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Original Research Paper

FORMULATION AND *IN-VITRO* EVALUATION OF PERIODONTAL FILMS CONTAINING OFLOXACIN

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Abstract

Ofloxacin is a used to treat periodontitis infections. For local delivery, ofloxacin films were prepared by solvent casting technique using ethyl cellulose, hydroxy propyl methylcellulose and eudragit RL-100 with dibutylphthalate and polyethylene glycol 400 as plasticizers. FTIR and UV spectroscopic methods revealed no interaction between ofloxacin and polymers. The films were evaluated for their thickness uniformity, folding endurance, weight uniformity, content uniformity, tensile strength, and surface pH. Formulation F6 released 96.40% of drug at the end of 120 h, was considered as best formulation.

Key Words: Periodontal pocket, Periodontal films, Local delivery

Introduction

The presence of periodontal pathogens such as *Porphyromonas gingivalis*, *Prevotella intermedia* and *Actinobacillus actinomycetemcomitans* are responsible for periodontal destruction. Therefore, an objective of periodontal treatment is to suppress or eliminate sub gingival periodontal pathogens. However, some patients may experience continued periodontal attachment loss, and this may be due to some periodontal pathogens that are inaccessible during mechanical periodontal therapy. Periodontal diseases are recognized as the major public health problem throughout the world. Daily oral hygiene plays a vital role in maintaining healthy teeth and gums. Periodontal disease can do occur in all age groups, ethnicities, races, genders and socioeconomic levels.

The term "Periodontal Disease" broadly defines several diseases associated with the periodontium. Changes in the micro flora, histopathological variations, clinical symptoms, and the location of the inflammation help to further delineate periodontal disease. Gingivitis, the moderate stage of the disease, caused by an accumulation of supragingival plaque is characterized by swelling, light bleeding and redness of marginal gingival. Gingivitis is associated with a change in micro flora, shifting from a gram-positive anaerobic flora to a more gram-negative flora. Periodontitis a more severe stage of periodontal disease, results in the resorption of the alveolar bone and detachment of the periodontal ligaments supporting the tooth.

One of the clinical features of the periodontal disease is the formation of a periodontal pocket, which is pathologically deepened sulcus. In normal sulcus, the gap between the gingiva and the tooth is normally between 1 and 3 mm deep. However, during periodontitis, the depth of pocket usually exceeds 5 mm. [1]

The main cause of periodontal disease is bacteria plaque, a sticky, colourless film that constantly forms on teeth. However, factors like smoking/ tobacco use, genetics, pregnancy and puberty, stress, medication, clenching or grinding teeth, diabetes

and poor nutrition also lead to periodontal diseases. Periodontal pathogens grow only where atmosphere and nutrient composition are strictly conductive to their requirements and the disease once established, causes major changes in the periodontal microenvironment. The gingival crevicular fluid (GCF) flow mucosa, gingival bleeding and localized pain are suggestive of the presence of periodontal pockets. [2,3]

Ofloxacin is a fluorinated carboxy quinolone exhibiting a marked bactericidal effect by inhibiting DNA gyrase. *In vitro* studies on bactericidal activity have suggested that ofloxacin is likely to be the most useful drug in the treatment and in preventing the periodontitis. It is a synthetic broad-spectrum antimicrobial agent for oral administration. The relative solubility characteristics of ofloxacin at room temperature indicate that it is soluble in aqueous solutions with pH between 2 and 5. It is sparingly to slightly soluble in aqueous solutions with pH 7 (solubility falls to 4 mg/mL) and freely soluble in aqueous solutions with pH above 9.[4]

Material and methods

Materials

Ofloxacin was a gift from Dr. Reddy's Laboratory, Hyderabad, India. Ethyl cellulose was obtained from KAPL (Bangalore, India), 47 cps hydroxy propyl methylcellulose (HPMC) was obtained from Rolex Chemical Industries (Mumbai, India), and Eudragit RL-100 was obtained from Rohm-pharm, Germany. Polyethylene glycol (PEG)-400, dibutyl pthalate was purchased from Loba Chemie, Mumbai. Chloroform was purchased from Ranbaxy fine chemicals Ltd, Acetone was purchased and HPLC-grade solvents from Ranbaxy Fine Chemicals Ltd, India, were also used in the study.

