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FORMULATION AND EVALUATION OF MOXIFLOXACIN PERIODONTAL FILMS

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ABSTRACT

Moxifloxacin is a broad spectrum antimicrobial agent, which is formulated into films and evaluated for the treatment of periodontitis. Chitosan films containing moxifloxacin in three different concentrations (10%,20% and 30% w/w to the weight of polymer), MBL-30%, MTL-30% were prepared by the solvent casting technique, using 1%v/v acetic acid solution. The prepared films were evaluated for various properties such as weight variation, tensile strength, stability studies, in-vitro release and moisture loss studies. Average weight and thickness among the different films was uniform. Tensile strength was minimum for single layer and maximum for bilayer and trilayer films. The stability studies did not show any significant changes. Static dissolution studies showed a burst release initially followed by a progressive fall in the release of the drug.

KEY WORDS: **Chitosan, Moxifloxacin, Periodontitis, Films.**

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INTRODUCTION

Periodontal disease is a term that encompasses several pathological conditions affecting the tooth supporting structures. Periodontal disease includes conditions such as chronic periodontitis, aggressive periodontitis, systemic disease associated periodontitis and necrotizing periodontitis[1]. These conditions are characterized by destruction of the periodontal ligament, resorption of the alveolar bone, and the migration of the junctional epithelium along with the tooth surface. The clinical signs of periodontitis are changes in the morphology of gingival tissues, bleeding upon probing as well as periodontal pocket formation. This pocket provides an ideal environment for the growth and proliferation of anaerobic pathogenic bacteria[2].Conventional therapy, based on scaling, surgery and the use of antibiotics or antimicrobials has been proposed[3].but due to bacterial resistance and toxic side effects of the administered antibiotics local delivery system are designed to maintain the antibiotic, in the gingival crevicular fluid at a concentration higher than that achieved by systemic administration[4].Moxifloxacin is a fourth generation fluoroquinolone with a broad antibacterial activity against Gram-positive and Gram-negative bacteria. Moxifloxacin shows bactericidal, concentration dependent, anti-infective. It interferes with bacterial survival by binding to DNA gyrase (topoisomerase II) and topoisomerase IV, essential bacterial enzymes involved in the replication, translation, repair and recombination of deoxyribonucleic acid[8].Chitosan is obtained by deacetylation of chitin, is a natural, non-toxic, biocompatible and biodegradable polysaccharide suitable for applications in pharamaceutical technology. Chemically it is poly-β-(1,4)-2-amino-deoxy-D-glucopyranose. It is soluble in dilute acid solutions like dilute lactic acid and dilute acetic acid. It is used as a film forming agent, gel forming agent, with its immunostimulatory activities, anticoagulant properties, antibacterial and antifungal action and for its action as a promoter to be used in periodontitis[5,6,7].

MATERIALS AND METHODS

A gift sample of moxifloxacin was obtained from Micro labs., Bangalore, Karnataka, chitosan from Central Institute of Fisheries Technology, Kochi and all other chemicals used were of analytical grade.

PREPARATION OF DENTAL FILMS

Chitosan (2%w/v) was soaked in acetic acid (1% v/v in water) for 24 hours to get a clear solution. This dispersion was filtered through a muslin cloth to remove the undissolved portion of the polymer, and the recquired amount of the drug (0,10,20and 30% w/w of the drug to the weight of polymer) was added and vortexed for 15 minutes, to dissolve the drug in chitosan solution. This dispersion was kept aside for 30 minutes for expulsion of air bubbles. The films were cast by pouring the dispersion into the center of leveled glass moulds, which were allowed to dry at room temperature for 24 hours. After drying the films were cut into strips of the required size (7×2 mm). these were wrapped in aluminium foil and stored in a dessicator until further use[9].Preperation of bilayer films : 15 ml of 2% chitosan cast solution without drug was poured into mould and dry at room temperature to form the first layer of bi-layer membrane. 20 ml chitosan cast solution with 30% drug was cast on the first layer and it was allowed dry at room temperature[10].Preparation of trilayer film : 15 ml of 2% chitosan cast solution without drug was poured into mould and dry at room temperature to form the the down layer of trilayer. 20 ml chitosan cast solution with 30% drug was cast on the down layer and it was allowed to dry to form the middle layer of the trilayer. And then add 15ml of 2% chitosan cast solution without drug was poured onto the previous membrane also after it had been dry again to form the upper layer of the trilayer.

