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Chitosan-Polyethylene Glycol Blend Films as Local Ophthalmic Drug Delivery Units: *in vitro* Studies and Factors Influencing Drug Release

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Chitosan and polyethylene glycol (PEG) blend films with gatifloxacin as model drug were fabricated for local ophthalmic delivery. Mechanical characterization and influence of various parameters on drug release were also studied. The results of drug release studies showed that the amount of gatifloxacin released increased with an increase in the proportion of polyethylene glycol and decreased as the amount of drug loaded in the film increased. Gatifloxacin release was also sensitive to ionic strength and declined as the film thickness, sodium alginate coat thickness, cross-linking time increased.

Key Words: Ophthalmic insert, Blend films, Gatifloxacin, *in vitro* studies.

INTRODUCTION

The field of ocular delivery is one of the most interesting and challenging endeavors facing pharmaceutical scientists. The unique anatomy, physiology and biochemistry of the eye render this organ impervious to foreign substances, thus presenting a constant challenge to the formulator to circumvent the protective barriers of the eye without causing permanent tissue damage[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/conjunctiva 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].

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Chitosan, a natural polymer obtained by the hydrolysis of chitin, is the second most abundant polysaccharide after cellulose. It exhibits excellent biodegradability, biocompatibility and antimicrobial activity[4,5]. Chitosan has good gel and film forming properties. It dissolves in dilute acetic acid solutions. Hence, uses of harsh and denaturing organic solvents, such as methylene chloride, are not needed for film preparation unlike many biodegradable polymers. The mucoadhesive performance of chitosan is significantly higher at neutral or slightly alkaline pH as in the tear film[6]. Therefore, chitosan has been investigated extensively in the pharmaceutical research for its potential use in the development of drug delivery systems including ophthalmic delivery[7-9]. Polyethylene glycol (PEG) is a water-soluble polymer that has been widely used in pharmaceutical preparations on account of its safety, hydrophilicity, biocompatibility, lack of antigenicity and low toxicity[10,11]. It is often blended or compounded with other polymers to be used in the field of drug-controlled release[12-14]. In addition, presence of poly(ethylene glycol) (PEG) chains can modulate the interfacial properties of the system and thus influence mucoadhesion and drug absorption in ocular drug delivery[15].

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.*[16] 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.

In the present study, the ability of chitosan-PEG blend films to deliver gatifloxacin in a sustained fashion so as to act as ophthalmic inserts and a study of some factors that may influence the drug release from chitosan-PEG films as function of the ratio of chitosan and PEG used, the loaded amount of gatifloxacin, the ionic strength of the release solution, the thickness of the drug loaded films, the coating layer of sodium alginate and the cross-linking time have been attempted.

EXPERIMENTAL

Chitosan and Gatifloxacin (as Gatifloxacin sesquihydrate) were gift samples from Cross Medineeds Pvt. Ltd., Chennai. PEG6000 was a product of BDH chemicals (Mumbai, India). Other reagents used were all of analytical grade.

Fabrication of drug loaded inserts: Chitosan-PEG blend films loaded with drug were produced by a casting-solvent evaporation technique. Solutions of chitosan and PEG, 2 wt %, were prepared with 2 wt % acetic acid solution and distilled water, respectively. These solutions were mixed in different proportions to obtain final PEG solution concentrations of 2.0, 4.0, 6.0 and 8.0 wt %. 0.2 g of gatifloxacin was dissolved, under stirring, in 50 mL of each one of these four resulting solutions to make them completely homogeneous. After that, they were sonicated in a sonication bath, left to stand until trapped air bubbles were removed and poured on a glass plate lined with aluminum foil of 8″ × 6″. These films were dried at 37 °C for 48 h and finally dried under vacuum at room temperature until constant weight. These dried films (with an average thickness of 50 μm, measured with vernier caliper), were cut into units of considerable measures to perform various tests.

Several chitosan-PEG drug loaded units were fabricated with varying PEG contents and designated as F-1, F-2, F-3 and F-4 (PEG contents were 2.0, 4.0, 6.0 and 8.0 wt %, respectively). Following the above method, different amounts of gatifloxacin (0.1 and 0.3 g) was dissolved in solutions (PEG contents ratio was 4.0 wt %), producing drug loaded films designated as F-5 and F-6, respectively. By changing the volume of the forming solution of F-2 poured onto the aluminum layered glass plate, drug loaded films were achieved with different thickness of 30 and 80 μm, marked as F-7 and F-8, respectively. In addition, F-2 films were dipped in sodium alginate solutions and dried. The thickness of the coating layer was determined to be 4 and 8 μm by aforementioned methods and they were marked as F-9 and F-10, respectively. Finally, F-2 inserts, were immersed in a 2 wt % tripolyphosphate (TPP) solution for different times to get different degrees of cross-linking. After being washed with distilled water, these films were dried as earlier formulations.

