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Sustained Released Opthalmic in Situ Hydrogel Of Levofloxacin From A Ph-Triggered In Situ Gelling

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Abstract

Background: Most of eye diseases are treated with topical application of eye drops. The poor bioavailability and therapeutic response exhibited by these conventional eye drops due to rapid precorneal elimination of the drug may be overcome by the use of in situ gelling system that are instilled as drops into the eye drops and undergo a sol-to-gel transition in the cul-de-sac.
Objective: The purpose of the present work was to develop sustain ophthalmic delivery to levofloxacin from a ph-triggered in situ gelling system.
Method: Polyacrylic acid (Carbopol 934) was used as the gelling agent in combination with hydroxypropyl methylcellulose (Methocel K4M) and HPMC K100LV which acted as viscosity enhancing agent. Compatibility studies of the drug excipients were carried out using FTIR.
Result: The prepared formulation were characterized for clarity, pH, drug content, gelling capacity, rheological studies, in vitro drug release study, sterility study and stability study. It is observed that the formulated system provided sustained release of drug for more than 8 hrs period.

Keywords: Carbopol 934, in situ gelling ophthalmic delivery system, levofloxacin hemihydrate.

INTRODUCTION:

Delivering drugs to front of the eye is an exceedingly complicated issue because of the numerous protective mechanisms that are present in the eye to shield the visual pathway from foreign chemical[1]. Topical delivery of eye drops into the lower cul-de-sac is the most common method of drug treatment for ocular diseases and diagnosis[2]. Eye drops that are conventional ophthalmic delivery system often result in poor bioavailability and therapeutic response since the tear fluid turnover and dynamics cause rapid precorneal elimination of the drug [3]. A high frequency of eye drop installation is associated with poor patient compliance. Inclusion of excess

drug in the formulation to overcome bioavailability problem is potentially dangerous if the drug solution drained from the eye is systemically absorbed from the nasolacrimal duct[4].

There are several ways of prolonging the presence of drugs in the precorneal area, such as increasing the viscosity of the dosage from the adding water-soluble polymers[5,6]. An alternative approach aimed at increasing the precorneal residence time of drug and consequently, their bioavailability is the use of polymeric solution which changes to a gel as a result of exposure to the physiological temperature, pH or ionic composition of the lachrymal fluid[7].

Depending on the method employed to cause sol-to-gel phase transition on the eye surface, the following three types of system are recognized: pH –triggered system e.g. cellulose acetate hydrogen phthalate latex[8], temperature –dependent system e.g. Pluronics[9] and Tetronics[10] and ion activated system e.g. Gelrite TM[11] and Carbopol[12].

The objective of the present work was to develop Sustain ophthalmic delivery of levofloxacin from a pH-triggered in situ gelling system a antibacterial drug levofloxacin, a third generation flurooquinolone derivative used in infection of eye such as acute conjunctivitis and the other eye infection. A combination of carbopol 934 and hydroxypropyl methylcellulose(HPMC) was investigated as a vehicle for the formulation of levofloxacin (0.5%w/v) which would gel when instilled into the eye, and provide sustained release of drug during treatment of conjunctivitis and some forms of ocular inflammation.

MATERIALS AND METHODS

Materials:

Levofloxacin hemihydrates was obtained from Yarrow Chem Pvt ltd. and the entire ingredient used were of analytical grade.

Compatibility study

Compatibility studies were carried out in order to establish that, there would be no interaction between the drug and the excipient (eg. polymer) used in the formulation. These studies were carried out by Perkin Elmer FTIR, spectrum BX, by a powder method. The In this study, the compatibility of pure drug i.e FT-IR spectrum of the pure drug and excipient was carried prior to the preparation of ophthalmic in situ hydrogel which indicate no interaction between Levofloxacin and polymers when compared with infrared spectrum of pure drug as all functional group frequencies were present. (shown in Fig.1,2)

METHOD OF PREPARATION

RESOURCES AND PROCEDURES USED.

Electronic Balance (Shimadzu Scientific, India), UV Spectroscopy (Shimadzu Scientific, India)

DRUGS AND CHEMICALS USED

Levofloxacin Procured from Yarrow chem, HPMCK4M, HPMC100LV, CARBOPOL 940 was procured from Tech vision enterprise Add HPMCK4M in Citrophosphate buffer pH6 in a small partwise with full stirring with glass rod. After complete addition of HPMCK4M, the solution is allowed to cool in cold water (ice). It is clear, colourless, viscous solution. Now, add and dissolve in Citrophosphate buffer pH6. Then levofloxacin hemihydrates were dissolved in 10ml of Citrophosphate buffer pH6. The drug solution was then added to the polymeric solution under constant stirring until a uniform solution was obtained. Now, WFI was added to make up the volume to 1000ml of solution, is filtered through filter paper by applying vaccum. The formulation was filled in vials under aseptic conditions, and evaluation was carried out. Method of preparation which are mentioned in table 1.