CHARACTERISATION OF THE FILMS

Fourier transform infrared (FTIR) spectroscopy of the drug alone, polymer alone, and polymer along with the drug. Physicochemical properties such as size, thickness, content uniformity, weight variation, folding endurance, tensile strength, percentage moisture loss and percentage moisture absorption of the prepared films were determined.

THICKNESS MEASUREMENT

The thickness of the polymer films (1×1) was determined by using a film thickness tester (digimatic micrometer mitutoyo, Japan). The thickness of the each film at six different places was determined and the average was calculated[11].

WEIGHT DETERMINATION

The weight variation test was carried out by weighing 6 films cut from different places of the same formulation and their individual weights were determined by using the digital balance. The mean value was calculated[12].

FOLDING ENDURANCE STUDIES

This study was determined by repeatedly folding a small strip of film, 2×2 cm in size, at the same place, till it broke[11-13].

TENSILE STRENGTH MEASUREMENT

The Tensile strength of the films was determined by the Universal strength testing machine. It consists of two load cell grips, the lower one is fixed and the upper one is movable. The test films of specific size (2 × 2 cm) were fixed between these cell grips and force was gradually applied till the film breaks. The tensile strength of the films was taken directly from the dial reading in kilograms Measurements were run in triplicate for each film[11].

ESTIMATION OF DRUG CONTENT

The drug loaded chitosan film of known weight (7 × 2 mm) were dissolved in the small volume of 1% (v/v) acetic acid and the drug solution was suitably diluted with 6.6 pH phosphate buffer and the absorbance was measured at 292nm[12].

PERCENTAGE MOISTURE ABSORPTION

The percentage moisture absorption test was carried out to check of known size were weighed and placed in a dessicator containing 100ml of saturated solution of aluminum chloride and 79.5% humidity was maintained. After three days the inserts were taken out and reweighed. The percentage moisture absorption was calculated using the formula.

$$\% \text{ moisture absorbance} = \frac{FW - IW}{IW} \times 100$$

Where IW = Initial weight, FW = Final weight.

PERCENTAGE MOISTURE LOSS

The percentage moisture loss test was carried out to check physical stability or integrity of the inserts. Periodontal inserts of known size were weighed and placed in a dissector containing 100ml of saturated Calcium chloride and 79.5% humidity was maintained. After three days the inserts were taken out and reweighed. The percentage moisture loss was calculated using the formula[13].

$$\% \text{ Moisture Loss} = \frac{IW - FW}{FW} \times 100$$

Where IW = Initial weight, FW = Final weight.

IN-VITRO DRUG RELEASE STUDIES

Since the pH of the gingival fluid lies between 6.5-6.8, phosphate buffer pH 6.6 was used as simulated gingival fluid for the dissolution studies and the films remain immobile in the periodontal pocket, a static dissolution model was adopted.A static dissolution method reported in the literature was adopted in the thesis. Sets of 3 films of known weight and dimension (7 × 2 mm) were placed separately in small test tubes containing 1.0 ml phosphate buffer, pH 6.6. the tubes were sealed and and kept at 37°C ±1 for 24 hours. The buffer was then drained off and replaced with a fresh 1.0 ml phosphate buffer pH 6.6. The concentration of drug in the buffer was

measured at 292nm .The procedure was continued for consecutive days[14].

STABILITY STUDIES

The stability of the drug loaded polymer films was studied at different temperatures using the reported procedure. The 3 films of size (7 × 2 mm) were weighed. The strips were wrapped in aluminum foil and placed in petridishes. These containers were stored at ambient humid conditions, at room temperature (27 ± 2°C), oven temperature (40 ± 2°C**)** and in refrigerator (5-8°C) for a period of 3 months. The samples were analyzed for physical changes such as color and texture. The drug content was estimated at an interval of 1 month using the procedures reported earlier in the thesis[13].