Drug-polymer compatibility

The compatibility between drug and polymer was studied using IR peak matching method.

Preparation of cast film containing ofloxacin

Periodontal films were prepared by solvent casting technique. Glass moulds were used for casting the films. Ethylcellulose, Eudragit RL-100 alone and in combination with hydroxyl propyl methyl cellulose were dissolved in chloroform and alcohol mixture with dibutyl phthalate as a plasticizer in a beaker using magnetic stirrer to get different concentration of polymeric solutions. Into these solutions, ofloxacin of required concentration was added. After complete mixing, the solution was poured into a clean glass mould placed on a horizontal plane. The solvent was allowed to evaporate slowly by inverting a glass funnel with a cotton plug in the stem of the funnel was placed on the mould at room temperature for 24 h. After complete evaporation of solvent, cast film was obtained. Inverted funnel was continuously kept on the mould to control drying rate. The prepared cast films were lined with butter paper and stored in desiccator. To accommodate different variables, batches of cast films were prepared. The compositions of films are given in Table 1.

Table 1: Composition of different batches of periodontal films containing ofloxacin

Ingredients	Film Code					
	F1	F2	F3	F4	F5	F6
Ofloxacin	120 mg	120 mg	120 mg	120 mg	120 mg	120 mg
Ethyl cellulose	-	-	460 mg	460 mg	460 mg	460 mg
Eudragit RL 100	460 mg	460 mg	460 mg	460 mg	460 mg	460 mg
HPMC	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Dibutyl phthalate	-	-	0.2 mL	0.2 mL	0.15 mL	0.15 mL
PEG 400	0.1 mL	0.1 mL	0.1 mL	0.1 mL	0.1 mL	0.1 mL
Alcohol	15 mL	15 mL	15 mL	15 mL	15 mL	-
Chloroform	-	-	-	-	-	15 mL

Evaluation of the films

Formulated films were subjected to the preliminary evaluation tests. Films with any imperfections, entrapped air, or differing in thickness, weight (or) content uniformity were excluded from further studies.

Thickness uniformity: The thickness of each film was measured using screw guage (thickness tester) at different positions of the film and the average was calculated.

Uniformity of weight: Film (size of 1 cm^2) was taken from different areas of film. The weight variation of each film was calculated.

Tensile strength: Tensile strength of the films was determined with Universal strength testing machine. The sensitivity of the machine is 1 g. It consists of two load cell grips; the lower one is fixed and the upper one is movable. The test film of specific size (4 cm^2) was fixed between these cell grips and force was gradually applied till the film breaks. The tensile strength of the film was taken directly from the dial reading in kilograms.

Drug content uniformity: Film (size of 1 cm^2) was taken from different areas of film and placed in a 10 mL volumetric flask; 10 mL of ethyl alcohol was added and kept aside till the film dissolve completely. From this solution, 1 mL was pipette out and diluted to 10 mL with double distilled water. The absorbance of the solution was measured at 300 nm. The polymer solution without drug serves as a blank. In case of HPMC film, combination of water and alcohol is used to dissolve the film.

Folding endurance: As described by Khanna et al[5], the folding endurance of the films was determined by repeatedly folding one film at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good film properties. The film was folded number of times at the same place without breaking gave the value of the folding endurance. This test was done on all the films for five times.

Surface pH: Periodontal films were left to swell for 1 h on the surface of the agar plate, prepared by dissolving 2% (w/v) agar in warmed double distilled water under stirring and then pouring the solution into the petridish to gelling / solidify at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen film. The mean of three readings was recorded.[6]

Viscosity: Aqueous solutions containing both polymer and plasticizer were prepared in the same concentration as that of films. Brookfield viscometer (LVDV-E model) attached to the helipath spindle number 18 was used. The viscosity was measured at 20 rpm at room temperature. The recorded values were the mean of five determinations**.**

In vitro drug release: In-vitro drug release was performed by taking 1 cm^2 of periodontal film in a vial containing one mL of double distilled water. One mL of double distilled water was withdrawn from 1st to 5th day, every day and immediately replaced with one mL of fresh double distilled water.[7] The drug content was estimated by measuring the absorbance after suitable dilution at 300 nm.

