SUSTAINED RELEASE IN SITU HYDROGEL USING SMART POLYMER -A CARBOPOL

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Abstract

The field of Ocular drug delivery is one of the interesting and challenging endeavors facing the pharmaceutical scientist. The most frequently used dosage forms i.e. ophthalmic solutions and suspensions are compromised in their effectiveness by several limitations, leading poor ocular bioavailability. *In situ* hydrogels are instilled as drops into the eye and undergoes a sol to gel transition in the cul-de-sac, improved ocular bioavailability by increasing the duration of contact with corneal tissue, thereby reducing the frequency of administration. The purpose of the present work was to develop pH-triggered an ophthalmic drug delivery system using combination of gelling agents with different mechanisms for *in situ* gelation of Ofloxacin hydrochloride, a fluoroquinolone antibiotic. *In situ* gels were prepared by simple dispersion method using Carbopol along with HPMC and then evaluated for pH, gelling capacity, drug content, rheological, gel strength and *in-vitro* diffusion studies and comparison with marketed eye drop formulation along with statistical studies. Among formulation batches C1- C6; optimized formulation F6 imparted sustained release property to the gel formed in situ and effective other evaluation parameters. The developed formulations were therapeutically efficacious, stable, non-irritant and provided sustained release of the drug overcoming convential drawbacks leading to better patient acceptance.

Keywords: In situ-forming systems; ophthalmic hydrogel; Ofloxacin Hydrochloride; carbopol, HPMC.

1. Introduction

Eye is most interesting organ due to its drug dispossition characteristics. Topical administration of anti-infective drug is the treatment of choice for diseases of anterior segments of the eye. When a drug solution is dropped into the eye, effective tear drainage and blinking result in a 10- fold reduction of drug concentration in 4-20 minutes. The limited permeability and rapid elimination results in low absorption and short duration of the therapeutic regimen [1]

Ocular therapy could be significantly improved if the pre-corneal residence time of drugs could be increased.

Various ophthalmic vehicles such as inserts, ointments, suspensions, and aqueous gels lengthen the residence time of instilled dose but have some drawbacks such as blurred vision from ointments or low patient compliance from inserts [40]. This problem can be overcome by using in situ gel forming ophthalmic drug delivery systems prepared from polymers that exhibit reversible phase transitions and pseudoplastic behavior to minimize interference with blinking[2].Depending on the method employed to cause sol to gel phase transition on the ocular surface, the following three types of systems have been recognized: pH-triggered - The polymers used in this system are Pseudolatexes - Carbomer (Carbopol), Cellulose acetate phthalate latex (CAP latex). Temperature-dependent - Poloxamers (Pluronic, Tetronics), Cellulose derivatives (MCHPMC), Xyloglucan. Ion-activated induced - Alginates, Gelrite® (Gellan gum). Such a system can be formulated as liquid as solution upon exposure to physiological pH condition of eye, shifts to gel phase which has a higher viscosity thus increasing the pre- corneal residence and can improve patient compliance. [2] With the advent of new generation of flouroquinolones such as Ofloxacin HCl, the treatment of gram positive bacterial infections has been achieved. This drug shows increased potency than all other topical antibiotics making it able to eradicate methicillin-resistant *Staphylococcus*species. Ofloxacin HCl penetrates at very high level into ocular tissues including the tear film, cornea, anterior chamber, and ciliary body due to its biphasic nature i.e. soluble in both lipid and aqueous solutions. Therefore, it can achieve very high concentration in the eye [3]. Hence, it was thought of combining the benefits of the drug with pH sensitive/mucoadhesive polymers such as carbopol and hydroxypropyl methylcellulose (viscosity enhancing agent) to come out with a formulation, which might outperform the conventional eye drops of the same drug. The formulation would be useful to treat external infections of the eye such as acute and subacute conjunctivitis, bacterial keratitis, bacterial endophthalmitis, and keratoconjunctivitis.

2. Materials and Method

Materials

Ofloxacin obtained from Yarrow chem. Pvt. Ltd Worli, Carbopol and HPMCK4M obtained from Yarrow chem. Pvt. Ltd.