Formulation number	Drug% Levoflox	HPMC K4M	HPMC100 LV	CARBOPOL 934	Citrophosphate buffer 6
LK1	0.5	0.5	-	-	100 ml to q.s
LK2		1.0	-	-	
LK3		1.5	-	-	
LK4		2	-	-	
LK5		1.5	-	0.5	
LM1		-	0.5		
LM2		-	1		

LM3		-	1.5		
LM4		-	2		
LM5		-	1.5	0.5	

Table No: 1 Ingrdients in Ophthalmic formulations

Composition of stimulated tear fluid (STF)

The composition of stimulated tear fluid used as sodium chloride 0.670g, sodium bicarbonate 0.200g, calcium chloride $2H_2O$ 0.008g, purified water q.s 100ml.

EVALUATION OF FORMULATION

1. Determination of visual appearance, clarity, and pH

The appearance and clarity were determined visually. The pH of the formulation was determined by using pH meter.

2. Gelling capacity

The gelling capacity was determined by placing a drop of the system in a test-tube containing 2ml of stimulated tear fluid (STF) freshly prepared and equilibrated at 37^0C. The visual assessment of gel formulation was carried out simultaneously. The time required for gelation as well as time taken for the formed gel to dissolve was also noted.

The flow behavior with the "+" sign indicate the vehicle is in the liquid form which shows gels slowly and dissolves rapidly.

The flow behavior with the "++" sign indicate the vehicle is in the liquid- gel like form and flows less readily, which shows gelation immediate and remain for a few hours.

The flow behavior with the "+++" sign indicate that the sample is in the gel form and is very difficult to flow which also shows immediate gelation and the gel remains for the extended period of time.

3. % Drug content

Uniform distribution of active ingredient is important to achieve dose uniformity. The drug content was determined by diluting 1ml of the formulation to 100 ml with stimulated tear fluid pH 7.4. Aliquot of 5ml was withdrawn and further diluted to 25 ml with STF. Levofloxacin hemihydrates concentration was then determined at 294nm by using UV-V is spectrophotometer.

4. Rheological studies

Viscosity of instilled formulation is an important factor in determining residence time of drug in the eye. The viscosity determination of prepared formulation was carried out using Brookfield viscometer, LVDV-II+PRO with spindle 62 at 20^0C temperature. Viscosity of sample was measured at different angular velocities. A typical run comprised changing angular velocity from 5to 200 rpm with equal weight from each rpm.

5. In vitro drug release study

In vitro release studies were carried out by chambered donor receiver compartment model (Franz diffusion cell). In vitro release of levofloxacin hemihydrates was carried out in formulation with using cellophane membrane.

The cellophane membrane previously soaked overnight in dissolution medium. The diffusion medium 100ml of stimulated tear fluid stirred at 50 rpm at 37^0C 0.5^0C.

One end of the diffusion tube was covered by cellophane membrane.

The 1ml formulation was spread on the cellophane membrane and the membrane was placed such that it just touches the diffusion medium (STF) present in receptor compartment. Aliquots, each of 1ml volume, were withdrawn at hourly intervals and replaced by an equal volume of the receptor medium.

The drug samples were withdrawn at the interval of one hour for the period of 8 hrs from diffusion medium and analyzed by a U.V spectrophotometer at 294nm using stimulated tear fluid as blank.

6. Sterility test

All ophthalmic preparation should be sterile therefore the test for sterility is very important evaluation parameter. The sterility was performed according to Indian pharmacopoeia.

Direct inoculation method was used. 2ml of liquid from test container was removed with a sterile pipette or with a sterile syringe or a needle. The test liquid was aseptically transferred to fluid thioglycolate medium

(20ml) and soyabean-casein digest medium (20ml) separately. The liquid was mixed with the media. The inoculated media were incubated for not less than 14 days at 30^0C to 35^0C in the case of fluid thioglycolate medium and 20^0C to 25^0C in the case of soyabean-casein digest medium.

