Gels:

The drug loaded polymeric solution were prepared by dissolving the desired concentration of drug and Poly acrylic Acid - Carbopol 934, NaCl, Benzalkonium chloride in the sufficient amount of distilled, deionised water with continuous stirring on a magnetic stirrer until homogenous solution is formed.

Then required concentration of Pluronic F -127 is dissolved in ice cold distilled, deionised water, separately and placing the mixture in refrigerator and agitating periodically to ensure complete dissolution.[7]

Ciprofloxacin Hcl Smart formulations were prepared under aseptic conditions by dissolving each of these polymeric dispersion in acetate buffer P^H 4 and final volume is made upto 100 ml as per the Table-1 with continuous stirring until thoroughly mixed.

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.[8]

Gelling Capacity

The gelling capacity of the prepared formulation was determined by placing a drop of the formulation in a vial containing 2 ml of freshly prepared phosphate buffer P^H 7.4 and visually observed. The time taken for its gelling was noted.[9]

Drug content assay

The drug content of in smart gel was determined by taking sample (2ml) volumetric flask and diluted with simulated tear fluid of pH 7.4 upto 100 ml Then the absorbance was measured at max (254 nm) using Jasco V-630 spectrophotometer to calculate the percentage of drug content.[10]

***In-vitro* release studies**

The apparatus consists of a cylindrical glass tube (with 22 mm internal diameter and 76 mm height), which was opened at both the ends. One 1 ml of formulation containing 0.3 mg of ciprofloxacin Hcl was spread uniformly in the surface of cellophane membrane previously soaked for 1 day in STF fluid in donor compartment and acceptor compartment filled with 50 mL simulated tear fluid (STF, composition: NaCl 0.67g, $NaHCO_3$ 0.20g, $CaCl_2 \cdot 2H_2O$ 0.008g, and distilled, deionized water to 100g) , temperature maintained was 37±2 ^{0}C with continuous stirring at 22 Rpm.. A quantity of 1 ml samples were withdrawn upto 8 hour with an hourly frequency the same amount is replaced with STF each time.

The released drug was estimated by using Jasco V-630 spectrophotometer at 254 nm.

Determination of Viscosity

The viscosity of formulated smart gels were determined. The viscosity was determined using a Brookfield Viscometer DV-I Prime. The sample holder taken for the viscosity measurement was filled with the samples and then inserted into a flow jacket mounted on the viscometer. The samples adaptor (spindle), rotated at an optimum speed was used to measure the viscosity of the preparation, the samples was allowed to settle for five minutes prior to taking the readings.

Sterility Testing

Sterility testing was performed for aerobic and anaerobic bacteria and fungi by using fluid thioglycolate incubation at 32°C and soybean casein digest medium incubation at 25°C respectively as per the Indian Pharmacopoeia. The method used for sterility testing was direct inoculation method.10 ml culture was added to 100 ml of culture medium. Both media were kept for incubation at for 14 days and observed for any microbial growth.[11]

Drug-Polymer Interaction Studies (Infrared Spectroscopy)

The infrared spectra (IR) of Ciprofloxacin HCl , Polyacrylic Acid (Carbopol 934) and , Pluronic F 127 (PF 127) and optimized F 3 Formulation was obtained using FTIR (Perkin-Elenmeyer 1600 Series).[12]

RESULTS AND DISCUSSION

Five batches of formulation designed and prepared as per the procedure discussed in composition of Table no-1.

TABLE:- 2: Physico-Chemical examination of Thermo - P^H Responsive Ciprofloxacin Ophthalmic Gels

Formulation code	Visual appearance	Clarity	Gelling capacity	% Drug content
F1	Light yellow	Clear	+	98.56
F2	Light yellow	Clear	++	97.88
F3	Light yellow	Clear	+++	99.35
F4	Light yellow	Clear	+++	97.18
F5	Light yellow	Cloudy	+++	97.25

NOTE: ++ indicates gelation is immediate and remains for few hours, +++ indicates gelation is immediate and remains for extended period

Visual Appearance and Clarity examination

visual appearance and clarity was light yellow and clear for all formulations respectively**.**

Gelling capacity

The viscosity and gelling capacity plays important role for in smart gels.The formulation should have an newtanion flow for easy instillation into the eye as a liquid which undergo sol-to-gel transition upon contact with physiological condition of the eye . All formulations were evaluated for the *in vitro* gelation capacity all formulation shown the immediate gelation with extended capability except formulation F1 as per the Table -2.

