INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com ISSN 2230 – 8407

Research Article

FORMULATION AND ASSESSMENT OF GEMIFLOXACIN MESYLATE OCULAR *IN SITU* GELLING SYSTEM

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Article Received on: 12/08/13 Revised on: 01/09/13 Approved for publication: 10/10/13

DOI: 10.7897/2230-8407.041009

IRJP is an official publication of Moksha Publishing House. Website: www.mokshaph.com

ABSTRACT

In situ gels are one of the most successful means of delivering the drug at ocular site with maximum bioavailability, which undergoes gelation upon instillation as drops into the eye due to physicochemical changes inherent to the biological fluids. The main aim of the present investigation was to obtain an ophthalmic drug delivery system with improved mucoadhesive and mechanical properties that could provide extended retention time for the treatment of ocular infections. For this *in situ* gels of Gemifloxacin Mesylate comprised of the combination of a thermosetting polymer, polaxamer with a mucoadhesive agent chitosan was developed. Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry techniques (DSC) were performed to know the compatibilities between drug and polymer. FTIR spectra and DSC thermograph of Gemifloxacin Mesylate formulations showed that there is no chemical interaction between drug and polymer and confirmed the stability of the drug. The gels were evaluated for pH, Gel strength, Gelling capacity, Rheology, Drug content uniformity and Ocular irritancy studies. *In vitro* drug release studies reveal that all the formulations showed sustained release of the drug in the range of 70.82 to 76.43 % for a period of 8 h. The optimized formulation was tested for ocular irritation study on male albino rabbit and the result indicated that the formulation was well tolerated, non-irritating and therapeutically efficacious. In conclusion *in situ* gelling systems containing polaxamer / chitosan solution are viable alternative to enhance bioavailability thus leads to an excellent potential alternative ophthalmic sustained-release formulation of Gemifloxacin Mesylate in ocular infections.

Keywords: Gemifloxacin Mesylate, *In situ* gels, Ocular irritancy studies, *In vitro* drug release.

INTRODUCTION

Gemifloxacin Mesylate is a new fluoroquinolone antibacterial agent with a broad spectrum of activity. It is a fourth generation fluoroquinolone, has high potency against Gram-positive, Gram-negative bacteria and its bactericidal activity is through inhibition of bacterial topoisomerase II and IV enzymes which are critical in the maintenance, synthesis and replication of DNA. Gemifloxacin mesylate showed good *in vivo* activity in a model of infective keratitis due to *St. aureus,* in comparision to all third generation fluoroquinolones[1]. It is freely soluble in water. Bioavailability is approximately 71 %. The half-life of drug is low that is 7 h. The purpose of the present investigation is to develop a sustained release, ophthalmic delivery system of Gemifloxacin Mesylate with more residence time in the eye which leads to improvement of bioavailability, patient compliance and to reduce the frequency of administration. The conventional liquid ophthalmic formulations are washed out from the precorneal area immediately upon instillation because of constant lacrimal secretion, nasolacrimal drainage and short precorneal residence time of the solution[2]. Narrow permeability of the cornea contributes to the low absorption of ocular drugs. Rapid elimination of the eye drops administered often results in a short duration of the therapeutic effect making a frequent dosing regimen necessary. As a result, frequent instillation of solution or higher drug concentration is needed to achieve the desired therapeutic response[3,4]. Due to tear drainage, most of the administered dose is absorbed via the naso-lacrimal duct to the GI tract, leading to side-effects[5]. Major advancement to overcome these disadvantages has been made by the development of *in situ*-forming gels. These systems consist of polymers that exhibit sol-to-gel phase transitions as a result of specific physical / chemical change induced by the physiological environment in the cul-de-sac as pH, temperature or a specific ion[6]. Such a system can be formulated as a liquid dosage form suitable to be administered by instillation into the eye, which upon exposure to physiological conditions of eye shifts to the gel phase, thus leads to increasing the pre-corneal residence time of the delivery system and enhancing ocular bioavailability. Polaxamer is non-ionic surface active agent, and block copolymers consisting of polyethylene oxide and polypropylene oxide units. Their relatively low toxicity and capacity to form clear gels make them particularly suitable for dermatological or ophthalmic formulations as well as in the area of controlled drug delivery systems and it is known for exhibiting the phenomenon of reverse thermal gelation under a certain concentration and temperature[7-9]. Though thermo sensitive copolymers are employed widely, they suffer from a major drawback of having weak mechanical strength, which leads to rapid erosion of polymer[10]. This problem can be solved by using blends of poloxamers with chitosan[11]. Chitosan, a natural polysaccharide derived from naturally abundant chitin, having excellent ocular compatibility[12-14]. Chitosan is a polycation on interacting with the polyanionic surface of mucosal surface of cornea it enhances the mucoadhesive properties. Gupta *et al*[15], developed timolol maleate isotonic solution base using chitosan / polaxamer that converted into gel at temperatures above 35°C and pH 6.9-7.0.