Mechanical properties: The tensile strength and the breaking elongation for dried drug loaded films 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.

Release studies: The drug loaded films were suspended in glass vials containing 10 mL of pH 7.4 (10 mM NaH_2PO_4-Na_2HPO_4-buffered solution) as medium and incubated at 37 °C. At appropriate time intervals aliquots of the solutions were withdrawn and the amount of gatifloxacin released from the drug loaded films were evaluated by UV spectrophotometry at 286 nm. Then an equal volume of the same 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: From the mechanical properties of the drug loaded films (Fig. 1.), it may be seen that the maximum value of tensile strength and elongation at breaking were both observed when the content of PEG was 6.0 wt %, indicating that blending is effective in improving the mechanical properties of the drug loaded films.

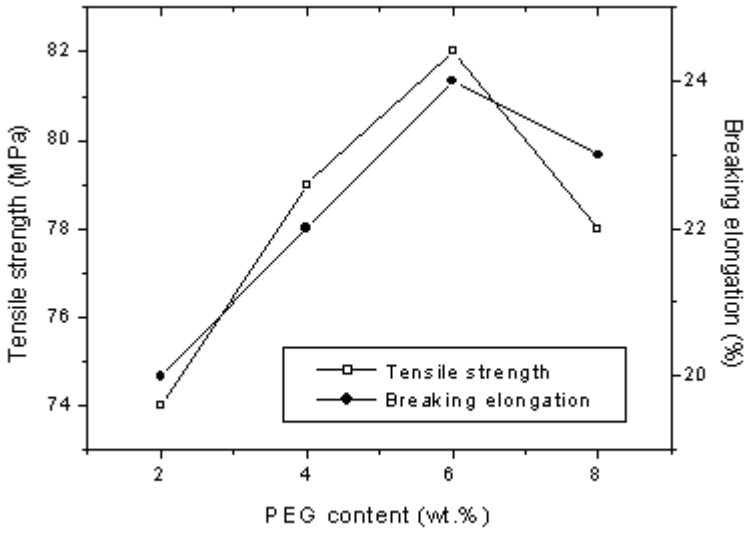

Fig. 1. Mechanical properties of drug-loaded chitosan-PEG films.

Release studies

Effect of the composition ratio of chitosan and PEG on gatifloxacin release: The influence of the different composition ratios of chitosan and PEG in the drug loaded films F-1, F-2, F-3 and F-4 on the release of gatifloxacin into 10 mM sodium phosphate buffer, pH 7.4 (ionic strength of 0.145 M) (Fig. 2), was such that the release rate of drug increased with increase in content of PEG. This could be because PEG is somewhat soluble in these aqueous solutions and it dissolves and leaves pores that accelerate the release of the drug from the matrix film.

Effect of the drug loaded amount: Testing of films F-5, F-2 and F-6 with different drug loaded amounts (Fig. 3) showed that higher the drug load, the lower the cumulative drug release rate was. But according to the fact that more drugs were loaded, the cumulative release amount is increasing. So more persistent release can be achieved by increasing the drug load.

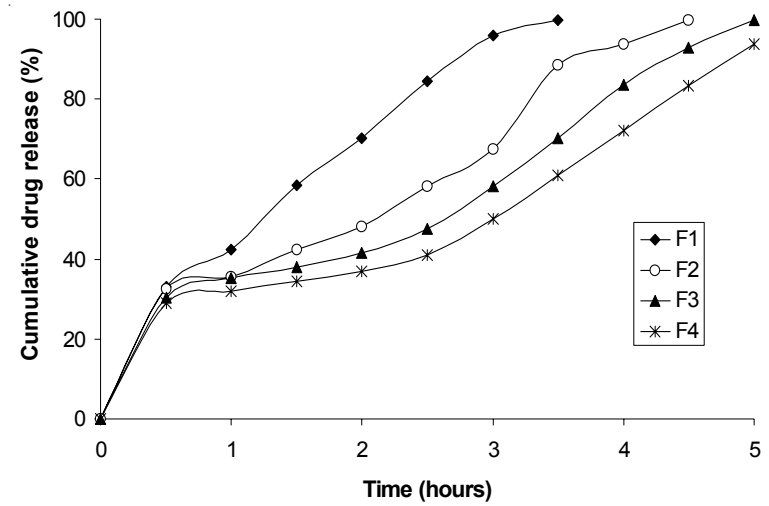

Fig. 2. Influence of the composition ratio of drug-loaded chitosan-PEG films on the controlled drug release process