Drug content assay

The drug content of all the formulations was within the range of 97.25 % to 99.35% as shown in Table No:-2, with uniform distribution of ciprofloxacin HCl in the smart ophthalmic formulations .

***In vitro* Release Studies**

Ciprofloxacin HCl, Release profile was shown in Figure -1,graph was plotted cumulative % Ciprofloxacin HCl. against Time (Hr). The comparative drug release gave an idea that F3 formulation containing 0.3 % Polyacrylic Acid (Carbopol 934) and Pluronic F 127 (PF 127) provides a sustained drug release upto 94.5 % over an 8th hour period with better ability to retain the drug amongst all the smart ophthalmic gels.

It is also observed that as the concentration of polymers increased the release of drug get decreased that was due formation of three dimensions network formed by cross linking of polymers by hydrogen bonds between ether group of carboxyl group of Polyacrylic Acid (Carbopol 934) and , Pluronic F 127 (PF 127) in presence of water.

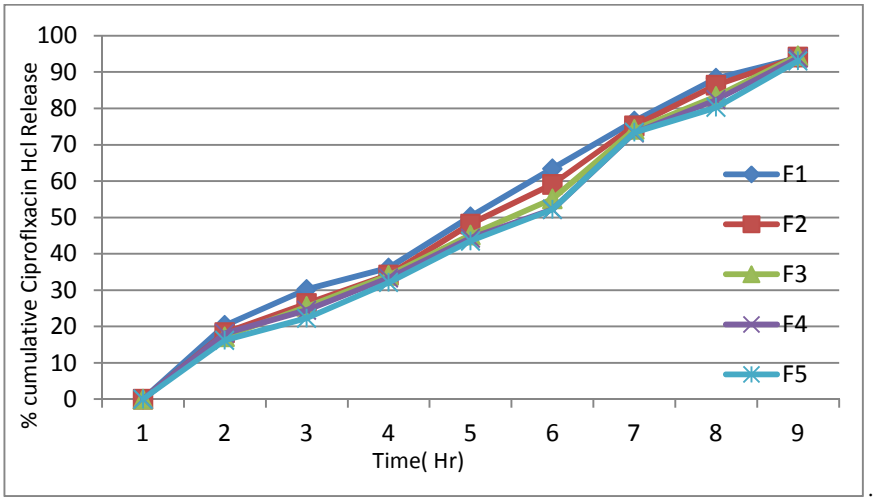

Figure:-1. *In vitro* Release Studies of Thermo - P^H Responsive Ciprofloxacin Ophthalmic Gels

Determination of Viscosity

The rheological behavior of the smart ophthalmic gels was studied in two conditions: in the Physiologic (37°C and P^H 7.4) and Non-Physiologic (25°C and P^H 4) conditions. An ideal gel should show a Newtonian flow with 10.3 Cps to 150.5 Cps in non-physiological condition while, pseudoplastic properties viscosity ranges from 20.2 Cps to 280.2 Cps at physiological conditions. In order to simulate the physiological disposition of gels more literally, the polymer solutions were diluted by simulated tear fluid (STF) in a ratio of 40:7 simulated tear fluid and then adjusted to physiological PH value (7.4 ± 0.1) by adding the required amount of sodium hydroxide before the rheological studies were conducted at 37 ± 0.1 °C.

However, at, physiologic conditions the shear stress of carbopol & pluronic solution was significantly greater than that of non-physiologic conditions. This observation can be explained by the formation of crosslinks between the two polymers, that is, the water molecules may act as a crosslinking agent to form hydrogen bonds between the carboxyl groups of Polyacrylic Acid (Carbopol 934) and ether groups of Pluronic F 127 (PF 127) ,which may lead to the formation of three-dimensional network and stronger gel. Results were tabulated in Table No:-3.