MATERIALS AND METHODS

Gemifloxacin mesylate sample was supplied by Kwality pharmaceuticals pvt.ltd. Polaxamer 188, Chitosan were obtained from Brass chemicals (Tirupathi). Other chemicals used were of analytical grade.

Preparation of Polaxamer-Chitosan Ophthalmic Gels

Polaxamer-chitosan *in situ*-gels, were prepared using the cold method[5,16]. The chitosan solutions (0.25 – 1 % w/w), were prepared by dispersing the required amount of polymer in acetic acid solution (2 % w/v) with continuous stirring until it is completely dissolved. For preparation of Polaxamer

solutions (12-15 % w/w), the required amount of polaxamer was dispersed in distilled water with continuous stirring for 1 h at room temperature. The partially dissolved Polaxamer solutions were stored in the refrigerator for 24 h (at 4ºC) until the entire polymer was completely dissolved. The chitosan / Polaxamer solutions were prepared by dispersing the required amount of Polaxamer in the desired concentration of chitosan with continuous stirring for 1 h. The partially dissolved solutions were then refrigerated for 24 h until solutions were completely mixed. For preparation of Gemifloxacin Mesylate containing polymer solutions, 0.15 % of Gemifloxacin Mesylate was added to the chitosan / Polaxamer solutions with continuous stirring until thoroughly mixed. Benzalkonium chloride solution (0.006 %) was added as preservative in all solutions. The pH of all formulations was adjusted to 7.4 ± 0.1 by 0.1 N NaOH. All formulations were kept at 4°C until further use. The composition of *in situ* gel of Gemifloxacin Mesylate was given in (Table 1).

Evaluation Parameters

The prepared *in situ* gel formulations were evaluated for pH measurement, Gel strength, Gelling capacity, Drug content, Rheological study, *In vitro* diffusion study, Antibacterial activity and ocular irritancy testing in rabbits. The results were shown in Table 2.

pH

pH is one of the most important parameter involved in the ophthalmic formulation. The developed formulations were evaluated for pH by using Elico India Systronics digital pH meter.[17]

Gel Strength

Gel strength is calculated using the gel strength apparatus. It contains two tubes; upper tube is attached with pan through thread in which weights are added. Two surfaces are tightly covered with egg membrane. 1 g of gel was kept between two surfaces detach is noted and the gel strength is calculated by using formula;

Gel strength = Mg / a

Where, M - Weight at which the two surfaces detaches

g - Gravitational force

a - Area of surfaces

Gelling Capacity

The gelling capacity of the prepared formulation is determined by placing a drop of the formulation in a vial containing 2 ml of freshly prepared simulated tear fluid and visually observed. The time taken for gelling is noted.[18]

Rheological Studies

The viscosity measurements can be calculated using Brookfield viscometer. The *in situ* gel formulations were placed in the sampler tube. The samples are analyzed both at room temperature at 25°C and thermo stated at 37°C ± 0.5°C by a circulating bath connected to the viscometer adaptor prior to each measurement. The angular velocity of the spindle was increased from 10 to 100 and the viscosity of the formulation is measured. All the formulations exhibited Newtonian and pseudo plastic flow properties before and after gelling in the simulated tear fluid.[1]

Drug Content

Accurately weighed amount Gemifloxacin mesylate *in situ* gel equivalent to 30 mg of drug was taken in a 100 ml volumetric flask. Simulated Tear Fluid (STF pH 7.4) was added to it and kept on magnetic stirrer to dissolve the drug. The volume was made to 100 ml with STF (pH 7.4) and filtered using Whatmann filter paper (No 42). 10 ml aliquot of the above solution was taken and diluted to 100 ml with STF (pH 7.4). The absorbance of sample solution was determined at 266 nm against STF (pH 7.4) as blank after suitable dilution with STF.[19]

