Availableonlineon www.jadd.in

Journal of Advanced Drug Delivery2014; 1(1); 2-8

ISSN: 2348-3792

Research Article

Studies on Development of in Situ gelling System of Ciprofloxacin

Mukesh B. Shinde* and Ganesh Dama[1]

*[1]Sharadchandra Pawar College of Pharamcy, Otur Pune India

Available online: February, 2014

ABSTRACT

Several polymeric systems have been used to fabricate ocular inserts for better ocular bioavailability and retention to drug of which gelling systems have shown advantages of convenient administration and increased contact time. The purpose of the present study was to develop a bioadhesive ocular insert of ciprofloxacin using polymeric system of sodium alginate as gelling and chitosan as bioadhesive agent. Polymeric ocular inserts of ciprofloxacin hydrochloride (CH) were composed using sodium alginate and chitosan with glycerine as plasticizer by solvent casting method. The ocular inserts were investigated for physicochemical properties (bioadesive, thickness, weight variation, folding endurance and surface pH).In vitrorelease studies were carried using a donor-receptor compartment model. Cumulative drug released from the formulation ranged from 95-99% within 8-12h. The formulation CH4 (2% sodium alginate and 1% chitosan) sustained the drug release for the longest period of time (12hrs). Optimized formulation CH4 shows zero order release.Ciprofloxacin hydrochloride inserts have appreciable film forming properties and were found to be good antimicrobial efficacy.

Keywords: Ciprofloxacin hydrochloride, Ocular insert, Bioadhesion, Chitosan,

INTRODUCTION

The human eye is a challenging subject for the topical administration of drugs. The basis of this can be found in the anatomical arrangement of surface tissues and in the permeability of the cornea. The protective operation of the eyelids and lachrymal system is such that there is rapid removal of material instilled into the eye, unless it is suitably small in volume and physiologically compatible with surface tissues[1].Low bioavailability of conventional eye drops is due to their short precorneal contact time. Effective tear drainage and blinking results in tenfold decrease in drug concentration in 4–20 min when the drug solution is administered in the form of drops[2]. Short precorneal contact time of administered eye drops often results in a short duration of therapeutic effect making a frequent dosing regimen[2]. The drug absorption also depends upon the chemical nature of the drugs. Sometimes the drug is transported via nasolacrimal duct to the GI tract, where it may be absorbed, and causing systemic side effects[3]. In order to avoid the above-mentioned side effects and increased effectiveness of the drug, a dosage form should be chosen, which increases the contact time of the drug in the eye. This may increase bioavailability and reduce the need for frequent administration, leading to improved patient compliance[4]. The most common way to achieve improved ocular bioavailability is by increasing the viscosity of the solution. Gels and ointments suffer low patient

compliance due to blurring of vision, though they have long residence time and are recommended for bedtime use[5,6]. Ophthalmic inserts are solid devices delivering drugs to the anterior segment of the eye. Inserts are in the form of thin disks or small cylinders made with appropriate polymeric material[7], whose size and shape are specially designed to fit into the lower or upper conjunctival sac[8,9,19]. Advantages and drawbacks of ocular inserts have been discussed in several reviews. Ciprofloxacin Hydrochloride is an extremely potent antibacterial agent with potent activity against most gram +ve and gram –ve bacteria. Chemically, it is 1-cyCHopropyl-6-fluoro-1,4-dihydro-4-oxo-7- (1-piperazinyl)-3-quinoline carboxylic acid Hydrochloride monohydrate. Ciprofloxacin Hydrochloride is the most commonly used drug for the treatment of ocular infections and is the best alternative to more toxic drugs such as aminoglycosides[15,16,17]. Ciprofloxacin Hydrochloride eye drops, which are available presently, need to be administered 1–2 drops every 15–30 min initially in acute infection and 1–2 drops administered 6 times daily or more in severe conditions[18]. The present study has been undertaken to overcome the limitations of frequent administration associated with present dosage regimen. The study aims at developing a ciprofloxacin Hydrochloride soluble ocular drug insert to improve the efficiency of the therapy and to meet patient compliance.