TABLE:- 3: Viscosity of Thermo - P^H Responsive Ciprofloxacin Ophthalmic Gels

Rheological studies Viscosity (Cps)	Stimulus & Conditions	FORMULATION CODE				
		F1	F2	F3	F4	F5
	In P^H 4 at 25°C Nonphysiological	10.3	28.3	60.5	100.52	150.5
	In P^H 7.4 at 37°C physiological	20.2	50.2	100.2	180.2	280.2

Sterility Testing

Sterility test passes as there is no growth or presence of microorganisms observed after the prescribed incubation period.

Drug Polymer Interactions

The FT-IR spectra of ciprofloxacin, polymers individually and selected F3 smart ophthalmic gels are depicted in Figure:–2, revealed that there was no significant modification in the functional group peaks in the spectrum of drug polymer mixture. Hence, no chemical interaction was observed between the drug and the polymers used in the formulation.

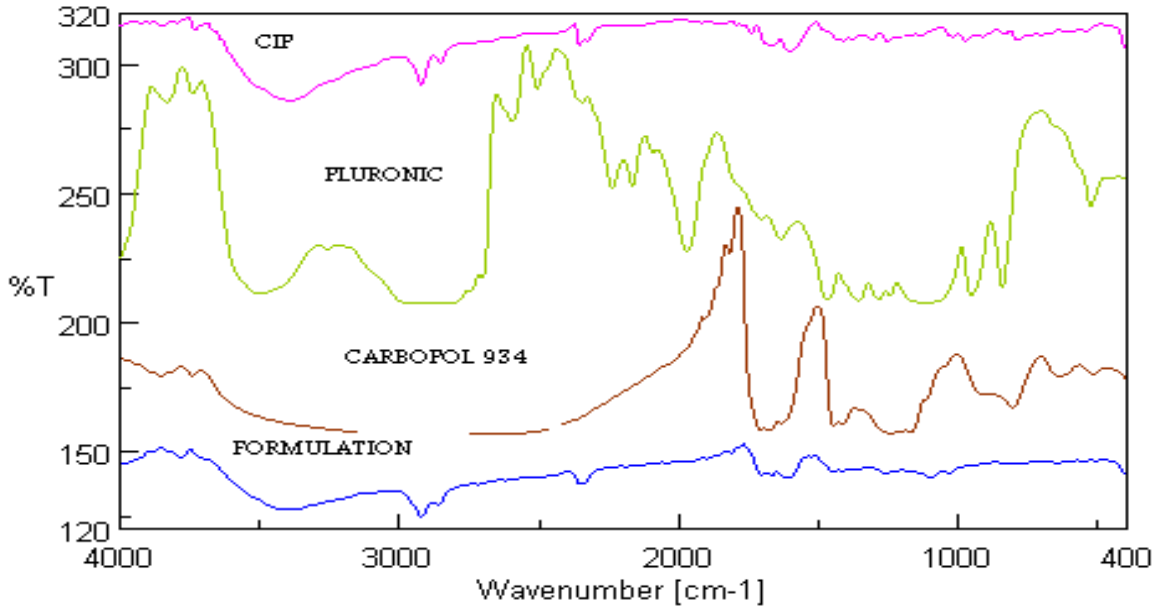

Figure:-2. FT-IR spectra of (CIP) ciprofloxacin, polymers and formulation (F3) smart ophthalmic gels

CONCLUSION

Thermo and P^H responsive polymers Pluronic F-127(PF 127) in 0.3% and Polyacrylic Acid (Carbopol 934) 12% concentrations was optimized for the preparation of smart drug delivery systems of ciprofloxacin which is solution during storage and handling ,the same is transformed to gel on ophthalmic application and hence controlled the release at local site.

Increase in the concentration of stimuli responsive polymers leads to increase in viscosity and decrease in drug release.

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