***In-vitro* Drug Release Studies**

In vitro release study of *in situ* gel solution was carried using Franz diffusion cell[20]. The formulation placed in donor compartment and freshly prepared simulated tear fluid in receptor compartment. Between donor and receptor compartment dialysis membrane is placed (0.22 ìm pore size). The whole assembly was placed on the thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37°C ± 0.5°C. 1 ml of sample is withdrawn at predetermined time interval of 1 h for 8 h and same volume of fresh medium is replaced. The withdrawn samples are diluted to 10 ml in a volumetric flask with STF buffer and analyzed by using UV-VIS spectrophotometer.[18]

***In-vitro* Release Kinetics**

The experimental results of the release studies were fitted according to the exponential equation

Zero order release equation:

$$Q = K_0 t \quad \text{----------(1)}$$

First order kinetics

$$Q_t = Q_0 e^{-K1t} \quad \text{----------(2)}$$

Higuchi's square root of time equation

$$Q = K_H t^{1/2} \quad \text{----------(3)}$$

Korse-Meyer Peppas equation

$$F = (M_t/M) = K_m t^n \quad \text{---------- (4)}$$

Hixson–Crowell model

$$W_0^{1/3} - W_t^{1/3} = K_S t \quad \text{----------(5)}$$

Where, Q = Amount of drug release at time t, M_t = drug release at time t, M = total amount of drug in dosage form, F = fraction of drug release at time t, K_0 = zero order release rate constant, Q_t is the amount of drug released in time *t*, Q_0 is the initial amount of drug in the solution and K_1 is the first order release constant. K_H = Higuchi square root of time release rate constant, K_m = constant depend on geometry of dosage form, n = diffusion exponent indicating the mechanism of drug release. w_0 is the initial amount of drug in the pharmaceutical dosage form. w_t is the remaining amount of drug in pharmaceutical dosage form at time t. K_S is a constant incorporating the surface–volume relation.

Sterility Testing

Sterility test was carried out according to IP method (1996). Sterility testing was done by incubating formulations for not less than 14 days at 20 to 25°C in the soyabean-casein digest medium to find the growth of fungi in the formulations.[21]

Antibacterial Activity

Antimicrobial efficiency and prolonged effect of optimized formulation of Gemifloxacin mesylate gel was carried on *Staphylococcus, Bacillus cereaus* strains. The inhibitory effect of Gemifloxacin Mesylate formulation on the studied microorganisms was evaluated using agar diffusion test. Wells were punched into the nutrient agar medium previously seeded with test organisms and wells were filled with 100 µl of the samples. After allowing diffusion of solution for two hour the plates were incubated for 24 h at 37°C and the diameters of inhibition zones were measured. The inhibitory effect of optimized gel formulation was compared with the standard drug solution.[20]

Ocular Irritancy Test

Ocular irritation potential of the *in situ* gels was carried out as per Draize test protocol. The experimental protocol was approved by the institutional animal ethical committee (ref. no: 930/ a/06/CPCSEA). Three rabbits (male) weighing 1.5 to 2 kg was used for the study. According to the Draize test, the amount of substance applied to the eye is normally 100 µl placed into the lower *cul-de-sac* with observation of the various criteria made at a designed required time interval of 1 h, 24 h, 48 h, 72h and 1 week after administration. The sterile formulation is instilled twice a day for a period of 7 days. Rabbits are observed periodically for redness, swelling and watering of the eye.[20]

Table 1: Composition of Various Formulations of Ocular *in situ* Gelling System of Gemifloxacin Mesylate

S. No	Formulation	Composition (%)		
		Gemifloxacin Mesylate	Polaxamer	% Chitosan
1	F1	0.15	12	0.25
2	F2	0.15	12	0.50
3	F3	0.15	12	0.75
4	F4	0.15	12	1.0
5	F5	0.15	15	0.25
6	F6	0.15	15	0.50
7	F7	0.15	15	0.75
8	F8	0.15	15	1.0

Table 2: Evaluation Parameters of Various Formulations of Ocular *in situ* Gels of Gemifloxacin Mesylate

S. No	Formulation	pH	Gelling capacity	Gel strength (Sec)	Viscosity (Pa. s)	% Drug content
1	F1	7.4	+	99	32.2	77.85
2	F2	7.2	+	101	32.8	78.23
3	F3	7.4	++	107	34.4	79.24
4	F4	6.8	+++	110	35.8	81.23
5	F5	7.4	++	112	33.5	85.76
6	F6	7.2	++	114	34.5	84.12
7	F7	6.8	+++	116	36.1	79.65
8	F8	7.4	+++	118	37.5	71.12

\+ Gels after few minutes, dissolves rapidly
++ Gelation occur immediately, remains for few hours
+++ Gelation occur immediately, remains for extended period