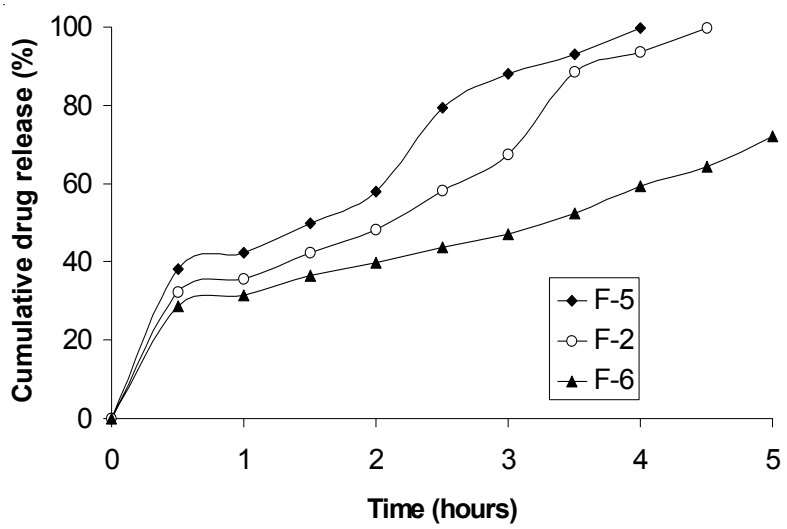

Fig. 3. Influence of the amount of drug-loaded in chitosan-PEG films on the controlled drug release process

Effect of the thickness of drug loaded films: The drug release from films F-7, F-2 and F-8 with different thicknesses (30, 50 and 80 μm, respectively), (Fig. 4) declined as the thickness of the films increased. This shows clearly that the thickness of the film changes the rate of the drug diffusion into the matrix film.

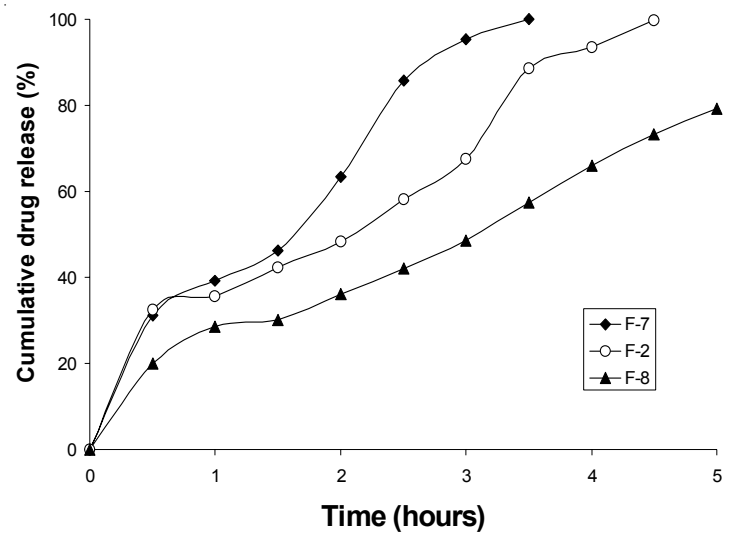

Fig. 4. Influence of film thickness of drug-loaded chitosan-PEG film on controlled drug release

Effect of ionic strength: Adding an appropriate amount NaCl to the 10 mM NaH_2PO_4-Na_2HPO_4 buffer, pH 7.4, produced different release media of different ionic strength (10, 20 and 30 mM). Fig. 5 shows that with the increase of ionic strength the drug release rate also increased. The result was possibly related to the decrease of osmotic pressure inside the film with the increase of the salt concentration and the weakened salt-bond between gatifloxacin and film matrix by salt ion.

