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Gatifloxacin Bipolymeric Ophthalmic Inserts: *in vitro* Studies on Drug Release

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A variety of conventional ophthalmic drug delivery options exist. However, once a day options are highly in need due to obvious reasons. Bipolymeric ophthalmic inserts of gelatin and alginate, cross-linked with Ca^{2+}, with gatifloxacin loaded in different concentrations, were obtained by a casting-solvent evaporation method. The inserts were characterized for their mechanical properties, as well as the studies of the factors that influence the drug releasing from these ophthalmic inserts. These factors included the component ratio of polymers, the loaded amount of gatifloxacin, the thickness of the drug loaded ophthalmic inserts and the cross-linking time with Ca^{2+} and others. The best values of the tensile strength and breaking elongation of bipolymeric ophthalmic inserts were obtained when the gelatin content was 50 % w/v. The results of *in vitro* drug release studies showed that the amount of gatifloxacin released decreased with an increase in the proportion of gelatin present in the inserts. Moreover, the release rate of drug decreased as the amount of drug load in the inserts increased. It was also observed that as the thickness of the inserts increased drug release decreased. When the cross-linking time of these ophthalmic inserts in the Ca^{2+} solution increased, the drug release rate decreased. All the results indicated that the gelatin-alginate bipolymeric inserts suitability in releasing gatifloxacin and to act potentially as a drug delivery system.

Key Words: Bipolymeric, Gatifloxacin, Ophthalmic inserts, Drug release studies.

INTRODUCTION

Topical application of drugs to the eye is the most popular and well-accepted route of administration for the treatment of various eye disorders. But the anatomy, physiology and barrier function of the cornea compromise

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the rapid absorption of drugs[1]. Frequent instillations of eye drops are necessary to maintain a therapeutic drug level in the tear film or at the site of action. But the frequent use of highly concentrated solutions may induce toxic side effects and cellular damage at the ocular surface[2]. Strategies to increase the bioavailability of ophthalmic drugs by prolonging the contact time between the preparation and therefore the drug and the corneal/conjunctival epithelium were required and the use of a water-soluble polymer to enhance the contact time and possibly also the penetration of the drug was first proposed by Swan[3].

Infections of the eye can rapidly damage important functional structures and lead to permanent vision loss or blindness. The prompt use of appropriate antibiotics is essential for preserving vision in the presence of severe eye infection such as bacterial keratitis or endophthalmitis. Gatifloxacin is relatively a new drug employed for the treatment of ocular infections. Recently, Levine *et al.*[4] reported that gatifloxacin exhibited remarkably better aqueous penetration following topical dosing in a rabbit model. In addition, of all the drugs studied gatifloxacin alone achieved concentrations in excess of the MIC_{90s} of gram-positive pathogens of concern. This justifies us the selection of drug. Gelatin is the major constituent of skin, bones and connective tissue. Because of its excellent biodegradability and biocompatibility, the denatured type collagen; gelatin has been used in medical industry as plasma expander, wound dressing, adhesive and absorbent pad, especially as matrix material for drug controlled release[5]. Gelatin, because of its low intensity and high brittleness, is rarely used alone, being often used after modification through several methods, such as cross-linking[6], grafting[7] and blending[8]. It is well known that blending is effective and convenient method to improve the performance of polymer materials. With regard to the excellent film forming properties of alginate, many new and original films materials has been achieved[9]. Sodium alginate, widely used in food and pharmaceutical industries, is water soluble salt of alginic acid, a naturally occurring non-toxic polysaccharide found in all species of brown algae. In addition, sodium alginate has a unique property of cross-linking in the presence of multivalent cations, such as Ca^{2+} in aqueous media and form insoluble calcium alginate. Depending on the degree of such cross-linking, alginate will reduce significantly its swelling in the presence of the solvent, resulting generally in a reduction of the permeability of different solutes. As a consequence, the release of embodied drugs in alginate matrices will be delayed, allowing these systems to be used in drug controlled release[10], which justifies the selection of bipolymeric blend.