MATERIALS AND METHODS

Materials

Ciprofloxacin Hydrochloride (CH) was obtained fromCipal ltd Mumbai, Water-soluble Chitosan, and Sodium alginate, purchased from Loba chemicals, all other reagents and solvents were of analytical grade.

Preparation of ocular inserts

The Ciprofloxacin ocular inserts based on sodium alginate and water soluble chitosan were prepared by solvent casting technique. Polymeric solutions were prepared by dissolving sodium alginate and chitosan at distinct compositions (Table 1 Insert codes: CH1, CH2, CH3, CH4 and CH4) along with 0.4% of ciprofloxacin hydrochloride (CH), and glycerine (10%) in distilled water. Chitosan was added in aqueous solution of sodium alginate and CH with constant stirring. The plasticizer was added thereafter and the drug polymer solutions were stirred for 12 h and allowed to stand overnight to remove any entrapped air bubbles. The pH range of the solutions was found to be 5-8. The solutions were then poured into glass ring (4 cm diameter and 12ml volume) placed over mercury in the glass petri dishes. Solvent was allowed to evaporate by placing the petri dishes in oven (40 ± 2°C). Dried films were carefully removed from the petri dish and then cut into (10mmX 5mm) oval shaped inserts with the help of a sharp edged blade.

Table 1Content of Ciprofloxacin Ocular Insert.

Insert Code	Polymer		Drug	Plasticizer
	Sodium Alginate %	Chitosan %	Ciprofloxacin %	Glycerin %
CH1	1.0	1.0	0.4	10
CH2	1.5	1.0	0.4	10
CH3	1.0	2.0	0.4	10
CH4	2.0	1.0	0.4	10
CH5	1.5	1.5	0.4	10

PHYSICOCHEMICAL EVALUATION

Thickness of Insert

The thickness of the insert was determined using a micrometer screw gauge Mitotoyo,

Japan) at five separate points of each insert. For each formulation, three randomly selected inserts were tested for their thickness

Weight Variation Test

Inserts from each batch were randomly selected and weighed individually on electronic balance (Metllertoldeol Switzerland). Mean weight of inserts (n=20)of each formulation was recorded.

Surface pH Determination

Inserts were left to swell for 5 hours on agar plate prepared by dissolving 2% (m/v) agar in warm simulated tear fluid (STF; sodium chloride: 0.670 g, sodium bicarbonate: 0.200 g, calcium chloride. $2H_2O$: 0.008 g, and purified water q.s. 100g of pH 7.2 under stirring and then pouring the solution into petri dish till gelling at room temperature. The surface pH was measured by means of a pH paper placed on the surface of swollen patch.

CHARACTERIZATION

Folding Endurance value

The folding endurance is expressed as the number of folds (number of times the insert is folded at the same place, either to break the specimen or to develop visible cracks. This test is important to check the ability of the sample to withstand folding. This also gives an indication of brittleness. The specimen was folded in the canter, between the fingers and the thumb and then opened. This was termed as one folding. The process was repeated till the insert showed breakage or cracks in centre of insert. The total folding operations were named as folding endurance value.

Drug Content uniformity:

Uniformity of the drug contents was determined by assaying the individual ocular inserts. Each insert was grounded in a glass pestle mortar and 5 ml of STF was added to make a suspension. The suspension so obtained was filtered and the filtrate was assayed spectrophotometrically at 292 nm. (UV-VIS Spectrophotometer Jasco V 530)

In vitro drug release studies:

In vitrodrug release study was carried out by using modified Franz diffusion cell. The commercial semi permeable cellophane membrane, pre-soaked overnight in the freshly prepared dissolution medium (STF pH7.2), and was tied to one end of a cylinder (open at both the sides) which acted as donor compartment. The ocular insert was placed inside the donor compartment in contact with the semi-permeable membrane. The donor compartment was attached to a stand and suspended in 25 ml of the dissolution medium maintained at 37±1°C in the way that touches the receptor medium surface. The dissolution medium was stirred at a low speed using magnetic stirrer. The aliquots of 5 ml were withdrawn at regular intervals for 12h and replaced by an equal volume of dissolution medium every time. The samples were analyzedspectrophotometrically at 292 nm. (UV-VIS Jasco Spectrophotometer- V 530 Japan)

In vitro Anti-microbial Efficacy:

The microbiological studies were carried out to ascertain the biological activity of the optimized formulation and marketed eye drops against microorganisms. *Staphylococcus aurous*and *Pseudomonas aeruginosa*were used as the test microorganisms. A layer of nutrient agar (20 mL) seeded with the test microorganism (0.2 mL) was allowed to solidify in the petri plate. Cups were made on the solidified agar layer with the help of sterile borer of 4 mm diameter. Then, volume of the formulations (optimized formulation and marketed eye drops) containing equivalent amounts of drug was poured into the cups. After keeping Petri plates at room temperature for 4 h, the plates were incubated at 37 °C for 24 h. The diameter of zone of inhibition was measured.

RESULTS AND DISCUSSION:

Physicochemical data presented in Table 2 shows thickness, weight, surface pH, folding endurance and drug content uniformity of the prepared inserts. The prepared inserts were translucent, colorless, smooth in texture, uniform in appearance and show no visible crack or imperfection. Each ocular insert had an area of approximately 277 mm. The insert had a thickness varying from 0.199 ± 0.0027 to 0.417 ± 0.0043mm and weight varying from 7.52±0.18 to 11.40±0.54 mg. It was found that the thickness and weight of the inserts were increased by increase in the total polymer concentration. The inserts were found to possess uniform weight and thickness within the batch. The recorded folding endurance for all batches was greater than 300, which is considered satisfactory and reveals good film properties. Surface pH was within range of 5.5 – 7 which shows that prepared inserts would not cause irritation in the eye. The drug content was consistent in all batches and varied from 97.9 ± 0.10% to 99.7± 0.15%.

Table 2 Physicochemical Parameter of the Ciprofloxacin Ocular Insert.

Insert Code	Weight (mg)	Thickness (mm)	Folding Endurance	Surface pH	% Drug Content
CH1	7.91 ±0.12	0.192±0.11	117±0.22	6.9±0.02	99.6±0.2
CH2	8.92 ±0.31	0.262±0.02	121±0.13	5.6±0.02	99.5±0.02
CH3	10.04 ±0.27	0.290±0.102	110±0.10	5.7±0.12	98.3±0.10
CH4	12.11 ±0.67	0.397±0.32	105±0.11	5.9±0.42	98.5±0.1
CH5	11.62 ±0.42	0.398±0.O2	132±0.13	6.0±0.32	99.0±0.2

In vitro drug release studies and Kinetic Modeling:

The cumulative percent of CH released from in situ gelling polymeric inserts CH1, CH2, CH3, CH4 and CH5, as a function of time is shown in Figure. 1, which reveal that 98% of drug was released from formulation a in 8 h, 96% of drug was released from formulation B in 10 h, 99% of drug was released from formulation CH3 in 10 h, 98% of drug was released from formulation CH4 in 12 h, and 95% of drug was released from formulation E in 10 h. These results suggested that CH was released in a sustained manner from formulation CH4, when the content of polymers was 2% Sodium alginate and 1 % of chitosan.