Table 3: *In vitro* Release Kinetics of Various Formulations of Ocular *in situ* Gelling Systems

Formulation	First order	Zero order	Higuchi	Korsmeyer Peppas	Hixson crowell
F1	0.965	0.967	0.979	0.980	0.978
F2	0.918	0.926	0.994	0.992	0.969
F3	0.989	0.911	0.998	0.997	0.965
F4	0.925	0.936	0.996	0.991	0.977
F5	0.973	0.973	0.976	0.979	0.964
F6	0.954	0.953	0.998	0.983	0.987
F7	0.974	0.974	0.964	0.973	0.989
F8	0.960	0.960	0.973	0.984	0.966

Table 4: Zone of Inhibition (ZOI) of optimized formulation of *in situ* gelling system of Gemifloxacin Mesylate on *Staphylococcus aureus* and *Bacillus cereaus*

S. NO	FORMULATION	ZONE OF INHIBITION (mm)	
		Staphylococcus aureus	*Bacillus cereaus*
1.	Standard drug	32 ± 1.1	33 ± 1.2
2	Optimized formulation (F8)	44 ± 4.2	45 ± 5.4

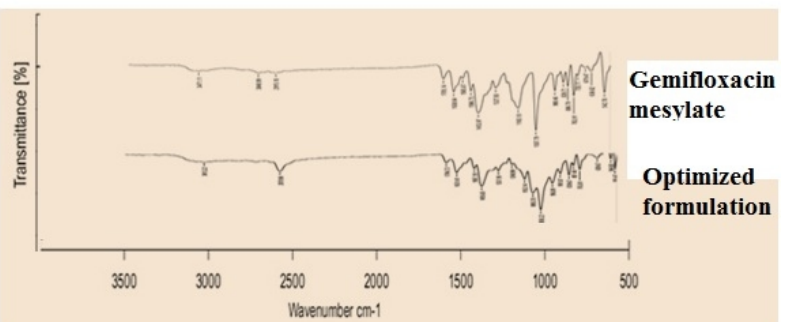

Figure1: FT-IR spectroscopy of Gemifloxacin Mesylate and Optimized Formulation

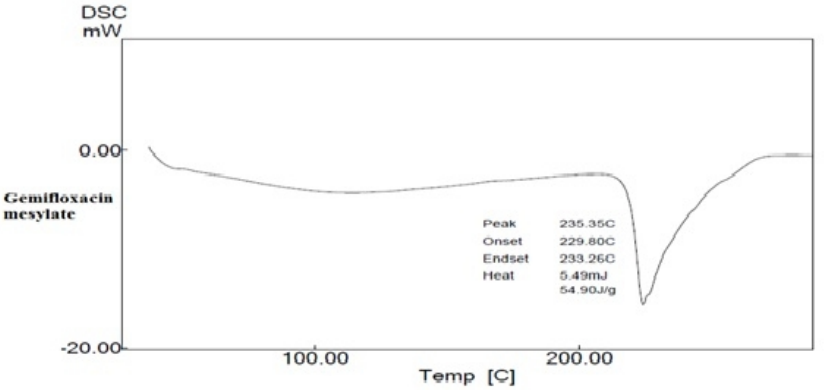

Figure 2: Differential Scanning Calorimetry of Pure Drug

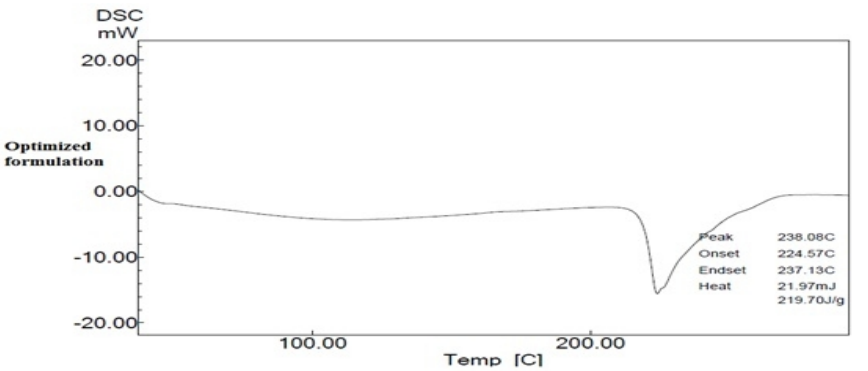

Figure 3: Differential Scanning Calorimetry of Optimized Formulation

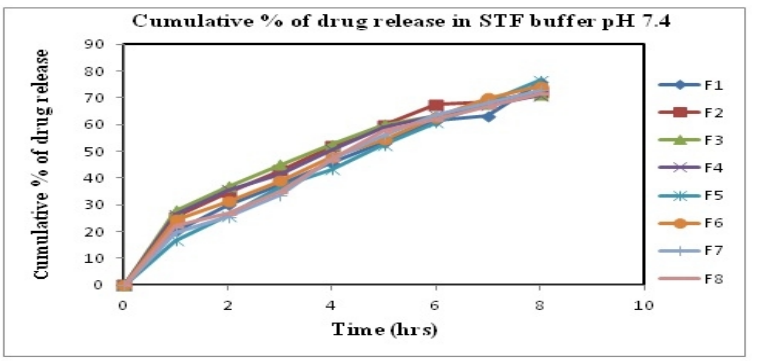

Figure 4: **Cumulative % of Drug Release of Various Formulations of *in situ* Gelling Systems of Gemifloxacin mesylate in STF buffer pH 7.4**

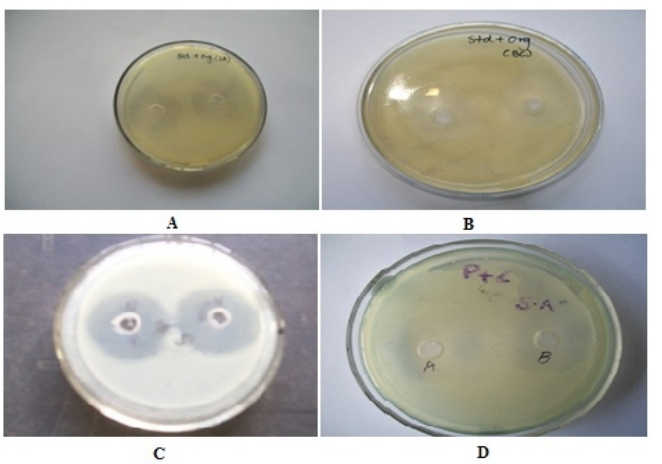

Figure 5: *In vitro* Efficacy of Gemifloxacin Mesylate Formulations

A = pure drug against *S. aereus*, B = pure drug against *B. cereus*, C = optimized formulation against *S. aereus*, D = optimized formulation against *B. cereus*