In present study, the gelatin-alginate bipolymeric ophthalmic inserts (BO inserts) were prepared which is capable of releasing gatifloxacin. In addition, we studied some factors that may have influence on the drug

release from these BO inserts as the ratio of gelatin and alginate used, the loaded amount of gatifloxacin, the thickness of the drug loaded ophthalmic inserts and the cross-linking time with Ca^{2+}, *etc*.

EXPERIMENTAL

Gatifloxacin was a gift sample from Cross Medineeds Pvt. Ltd. (Chennai, India). Other ingredients used were all of analytical grade or better.

Preparation of drug loaded ophthalmic inserts: Drug loaded BO inserts were produced by a casting-solvent evaporation technique. Solutions of gelatin and alginate, 2 % (w/v), were prepared with distilled water. These solutions were mixed in different proportions to obtain final gelatin amounts of 20, 50 and 80 % (w/v). 0.2 g of gatifloxacin was dissolved, under stirring, in 50 mL of each one of these three resulting solutions to make them completely homogeneous. After that, they were sonicated, left undisturbed till trapped air bubbles were removed and poured on a glass plate lined with aluminum foil of 8″ × 6″. The BO inserts were dried in an oven at 37 °C until constant weight. Subsequently, the dried BO inserts were immersed into a 5 % (w/v) $CaCl_2$ solution to permit cross-linking for 15 min. Next, they were washed with distilled water, put on a glass plate and oven-dried at 37 °C for 48 h and finally dried under vacuum at room temperature until constant weight. These dried BO inserts, with a thickness of approximately 40 μm, were cut into 1 square inch sections for further studies. The several drug loaded BO inserts, prepared with gatifloxacin, were designated as DSS-1, DSS-2 and DSS-3.

Following the above method, 0.1 or 0.3 g of gatifloxacin was dissolved in a solution of gelatin and alginate (50:50 %w/v), producing drug loaded BO inserts designated as DSS-4 and DSS-5, respectively. By changing the volume of the forming solution of DSS-2 poured on the glass plate, it was achieved drug loaded BO inserts with different thickness of *ca.* 30 μm and *ca.* 55 μm, marked as DSS-6 and DSS-7, respectively. Finally, using DSS-2 inserts as sample, we immersed it into a 5 % (w/v) $CaCl_2$ solution for different time to get different degrees of cross-linking.

Mechanical properties: The tensile strength and the breaking elongation for dried drug loaded BO inserts were determined on an automatic tensometer (M/s Prolific Pvt.Ltd., Noida, India). All samples were preconditioned at 20 °C and 65 % relative humidity, for 24 h prior to mechanical testing. Six identical studies were carried out in parallel for each batch subjected to the study.

Drug release studies: The drug loaded BO inserts were suspended in glass vials containing 10 mL of simulated tear fluid (pH 7.4) as medium and incubated at 37 °C. At appropriate time intervals the solutions were

withdrawn and the amount of gatifloxacin released from the drug loaded BO inserts were evaluated by UV spectrophotometer at 285 nm. Then, an equal volume of dissolution medium was added back to maintain a constant volume. Six identical studies were carried out in parallel for each batch subjected to the study.

RESULTS AND DISCUSSION

Mechanical properties: Fig. 1 shows the mechanical properties of the drug loaded BO inserts. From the figure, it may be seen that the maximum value of tensile strength (108.9 MPa) and breaking elongation (20.8 %) were both observed with formulation DSS-2 when the content of gelatin was 50 % (w/v). The results indicated that bipolymeric blending is effective in improving the mechanical properties of the drug loaded BO inserts.