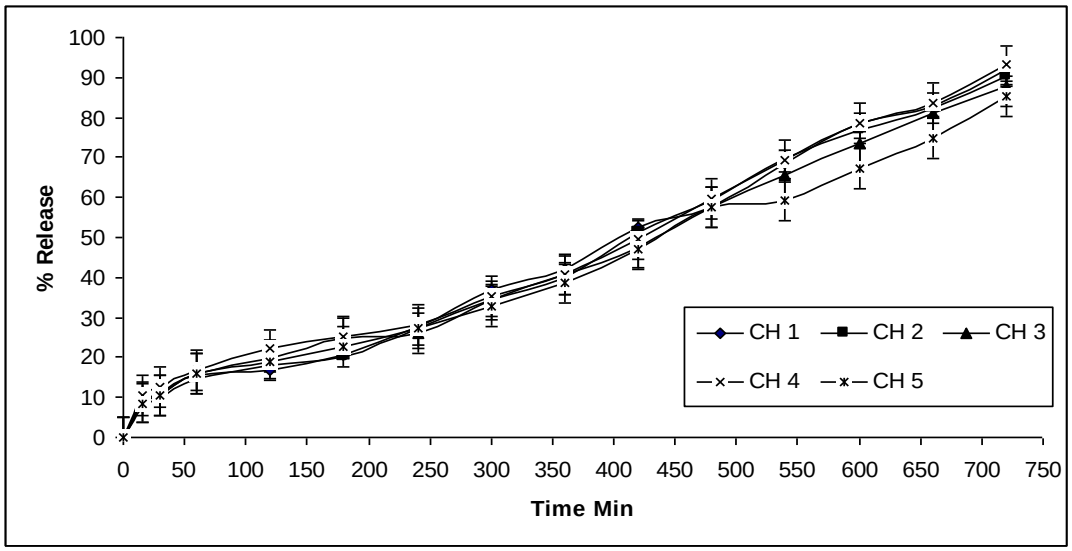

Figure 1 Percentage release study

The formulation CH4 showed the potential of sustaining the drug release for the longest period of time and hence formulation CH4 was selected as optimized formulation. In order to understand the drug release mechanism, the release data was tested assuming common kinetic model (Table 3).The best-fit kinetic model for the optimized formulation CH4 was the zero order kinetic model (R = 0.9853, k = 0.1643). There was not sufficient linearity for Peppas, Hixon Crowell and first order kinetic models. The drug release form such system is controlled by the dissolution fluid, which permeate through the superficial polymer layer and create sufficient internal pressure to drive the drug out. During dissolution the sodium alginate present in the film absorbs a significant amount of water to hydrate, swell and form a stable hydrogel upon exposure to the divalent cations Ca+2 present in STF.

Table 3 Kinetic Model for the formulation of the Ciprofloxacin Ocular Insert

Kinetic Model	Parameter	Formulation				
		CH1	CH2	CH3	CH4	CH5
Zero Order	R	0.9916	0.9887	0.9924	0.9848	0.9867
	K	0.1259	0.1245	0.1209	0.1278	0.1148
	t-Test	27.585	28.992	23.818	20.450	21.911
First Order	R	0.9223	0.9331	0.9404	0.8663	0.9433
	K	-0.005	-0.0024	-0.0022	-0.0027	-0.0020
	t-Test	8.603	9.353	9.948	6.254	10.247
Matrix	R	0.9338	0.9322	0.9402	0.9336	0.9451
	K	2.7507	2.7152	2.6501	2.8005	2.5222
	t-Test	9.414	9.283	9.948	9.397	10.431
Peppas	R	0.9604	0.9694	0.9690	0.9598	0.9704
	K	1.1893	0.9888	1.3524	1.6959	1.3960
	t-Test	12.422	14.233	14.134	12.324	14.728
Hixon Crowell	R	0.9622	0.9665	0.9691	0.9365	0.99704
	K	-0.006	-0.0006	-0.0006	-0.0007	-0.0005
	t-Test	12.735	13.583	14.170	9.632	14.487

In vitro antimicrobial Efficacy:

The optimized gel forming ocular insert CH showed antimicrobial activity when tested microbiologically by cup plate technique. CHzones of inhibition were obtained in case of formulation C and eye drops in the market. The diameter of zone of inhibition produced by formulation C against both test organisms were greater than those produced by marketed eye drops of the market (Table 4). The antimicrobial effect of the CH bioadhesive formulation is probably due to a fairly constant release of drug from the cross-linked hydrogel drug reservoir which permits drug to be released to the target site relatively slowly

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Table 4 Antimicrobial Efficacy testing

Microbial Strain	Zone of Inhibition Marketed perpetration	Zone of Inhibition optimized Formulation
Staphylococcus aurous	3.2 ± 0.67	2.9 ±0.53
Pseudomonas aroginosa	2.8 ± 0.58	1.2 ±0.12
E. coli	3.3 ± 0.87	2.2 ±0.67

CONCLUSION

Sodium alginate–chitosan ocular inserts of ciprofloxacinhydrochloride showed appreciable film forming properties. The inserts were found to be uniform, tough, elastic and bioadhesive. On the basis of in vitro, and microbiological studies, it could be concluded that ciprofloxacinhydrochloride could be successfully administered through gel forming controlled release ocular inserts for treatment of bacterial keratitis and conjunctivitis.

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