RESULT AND DISCUSSION

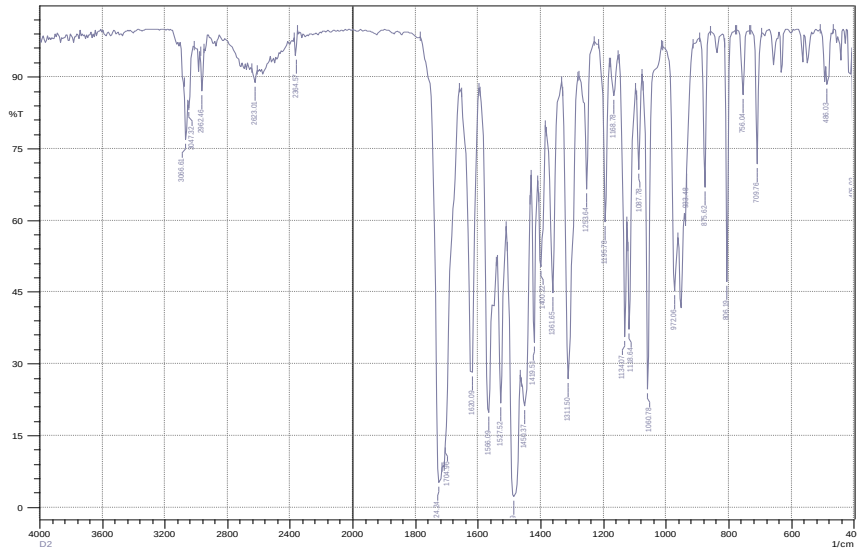

Fig: 1 IR spectra of Levofloxacin sample

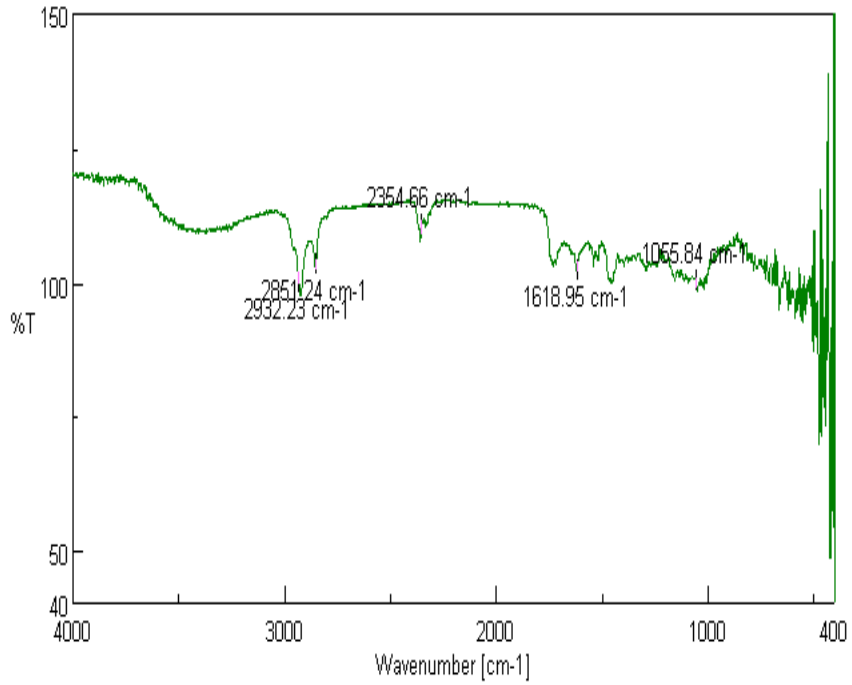

Fig.2 IR spectra of Mixture

Ophthalmic in situ gelling system can be formulated using Carbopol 934 as pH-triggered polymer along with HPMC K4M and HPMC K 100LV as viscosity enhancing agent and beneficial in improving the residence time and drug release characteristics.

The identification and characterization of levofloxacin hemihydrate show that it complies with standard. Infrared spectroscopy studies of levofloxacin hemihydrate, carbopol 934, HPMC K4M and HPMC K 100LV alone and their physical mixture revealed that, levofloxacin hemihydrate is compatable with the entire polymer used it interpreted by IR spectrum (Fig.1,2).

The appearance, pH, gelling capacity, % drug content was acceptable for all five formulation, but the formulation LM5 shows better result.

The result obtained from the rheological study of prepared in situ gelling system revealed that the viscosity decreases as the angular velocity increases. In this study, formulation LM5 shows better rheological characteristics. In vitro drug release study, all five formulations showed sustained drug release for a period of 8 hour and follow zero order release rate.
Formulation LM5 showed most sustained drug release. In sterility study, there was no appearance of turbidity and hence no evidence of microbial growth in formulation. From this study, formulation LM5 was selected as optimized formulation.

CONCULSION

Levofloxacin hemihydrate which is a broad spectrum anti-bacterial agent used in treatment of ocular infection was successfully formulated as in situ gel using polymer. The formulated system provided sustained release of drug for more than 8 hrs period. The developed formulation is a viable alternative to conventional eye drop due to its ability to enhance the bioavailability through its precorneal residence time and ability to sustain release of the drug. Also important is its ease of administration and decreased frequency of administration resulting in better patient compliance.