Method

Preparation of in situ hydrogel

i. The carbopol 974 P and HPMC K4M solution were prepared by dispersing the required amount in Citrophosphate buffer pH6, this mixture was allowed to swell overnight.
ii. Solution A of Ofloxacin is prepared Citrophosphate buffer pH 6 and it is added to the carbopol and HPMC K4M mixture with constant slow stirring, Solution B, Mannitol and Methyl paraben were added to all formulations as isotonicity agent and preservative, respectively. Add Solution B to solution a pH of the formulation adjusted to 6 using 0.1 N NaOH then the formulation was autoclaved 15 psi pressure for 20 min.

Formulation Code	Ofloxacin HCl (%w/w)	Carbopol 974	HPMC K4M
C1	0.3	0.1	1
C2	0.3	0.2	1
C3	0.3	0.3	1
C4	0.3	0.4	1
C5	0.3	0.5	1

Table no 1: Material used in formulations

Methyl paraben : 0.01%

Manitol: 5% w/v

Composition of STF

The composition of artificial tear fluid used is Sodium Chloride NaCl 0.670 g, Sodium bicarbonate ($NaHCO_3$) 0.200 g, Calcium chloride ($CaCl_2$) 0.008 g, purified water 100 ml.[7]

CHARACTERIZATION OF THE FORMULATION

Clarity

The clarity of the in situ gels before and after gelling was determined by visual examination of the formulations under light, alternatively against white and black background.[8]

pH

The pH of the in situ gel was determined using calibrated pH meter. Readings are carried out in triplicate and an average of these readings is taken as the pH of the gel.[9]

Drug content estimation

The estimation of drug content was carried out by diluting 1 ml of prepared formulation in 100 ml of distilled water and analysed using UV-visible spectrophotometer (Shimadzu UV-1700 PC, Shimadzu Corporation, and Japan).[10]

Rheological Studies

The viscosity of the instilled formulation plays an important role in determining the residence time of drug in the eye. Rheology of the formulation was determined before and after gelation by using either the Brookfield's viscometer (RVT model).[11]

Gelling Capacity

The gelling capacity of the formulated in situ gel was analysed by placing a drop of system in vials containing 1 ml of simulated tear fluid (STF). The STF was freshly prepared and equilibrated at 37ºC, also visually assessing the gel formation and noting the time for gelation as well as time taken for the gel formed to dissolve.[12]

RESULT AND DISCUSSION

EVALUATION PARAMETERS FOR IN SITU HYDROGELS

Clarity

The clarity of all formulations was found to be satisfactory. The terminal sterilization of the formulations by autoclaving had no effect on the clarity and other physiochemical properties of the formulations, No changes were observed after autoclaving.

pH

The pH of the formulations was found to be satisfactory and lies in the range of 5-7. The formulations were liquid at room temperature and at the pH formulated.

Drug content estimation

The percent drug content for formulations was found to be in acceptable range for all the formulations. Solubility of the drugs in the vehicle may affect the drug content. The determined drug content of all the formulations and results are shown in (Table 3). The percent drug content of Carbopol 974 formulations was found to be in between 94.11% to 94.93% for Ofloxacin HCl.

Table 3: Gellan gum formulation % drug content of Ofloxacin HCl

Formulation code	Ofloxacin	% Drug Content (n=3 mean ± SD)	% Drug Content (n=3 mean ± SD)
OC1	94.72± 0.004	94.72± 0.004	88.53±0.001
OC2	94.77± 0.004	94.77± 0.004	88.67± 0.0027
OC3	94.11±0.0005	94.11±0.0005	88.80± 0.001
OC4	94.81± 0.003	94.11±0.0005	88.70± 0.001
OC 5	94.93± 0.003	94.81± 0.003	88.77±0.001
OC6	94.93± 0.003	94.93± 0.003	88.94±0.0009

Rheological Studies

The rheological studies revealed that the viscosity of the formulation increases when the concentration of the polymer is increased. The rheological data of the formulation is shown in (Table 4).