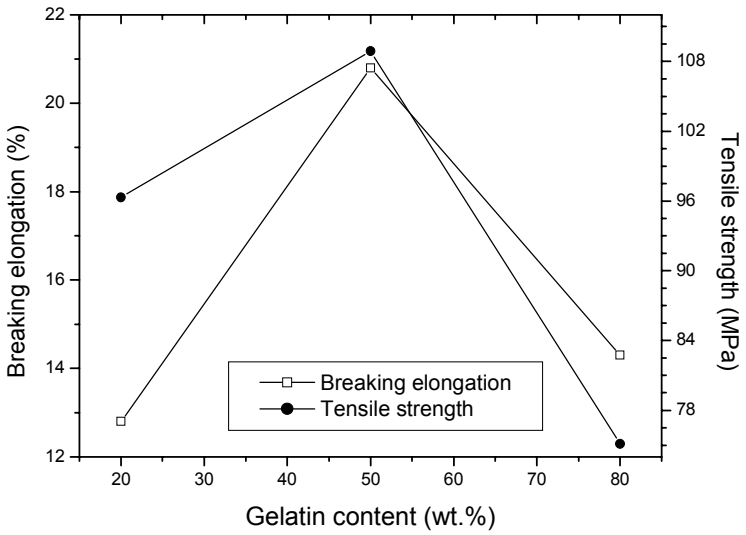

Fig. 1. Mechanical properties of gatifloxacin loaded BO inserts

Release studies

Effect of the composition ratio of bipolymers on gatifloxacin release: The influence of the different composition ratios of bipolymers in the drug loaded ophthalmic inserts DSS-1, DSS-2 and DSS-3 (20, 50 and 80 % (w/v) of gelatin, respectively) was investigated in this experiment. The release medium conditions, were as mentioned earlier. As Fig. 2 shows, the results of the release increased from 42.2 to 100 % as the content of gelatin increased from 20 to 80 %. In other words, as the alginate content decreased, the formation of the insoluble calcium alginate, resultant from sodium alginate

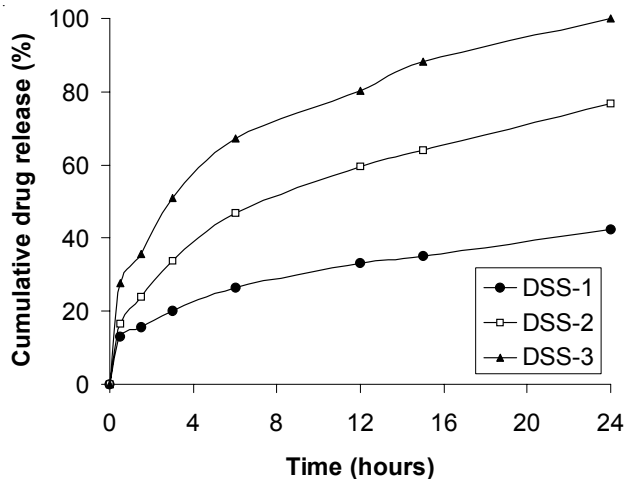

Fig. 2. Influence of the composition of the gelatin in gatifloxacin loaded BO inserts on drug release

cross-linking with Ca^{2+}, decreased. Yet, as gelatin is a kind of soluble macromolecule, it dissolves and leaves pores that accelerate the release of the drug from the BO inserts.

Effect of the drug load on gatifloxacin release: BO inserts DSS-4, DSS-2 and DSS-5 with different drug load (0.1, 0.2 and 0.3 g, of gatifloxacin, respectively) were subjected drug release studies. From Fig. 3, it may be concluded that the more drugs loaded, the lower the drug release rate was. So we can get a more persistent release by increasing the drug loaded amount.

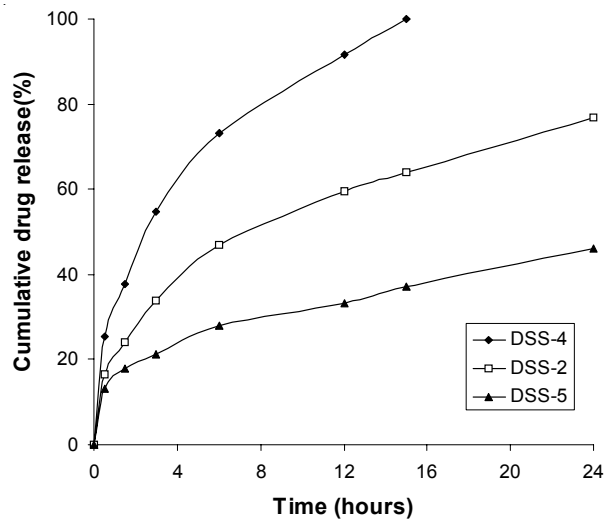

Fig. 3. Influence of drug load on gatifloxacin release

Effect of the thickness on gatifloxacin release: The drug release from BO inserts DSS-6, DSS-2 and DSS-7, with different thickness, was investigated by subjecting the BO inserts for drug release studies. From Fig. 4, it can be observed that the drug release declined as the thickness of the ophthalmic inserts increased. This clearly indicates that the thickness of the inserts changes the rate of the drug diffusion.