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Availability of data and materials: This declaration is not applicable

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Conflict of interest: Author declared no conflict of interest

REFERENCE:

1. worakul N., Robinson J. R.. Ocular pharmacokinetics / pharmacodynamics. Eur. J. Pharm. Biopharm., 1997; 44: 71-83.
2. Jarvinen K., Jarvinen T., Urtti A.. Ocular absorption following topical delivery. Adv. Drug Del. Rev., 1995; 6: 3-19.
3. Schoenwald T. J . Ocular drug delivery: pharmacokinetic considerations. Cli. pharmacokinet., 1990; 18: 255-269.
4. Middleton D.L., Leung S.S., Robinson J. R.. Bioadhesive Drug Delivery system. CRC Press, Boca Raton, 1990; 179-202.
5. Thermes F, Roizer A., Plazonnet B., et al. Bioadhesion the effect of Polyacrylic acid on the ocular bioavailability of timolol. Int. J. pharm., 1992; 81: 59-65
6. Felt O., Furrer P., Mayer J. M., et al. Topical use of chitosan in ophthal mology: tolerance assessment and evaluation of precorneal retention.Int. J. Pharm., 1999; 180: 185-193.
7. Sechoy O, Tissie G., Sebastian C., et al. A new long acting ophthalmic formulation of carteolol containing alginic acid. Int. J. pharm., 2000; 207: 109-116.
8. Gurny R., Boye T., Ibrahim H.. Ocular therapy with nanoparticle system for controlled drug delivery. J. control. Rel.,1985; 2: 353-361.
9. Miller S. C., Donovan M.D.. Effect of poloxamer 407 gel on the mitotic activity of pilocarpine nitrate in rabbits. Int. J. pharm., 1982; 2: 353-361.
10. Spancake C. W., Mitra A.k., Kildsig D. O.. kinetics of aspirin hydrolysis in aqueous solution and gels of poloxamines (Tetronic 1508). Influence of microenvironment. Int. J. pharm., 1991; 75: 231-239.
11. Rozier A., Manuel C., Groove J., et al. Gelrite: A novel, ion- activated, in situ gelling polymer for ophthalmic vehicles. Effect on bioavailability of timolol. Int. J. pharm. 1989; 57: 163-168.
12. Sanzgiri Y. D., Maschi S., Crescenzi V., et al. Gellan based system for ophthalmic sustained delivery of methylprednisolone. J. control. Rel., 1993; 26: 195-201.
13. Pavia Donald L., Lampman Gary M., Kriz George S., introduction to spectroscopy, Third edition :13-101.
14. Srividya B, Rita M, Cardoza, Amin PD Sustained ophthalmic delivery of ofloxacin from a pH triggered in situ gelling system. J Control Release. 2003; 30: 129-138.

15. Eaga Chandra Mohan, Jagan Mohan KanduKuri, Venkateshan Allenki. Preparation and Evaluation of Insitu Gels for Ocular Drug Delivery. J Pharm Res. 2009; 2(6): 1089-1094.
16. Balasubramaniam, J.et al In vitro and in vivo evaluation of the Gelrite gellan gum-based ocular delivery system for indomethacin. Acta Pharm., (2003). 53, 251–261.
17. Sindhu Abraham, Sharon Furtoda, Bharath S, Basavaraj BV, Deveswaran R and Madhavan N. Sustained ophthalmic delivery of ofloxacin from an ion-activated in situ gelling system. Pak J Pharm Sci. 2009; 22 (2): 175- 179.
18. Naseem A, Charoo, Kanchan Kohhli, Asgar Ali. Preparation of in situ forming ophthalmic gels of ciprofloxacin Hydrochloride for the treatment of Bacterial Conjunctivitis: In vitro and in vivo Studies. J Pharm Sci, 2003; 92 (2): 407-415.
19. Satish kumar P et al: In situ ophthalmic gel of Ciprofloxacin Hydrochloride for once a day sustained delivery. Drug Development and Industrial Pharmacy, 34:445–452, 2008.
20. Indu, P., Kaur, A.G., Anil, K.S., eepika, A. Vesicular systems in ocular drug delivery an overview. Int J Pharm. 2004; 269: 1–14. [221Hdoi:10.1016/j.ijpharm. 2003.09.016]
21. Wagh VD, Inamdar B, Samanta MK. Polymers used in ocular dosage form and drug delivery systems. Asian J Pharma. 2008; 12–17. 6. Indu, P., Kaur, A.G., Anil, K.S., eepika, A.Vesicular systems in ocular drug delivery an overview.Int J Pharm. 2004; 269: 1–14.[221Hdoi:10.1016/j.ijpharm.2003.09.016]
22. Singh Satish K., Bandyopadhya, Paramita.Pharmacia Corporation. Ophthalmic formulation with novel gum composition.US 7128928, 2006.