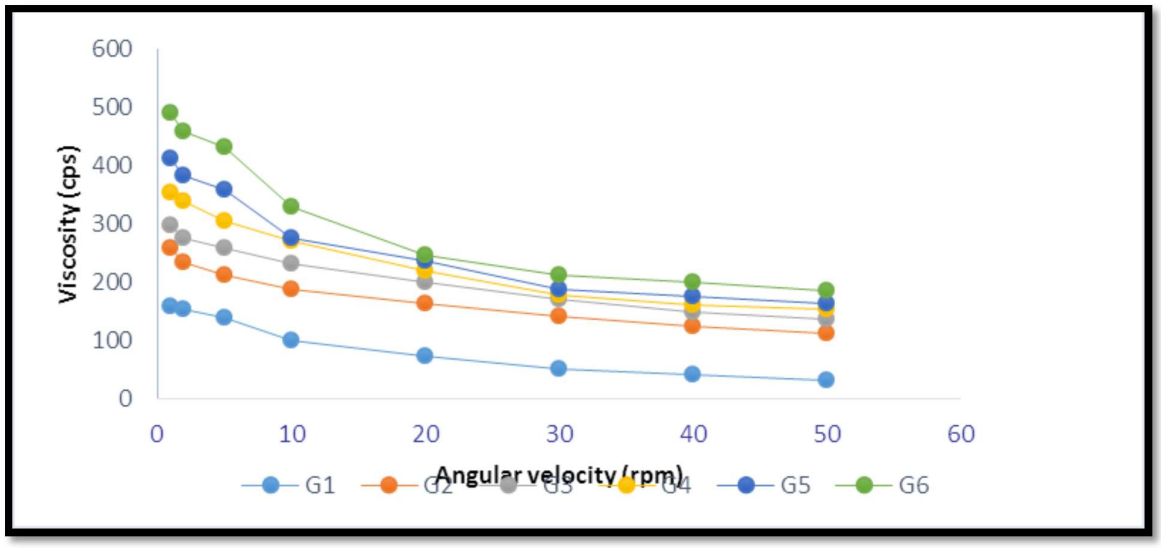

Fig 1: Carbopol formulation rheography. (Angular velocity Vs Viscosity)

Gelling Capacity

One of the most important features of the in situ gelling system is its gelling capacity. The prepared formulation should have maximum gelling capacity to make possible the sustained release of the drug to the ocular tissue. The gel that is formed in situ should maintain its integrity without dissolving or abrading for a long period of time.

The gelling capacity of the Gellan Gum formulations are shown in (Table 5) and the signs are described as:

(+) – Gels after few minutes and dissolves quickly

(++) – Gels immediately and remains for few hours

(+++) – Gels immediately and remains for extended period

Table 5: Gelling capacity of Gellan Gum formulation

S r.no	Formulation code	Concentration (%w/v)	Gelling capacity
1	OC1	0.0325	+
2	OC2	0.030	++
3	OC3	0.035	++
4	OC4	0.040	++
5	OC5	0.045	+++
6	OC6	0.050	+++

In the prepared formulations the gelling capacity of the OC5 and OC6 formulations had good gelling capacity.

In vitro release study

In-vitro release studies are carried out using bichambered donor receiver compartment model (Franz diffusion cell). Dialysis membrane is previously soaked overnight in the dissolution medium. The assembly is placed on magnetic stirrer maintaining the temperature up to 37 ± 0.5 ºC. Accurately measured 1 ml of the formulation is pipette into the assembly. Dialysis membrane, which is in contact with receptor medium just touch the receptor medium. The receptor medium is stirred continuously with 20 rpm to simulate the blinking action of eyelids. Samples were withdrawn at periodic intervals. The appropriate dilution is done with STF. UV Spectrophotometer was used for analysing the drug content. The % drug release data of ofloxacin HCl , OC1 to OC6 formulations is shown in (Table 6) and (Table 7).

Table 6: % Drug release data of ofloxacin HCl for OC1 to OC6 formulation

Time	OC1	OC2	OC3	OC4	OC5	OC6
30	19.227	79.279	27.979	76.353	43.654	41.000
60	31.773	73.706	40.208	81.615	52.125	60.931
90	43.654	85.630	53.701	99.223	61.179	69.623
120	52.125	88.983	62.717		67.752	88.181
150	61.179	89.728	73.502		94.676	
180	67.752	98.78	90.12			
210	94.676					

Conclusion

From the previous study, it could be concluded that ofloxacin would be successfully formulated as mucoadhesive ion sensitive system for the treatment of eye infections. Ofloxacin in situ forming gel formulae composed of Carbopol and showed optimum mucoadhesion properties, prolonged the precorneal residence time and drug release, improved ocular bioavailability, with a decreased frequency of administration, and hence increased the patient compliance compared with the marketed conventional eye drops. According to drug release and other evaluation parameters OC3 shows better result than other and as Carbopol quantity increases the drug release is faster and time required for sustained effect is lowered.

References

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 ophthalmology : 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.