Table 1
Physical characterization of Chitosan films containing different concentrations of moxifloxacin

Film type	Weight variation(mg)	Thickness(mm) AM±SD	Folding Endurance	Tensile Strength (Kg/sq.mm.) AM ± SD
CP	0.999 ± 0.019	0.11 ± 0.012	345.66 ± 16.01	1.27 ± 0.070
MSL-10%	1.267 ± 0.014	0.124 ± 0.015	304.33 ± 12.89	1.746 ± 0.05
MSL-20%	1.797 ± 0.003	0.137 ± 0.212	285 ± 11.13	2.03 ± 0.096
MSL-30%	2.240 ± 0.012	0.142 ± 0.023	227.66 ± 15.044	2.35 ± 0.087
MBL-30%	2.841 ± 0.009	0.202 ± 0.017	182 ± 10.53	2.83 ± 0.080
MTL-30%	3.196 ± 0.017	0.316 ± 0.056	159 ± 9	3.36 ± 0.079

Each value is a mean and standard deviation of six determinations. CP = Chitosan polymer, MSL-10,20,30 = Moxifloxacin single layer with 10% 20% and 30%, MBL-30% = Moxifloxacin bilayer with 30% and MTL – 30% = Moxifloxacin trilayer with 30%.

Table 2
Data for drug content estimation of Chitosan films containing moxifloxacin

Film type	Theorotical drug loading*(mg)	% drug loading
CP	---	---
MSL-10%	132	97.76
MSL-20%	264	97.16
MSL-30%	396	90.12
MBL-30%	396	86.60
MTL-30%	396	85.24

Table 3
Data for % moisture loss and % moisture absorption

Film type	% Moisture loss	% Moisture absorption
CP	19.56 ± 6.23	23.61 ± 8.13
MSL-10%	26.76 ± 9.17	26.53 ± 11.24
MSL-20%	28.83 ± 15.43	26.05 ± 7.56
MSL-30%	30.81 ± 7.56	28.57 ± 19.27
MBL-30%	39.21 ± 8.02	32.54 ± 10.8
MTL-30%	43.94 ± 12.13	34.75 ± 8.46

Each value is a mean and standard deviation of six determinations. CP = Chitosan polymer, MSL- 10,20,30 = Moxifloxacin single layer with 10% 20% and 30%, MBL-30% = Moxifloxacin bilayer with 30% and MTL – 30% = Moxifloxacin trilayer with 30%.

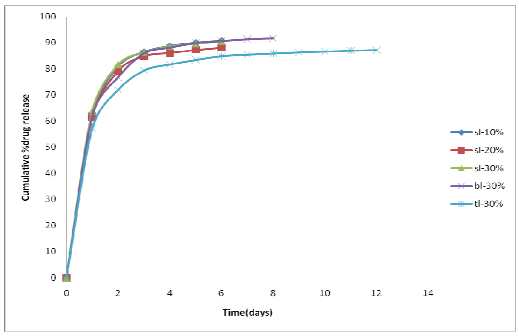

Figure 1
Cumulative % release v/s time (days)

Table 4
kinetic data for moxifloxacin periodontal films

Film type	First order	Higuchi equation	Korsemeyer-peppas equation
	R^2	R^2	R^2
MSL-10%	0.859	0.869	0.388
MSL-20%	0.810	0.860	0.385
MSL-30%	0.845	0.859	0.384
MBL-30%	0.843	0.822	0.387
MTL-30%	0.751	0.726	0.371