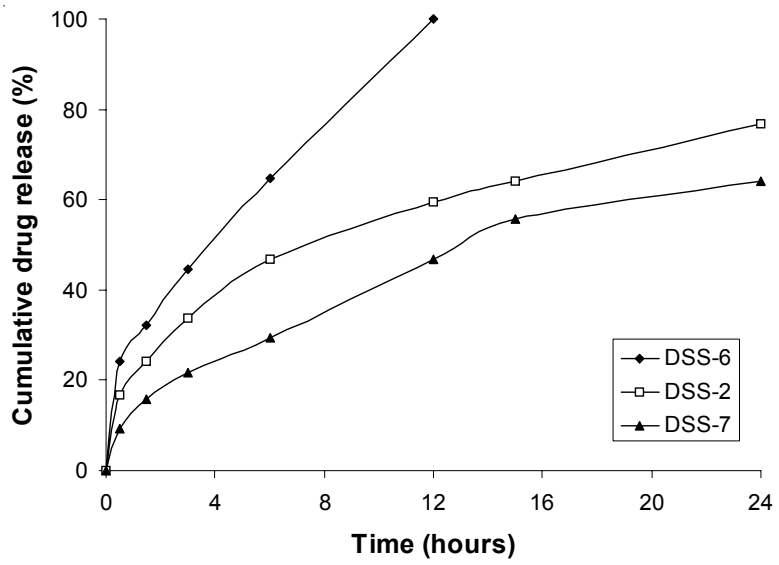

Fig. 4. Influence of BO insert thickness on gatifloxacin release

Effect of cross-linking time on gatifloxacin release: Drug loaded BO inserts DSS-2 cross-linked at different time were produced by casting-solvent evaporation method. The drug loss during the cross-linking process was estimated by UV spectrophotometer at 285 nm. After that, the BO inserts were subjected to drug release studies. The results in Table-1, show that the amount of drug lost during the cross-linking process did not change significantly, being less than 6.1 % for all samples tested. However, it may be seen in Fig. 5 that, the longer the cross-linking process, slowest will be the drug released, due to a higher degree of cross-linking formed in the matrix, causing a delay in the rate of drug release.

TABLE-1
INFLUENCE OF CROSS-LINKING TIME ON
GATIFLOXACIN LOSS RATE

Cross linking time (min)	5	15	30
Drug loss (%)	4.1	5.3	6.1

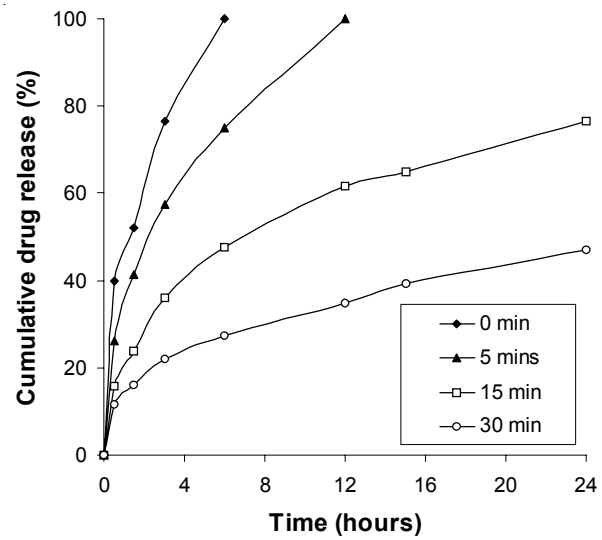

Fig. 5. Influence of cross-linking time on gatifloxacin release

Conclusion

Gatifloxacin releasing BO inserts was produced by a casting-solvent evaporation method. The results indicated that the polymeric composition, drug load, thickness of the inserts and cross-linking time all had relevant influence on the release properties. The BO inserts can lead to a successful application for localized drug delivery after optimization of dose release followed by animal studies and extensive clinical trials, which shall further the study.

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