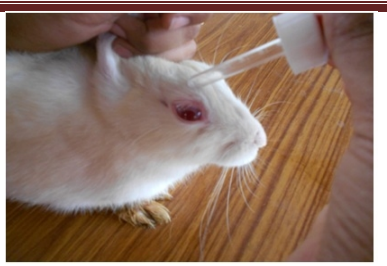

Figure 6: **Installation of Optimized Formulation into Rabbit Eye**

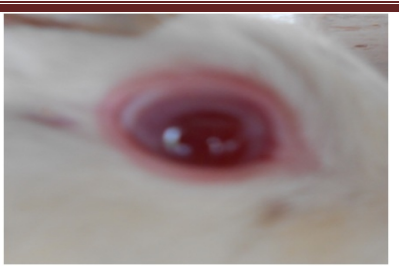

Figure 7: After Treatment with Gemifloxacin Mesylate

RESULTS AND DISCUSSION

Compatibility Studies

Fourier Transform Infrared Spectroscopy (FT-IR)

IR spectra of Gemifloxacin Mesylate and optimized formulation were shown in Figure 1. An IR spectrum of pure Gemifloxacin Mesylate showed the peaks 1037.79 cm^{-1} (C-F bonding), 2915.18 cm^{-1} (C-H stretching of OCH_3), 3471.11 cm^{-1} (-NH_2 primary amino group), 1453 cm^{-1} (C=C ring stretching), 1705.14 cm^{-1} (C=O aromatic carboxylic acid), 1506.75 cm^{-1} (aromatic C=C). These peaks can be considered as characteristic peaks of Gemifloxacin Mesylate and were not affected with polymers and prominently observed in IR spectra of Gemifloxacin Mesylate formulation as shown in (Figure 1). This indicated that there was no interaction between Gemifloxacin Mesylate and polymers.

Differential Scanning Calorimetry (DSC)

The DSC thermograms of the pure drug showed sharp distinct endothermic peak at 235.35^0c corresponding to melting point temperature. There was no appreciable change in the melting endotherm of pure drug in the formulation. This indicates that there was no incompatibility between drug and polymers and confirms the compatibility of drug and the polymers as shown in (Figure 2 and 3).