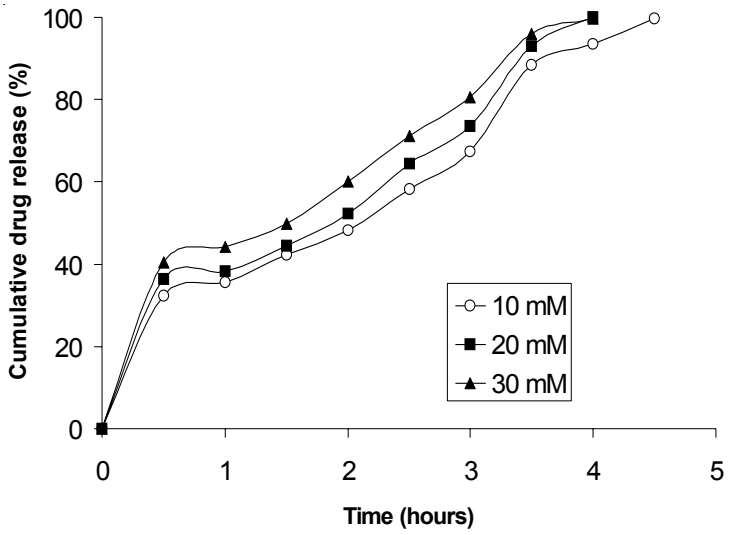

Fig. 5. Influence of ionic strength of the release medium on gatifloxacin controlled release from chitosan-PEG films containing the drug

Effect of sodium alginate coating of drug loaded film: The effects of sodium alginate coating layers of drug loaded films (Fig. 6) lead to the conclusion that the sodium alginate coating layer can prolong the drug's release efficiently. The main reason was that there were strong electrostatic interactions between the molecules of chitosan and sodium alginate at high pH[17].

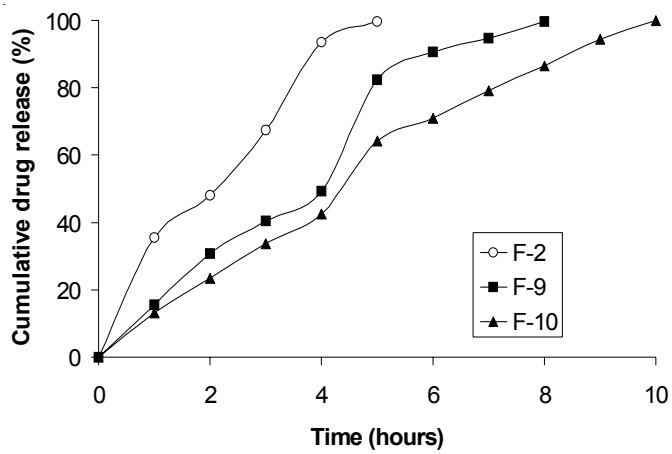

Fig. 6. Influence of sodium alginate coating layer on gatifloxacin controlled release from chitosan-PEG films containing the drug into simulated intestinal fluid

Effect of cross-linking time: Testing of drug loaded films (F-2) cross-linked for different times (Fig. 7) showed that the longer the cross-linking process, the more slow was the drug released, due to a higher degree of cross-linking formed in the matrix, causing a delay probably in the diffusional release of drug.

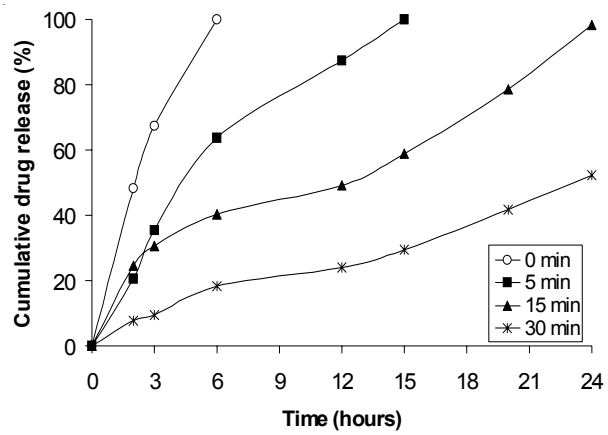

Fig. 7. Influence of cross-linking time in 2 wt % TPP solution on the gatifloxacin controlled release from chitosan-PEG films

Conclusion

Gatifloxacin local ophthalmic drug delivery units based on chitosan and PEG blend films were fabricated by a casting-solvent evaporation method. The films' characteristics were studied *in vitro* and its ability in releasing the drug in a sustained fashion so as to act as ophthalmic inserts. The films' mechanical property was good. The results of drug release studies showed that the amount of gatifloxacin released increased with an increase in the proportion of PEG and decreased as the amount of drug loaded in the film increased. Gatifloxacin release was also sensitive to ionic strength and declined as the film thickness and sodium alginate coat thickness increased. In addition the longer the cross-linking time of the films the more slowly the drug release was. Of the studied formulations and conditions, formulation F-2 with a cross linking time of 15 min was capable of releasing the loaded drug for 24 h; establishing their suitability to act as local ophthalmic drug delivery units. These gatifloxacin ophthalmic 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 be for further study.

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