Ageing: Optimized medicated films were subjected to stability testing. Films were placed in a glass beaker lined with aluminum foil and kept in a humidity chamber maintained at 40 ± 2°C and 75 ± 5% RH for 1 month. Changes in the appearance and drug content of the stored films were investigated after storage.[8]

Results and discussion

FT-IR spectra of ofloxacin alone and its combination with polymers are shown in Fig. 1. FTIR spectra of the pure ofloxacin and the drug polymer mixture showed characteristic bands at 2520.51 cm^{-1}, 2135.78 cm^{-1}, 1803.12 cm^{-1}, and 1464.67 cm^{-1} due to functional groups, indicating the chemical stability ofloxacin in the chosen polymeric mixture. This also indicates that ofloxacin is not involved in any chemical reactions with the polymers used.[9]

In the preparation of films, it was observed that the addition of the plasticizer produced a film of good strength. The films were translucent and visually smooth surfaced. The developed method of preparation of films was reproducible.

In the folding endurance study, the films did not show any cracks even after folding for more than 300 times. Hence it was taken as the end point. Folding endurance did not vary when the

comparison was made between dummy films and drug-loaded films (Table 2). The viscosities of the solutions used for the preparation of films were found to range from 12.10 to 33.70 cps for films F1 to F6. Viscosity of the solution of film F6 was highest when compared to others, because of the presence of ethyl cellulose.