Evaluation Parameters

pH

The pH of *in situ* gels was found to be 6.8 to 7.4 for all the formulations.

Gel Strength and Gelling Capacity

All formulations of Gemifloxacin mesylate exhibited good gel strength. The gelling capacity of the prepared formulation was evaluated for gelling property, which will then undergo rapid sol to gel transition depending on the mechanism of polymer. Moreover, to facilitate sustained release of drug to the ocular tissue, the *in situ* formed gel should preserve its integrity without dissolving or eroding for a prolonged period of time. All the formulations gelled instantaneously (less than a minute) on contact with STF. By visual inspection, the formulations formed a translucent clear matrix on addition to the STF.

Rheological Studies

All the selected formulations were shear thinning exhibiting pseudo plastic behavior and increase in the shear rate was observed with increasing in the angular velocity. The viscosity of all formulations was found to be in the range of 32.2 to 37.5.

Drug Content

The *in situ* gels of Gemifloxacin Mesylate compiled with the requirement of assay. The results for drug content were found to be in the range of 77.85 to 85.76 %.

In-vitro Drug Release Studies

The *in vitro* drug releases of all formulations are from 70.82 % to 76.43 % at the end of 8 h (Figure 4). Slow releasing effect of drug from chitosan containing thermo reversible *in situ* gels can be explained by the increase of viscosity due to increase of polymer concentration. In this investigation, the curve fitting method to release profiles indicated Higuchi model but the analysis of kinetic data from korsmayer peppas indicated that all formulations following non-Fickian release kinetics indicated that the drug release was related to both gel dissolution and drug diffusion mechanism. The results were shown in Table 3.

Sterility Testing

The optimized formulation F8 passed the sterility test as there was no appearance of turbidity and hence no evidence of microbial growth when incubated for not less than 14 days at $20\text{-}25^0$ C in soyabean casein digest medium.

Antibacterial Activity

The result of the antimicrobial efficacy tests were shown in (Table 4). The ZOI (zone of inhibition) values for the prepared formulations were higher than the ZOI values of the standard preparation for both tested organisms (Figure 5). The higher ZOI values obtained for the formulation F8 in comparison to the standard could be attributed to the slow and prolonged diffusion of the drug from the polymeric solution due to its higher viscosity. The study indicated that Gemifloxacin mesylate retained its antimicrobial efficacy when formulated as an *in situ* gelling system and the drug was active against the selected strains of micro-organisms.

Ocular Irritation Studies

Ocular irritation studies were carried on two male albino rabbits each weighing 1.5 - 2 kg. Optimized formulation F8 was used for this test. The sterile formulation was instilled twice a day for a period of 7 days and the rabbits were observed periodically for redness, swelling and watering of the eye (Figure 6 and 7). The formulation was found to be nonirritating with no ocular damage or abnormal clinical signs to the cornea, iris or conjunctivae observed. Hence the formulation was suitable for the eye instillation and viable alternative to conventional ophthalmic formulation.

CONCLUSION

This study showed the feasibility of *in vitro* gel forming from aqueous solutions of polaxamer / chitosan is a promising tool for the topical treatment of ocular disease. Gemifloxacin Mesylate (0.15 % w/v %), a fluroquinolone and broad-spectrum antibacterial agent used in the treatment of infective keratitis, was successfully formulated in thermosensitive *In situ* gel-forming eye-drop using polaxamer / chitosan combination. The formulation (F8) formed by polaxamer / chitosan (15 % polaxamer and 1 % chitosan), which in

addition to sustain the Gemifloxacin Mesylate *in vitro*, we showed that the formulation prepared by polaxamer 15 % and chitosan 1 % had good gel strength in comparison to others and had no ocular irritancy. Taking this consideration, many poor bioavailability drugs intended for ocular delivery can be formulated as *in situ* gelling systems and act as viable alternative to conventional eye drops to enhance pre-corneal residence time there by bioavailability and efficacy are enhanced. These formulations outstand for being simple to prepare can conquer better patient compliance in a multi dose regime, which would be critical factor for successful therapy.

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Cite this article as:
Rajalakshmi R, Padmaja C, Radhika N, Kumuda P, Pavan kumar P, Ujjwala B, Vinesha V. Formulation and assessment of Gemifloxacin mesylate ocular In situ gelling system. Int. Res. J. Pharm. 2013; 4(10):33-38 http://dx.doi.org/10.7897/2230-8407.041009

Source of support: Nil, Conflict of interest: None Declared