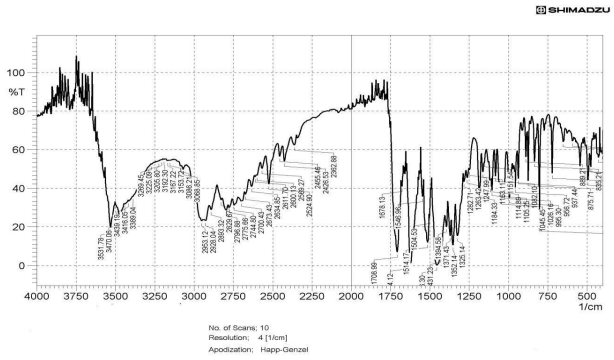

Figure 2
FTIR Spectra of pure moxifloxacin drug

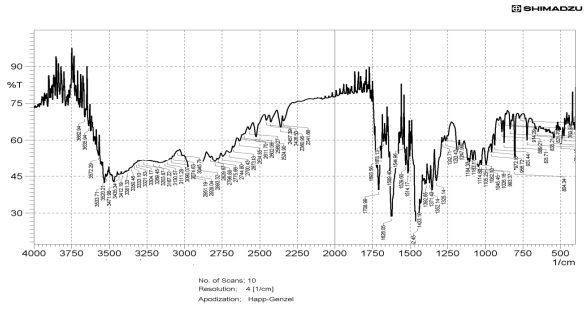

Figure 3
FTIR spectra of optimized formulation of moxifloxacin film

RESULTS AND DISCUSSION

The optimum loading for better, flexible films was found to be 30% or less than that. For the present investigation, chitosan films containing moxifloxacin with three different concentrations, that is 10, 20 and 30% to the weight of the polymer of single layer as well as bilayer with 30% and trilayer with 30% of drug were prepared using solvent casting technique. The prepared films containing moxifloxacin trilayer with 30% drug concentration has shown the extended drug release for 12 days.The FTIR studies from the spectra [Figure 3] confirmed the absence of any chemical interaction between the drug and the polymer. Macroscopical features revealed that the drug had dissolved in the polymer matrix rather than dispersing.The physicochemical evaluation data presented in [Table 1] showed that the average weight of the films ranged from 0.999 to 3.196 mg. The maximum weight was observed with trilayer with 30% drug loaded films.the thickness of the films ranged from 0.11 to 3.16 mm. The thickness was observed more with the trilayer 30%.The tensile strength of the films ranged from 1.27 to 3.36 kg/sq.mm, tensile strength was minimum for plain films and maximum for trilayer film containing 30% of moxifloxacin. The folding endurance studies showed that plain inserts exhibited maximum folding endurance followed by drug loaded inserts respectively.All the films were found to contain an almost uniform quantity of the drug, as per content uniformity studies [table 2] indicating reproducibility of the technique. The percentage moisture loss varied between 19.56 to 43.94 and the percentage moisture absorption was found to be in the range of 23.61 to 34.75.The release time profile for different concentrations of moxifloxacin from chitosan films are shown in figure 3. The release profile showed that there was rapid initial release of the drug on day one, that is, 62.65, 61.64, 63.73, 62.05 and 57.26% from the MSL-10%,MSL-20%, MSL-30%, MBL-30% AND MTL-30% respectively. A perusal of figure 1 indicated that the initial rapid release must have been because of the burst effect, due to elution of the drugs from the outer surface and cut edges of the matrix. Once the burst effect was completed, the slow and sustained release was seen up for respective days. The inserts MSL-10, MSL-20 and MSL-30 showed 90.71%, 88.04 % and 90.42% respectively at the end of 6 days. The bilayer insert (MBL-30) showed 91.64% at the end of 8 days. The trilayer insert (MTL-30) showed 87.10 % respectively at the end of 12 days of static dissolution period. Initial burst effect was reduced once the chitosan strips were formulated in multilayer form and also release of drug was extended and controlled up to 12 days. The plots of the cumulative amount of drug release per unit surface area against sq. root of time, confirms to Higuchi's diffusion model i.e., the release kinetics of moxifloxacin from chitosan strips followed first order. The initial burst release is essential to achieve high concentration of drug in gingival sulcus. This is a primary objective of the periodontal therapy.

CONCLUSION

A number of delivery systems have been investigated for use in periodontal disease, but still an ideal targeted delivery system is yet to be developed. The greatest advantages associated with the use of intra-pocket delivery systems over systemic delivery are that the administration is less time consuming than mechanical debridement and a lesser amount of drug is sufficient to achieve effective concentration at the site.Evaluation parameters like thickness, tensile strength and folding endurance indicates that inserts were mechanically stable in all the inserts formulations.Percentage weight variation and drug content uniformity found to be uniform in all the formulations.The FT-IR and DSC spectra revealed that, there was no interaction between polymer and drug. Hence, Polymer used was compatible with the drug.*In-vitro* drug release showed an abrupt release in the first day in

single layer whereas this initial burst release was controlled by formulating in to bilayer and trilayer which was controlled the release uniformity in a specified period of time.All the inserts were found to be stable over the storage period of 90 days and condition tested.From this study it can be concluded that bilayer and trilayer were developed which can be delivered drug up to 8 and 12 days respectively.

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