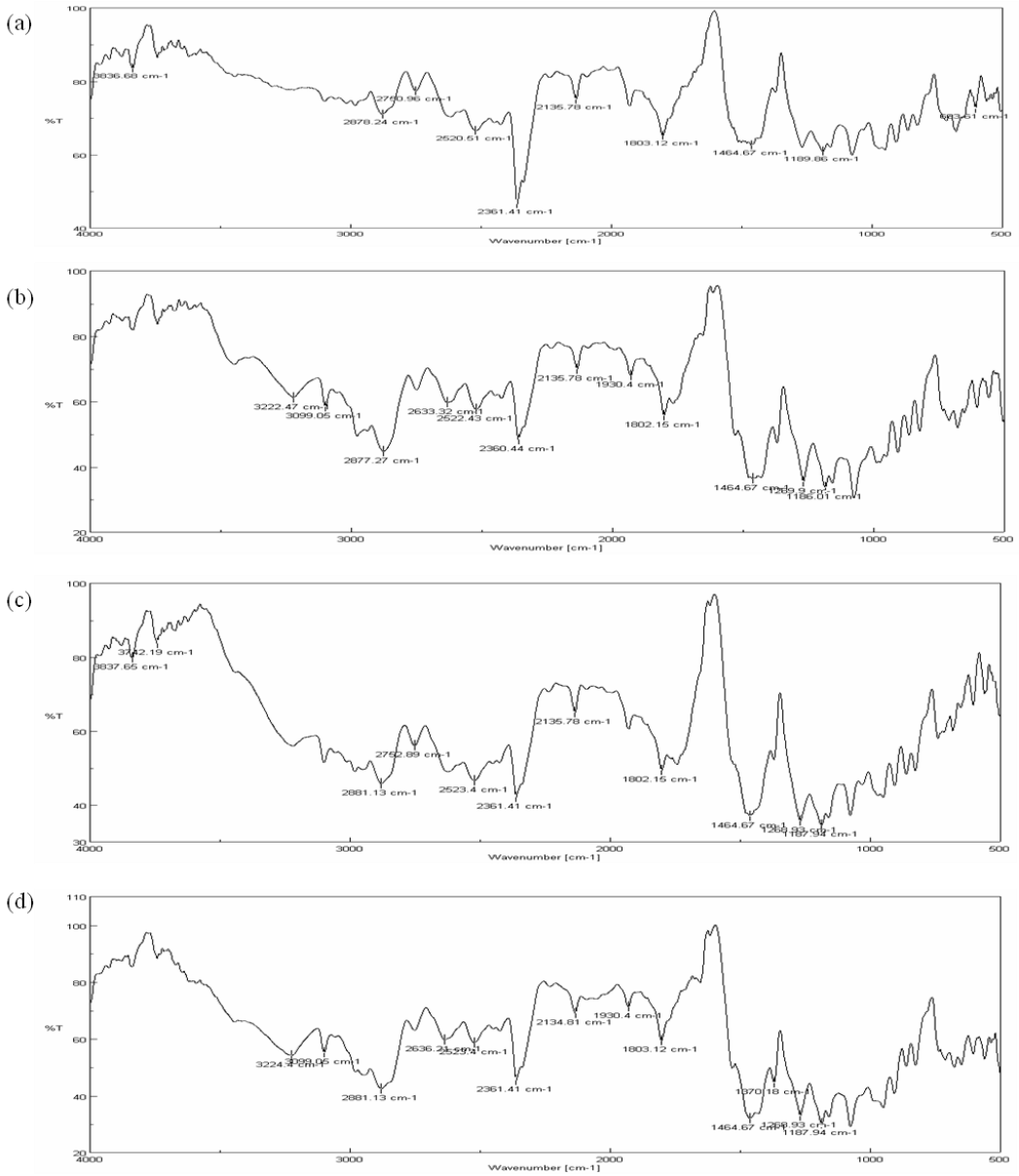

Fig. 1. FTIR spectra of drug and polymers (a) Ofloxacin pure, (b) Ofloxacin and ethyl cellulose mixture, (c) Ofloxacin and eudragit RL-100 mixture, (d) Ofloxacin and HPMC 47 cps mixture

In vitro release studies performed using double distilled water showed an initial burst release (Fig. 2), which is expected to kill most of the periodontal organisms, followed by controlled release, sufficient to inhibit the growth of the micro-organisms. Periodontal films made of ethyl cellulose (F6) were better than others because the extent of release was maintained for about 5 days. All the formulations showed initial burst release, followed by controlled release in later phases. Higher drug release from films F1, F2, and F3 showed 97.7, 98.9, and 96.8% respectively. The higher drug release from these films was possible because of the formation of more pores and channels due to presence of higher HPMC content. As HPMC act as resorbable carriers, it dissolved readily during *in vitro* drug release. In the aging

studies, the films did not exhibit any changes in the physicochemical properties and release profile, over a period of one month (data not shown).

Table 2. Physicochemical characteristics of periodontal films containing ofloxacin

Flim code	Thickness (mm)	Weight (mg)	Tensile strength (kg)	Folding endurance	Cum. release (%)
F1	225	32.107	5.765	>250	89.65
F2	223	33.400	4.575	>250	85.40
F3	221	34.510	2.338	>250	88.53
F4	222	35.740	2.304	>250	75.42
F5	210	33.450	2.543	>250	78.98
F6	236	32.425	2.653	>250	90.56

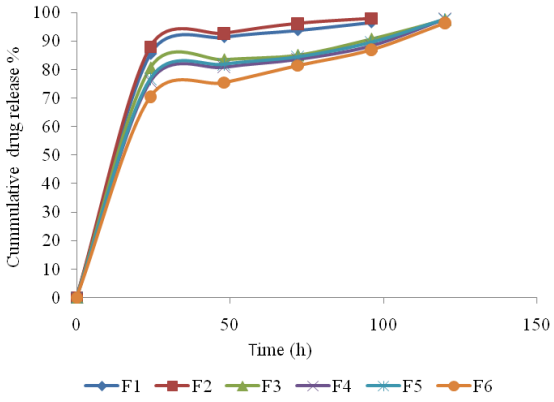

Fig 2: Drug release profile of different batches of periodontal films (F1 to 6)

Conclusion

The advantages of intra-pocket delivery over systemic delivery in periodontitis are that administration is less time-consuming than mechanical debridement and a lower dose of drug would be required to achieve effective therapeutic concentration at the site of action. The drug-loaded chitosan films were flexible, demonstrated satisfactory physicochemical characteristics. Although the films showed an initial burst release of drug, release was sustained for up to 10 days for uncrosslinked and crosslinked films, respectively. Thus chitosan films loaded with ofloxacin, particularly those crosslinked with gluteraldehyde, may have a role for the therapy of periodontitis.

Declaration of Interest

It is hereby declared that this paper does not have any conflict of interest.

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