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FORMULATION AND EVALUATION OF DENTAL IMPLANT OF MOXIFLOXACIN HCL FOR THE TREATMENT OF PERIODONTITIS

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ABSTRACT

Dental implant for the treatment of periodontitis was developed for site specific delivery of Moxifloxacin HCl a broad spectrum antibiotic. Moxifloxacin HCl Dental implant was prepared by solvent casting technique using ethyl cellulose and other co-polymers (HPMC-K100M or Eudragit RL100) in chloroform: Methanol solvent with Peg 400 and Dibutyl Phthalate as plasticizers. Drug excipients compatibility was studied using FTIR. The Dental implant were evaluated for their thickness uniformity, folding endurance, weight uniformity, content uniformity, surface pH, In-vitro drug release and in-vitro antibacterial activity. In-vitro drug release was subjected to curve fitting using different equations and kinetic models to reveal release kinetics. The in vitro drug release data showed that implant shows initially burst release followed by prolonged release. Stability studies revealed that the drug remained intact and stable in the Dental implant during storage.

KEY WORDS

Dental implant,periodontitis, Moxifloxacin HCl, ethyl cellulose,HPMC-K100M, Eudragit RL100.

INTRODUCTION

Periodontitis, i.e., ‘‘peri’’ = around, ‘‘odont’’ = tooth, ‘‘itis’’ = inflammation, refers to a number of inflammatory diseases affecting the periodontium. Periodontal disease is an infection that involves the inflammatory process and the immune response. The presence of periodontal pathogens such as Porphyromonas gingivalis, Prevotella intermedia, Treponema denticola and Actionobacillus actinmycetemcomitans are responsible for periodontal destruction. It refers to acute and chronic disorder of the soft tissues surrounding the teeth which eventually leads to loss of supporting bone. Apart from scaling and planning, systemic antibiotic therapy is employed in treating periodontitis. Systemic antimicrobials such as adjuncts to mechanical therapy have had positive effect on clinical as well such as microbiological parameters. But the impact of this approach is reduced by the fact that the antibiotic is normally difficult to maintain in therapeutic concentrations at the site over the course of the treatment period. Due to these negative effects, the use of local drug delivery devices containing antibiotics may be explored. These devices can maintain extremely high local concentrations of drug for prolong period. Several implantable devices like fibers, films, Dental implant and gels were studied. Thus the Dental implant could be easily placed into periodontal pocket, and be capable of delivering therapeutic concentration of Moxifloxacin for dose, prolonged period of time with a much lower dose. A local drug delivery system delivering the therapeutic agent at sufficient levels inside the pocket and at

the same time minimizing the side effects associated with systemic drug administration.

Moxifloxacin HCl is a Group 4 flouoroquinolone with activity against a broad spectrum of gram positive, gram negative and anaerobic bacteria pathogens. Dental implants were prepared by solvent casting technique. Glass petri plates were used for casting the films. Ethyl cellulose, Eudragit RL 100, hydroxyl propyl methyl cellulose K100M, hydroxyl propyl cellulose combinations were dissolved in Chloroform and Methanol (10:3ml) mixture with Peg400 and Dibutyl phthalate as a plasticizer.

MATERIAL AND METHOD

Moxifloxacin HCl was received as a gift sample from Simpex Pharma Pvt. Ltd, Kotdwar, Uttarakhand and Eudragit RL 100 was a gift sample from Evonik Degussa, Mumbai. Other chemicals and reagents were procured from Loba Chemie, Mumbai. All the chemicals and reagents used in the formulation and evaluation were of analytical grade.

Drug Excipient Compatibility:

The compatibility study was carried out at 55^0C for 14 days with moisture and without moisture in hermetically sealed glass container of individual drug and Drug : Excipient (1:1). Individual IR graph were taken before placing the ingredient and drug into the glass vials and these vials were kept for 14 days for 55^0C in duration of 14 days all the vials were observed for any colour change, gas formation caking and liquification and lastly after 14 days its IR was studied. IR Spectral analysis of pure Moxifloxacin hydrochloride, pure excipients and combination of the drug with these excipients was carried out to investigate any changes in chemical composition of the drug after combining it with the excipients.

Preparation of cast Dental implant containing Moxifloxacin HCl:-

Dental implant was prepared by solvent casting technique. Glass petri plates were used for casting the implant. Ethyl cellulose, Eudragit RL 100, hydroxyl propyl methyl cellulose K100M, hydroxyl propyl cellulose combinations were dissolved in Chloroform and Methanol (10:3ml) mixture with Peg400 and Dibutyl phthalate as a plasticizer in a beaker using magnetic stirrer to get different concentrations of polymeric solutions. Into these solutions Moxifloxacin HCl of required quantity was added. After complete mixing, the solution was poured into a clean glass petri plate placed on a horizontal plane. The solvent was allowed to evaporate slowly by inverting a glass funnel plugged with cotton in the stem at room temperature for 24 hours.

Table no 1. Formulation of periodontal film of Moxifloxacin HCl

CONTENT	F 1	F 2	F 3	F 4	F 5	F6
Moxifloxacin Hcl (mg)	110	110	110	110	110	110
EC (mg)	500	600	500	600	500	600
HPMC K100M (mg)	50	100	-	-	-	-
HPC (mg)	-	-	50	100	-	-
E RL100 (mg)	-	-	-	-	50	100
PEG 400 (ml)	0.1	0.1	0.1	0.1	0.1	0.1
DBP (ml)	0.2	0.2	0.2	0.2	0.2	0.2
Chloroform:Methanol(ml)	10:3	10:3	10:3	10:3	10:3	10:3

EVALUTION OF PERIODONTAL FILM

Appearance:-

The Dental implant were visually inspected for any change in colour and physical form or Appearance.

Thickness uniformity:-

Thickness of the implant was measured using digital Vernier calliper (Aero Space) at different areas of the implant and the average was calculated. The results of the study was as shown in **Table no. 2**

Weight variation:-

Uniformity in the weight the Dental implant was determined. Five implant of $1cm^2$ each were weighed on an electronic balance and the mean

weight was recorded. The results of the study was as shown in **Table No. 2**

Table no.2 Physical Evaluation of Dental Implantof Moxifloxacin HCl

Formulation	Thickness uniformity mm n=5(SD)	Weight uniformity mg (SD) n=3	Folding endurance n=3	% Moisture Loss n=3	Surface pH	% Drug content n=3	Tensile Strength gm/cm^2
F1	0.135 (0.012)	12.5 (0.4)	139	3.05	6-7	91.3 (0.98)	16.97
F2	0.165 (0.017)	16.12 (0.5)	163	3.41	6-7	93.1 (1.01)	23.2
F3	0.137 (0.017)	11.8 (0.8)	145	3.96	6-7	90.9 (1.03)	16.2
F4	0.167 (0.018)	15.82 (0.6)	167	3.63	6-7	92.8 (1.20)	21.87
F5	0.127 (0.015)	12.4 (0.5)	158	3.07	6-7	91.8 (1.13)	18.47
F6	0.157 (0.017)	14.7 (0.6)	179	2.87	6-7	94.5 (1.3)	26.75

Folding endurance:

The folding endurance is expressed as the number of folds (number of times the film 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 center, between the fingers and the thumb and then opened. This was termed as one folding. The process was repeated till the film showed breakage or cracks in center of film. The total folding operations were named as folding endurance value. The results of the study was as shown in Table **no.2**

Percentage Moisture Loss:-

The percentage moisture loss was carried out to check integrity of the implant at dry conditions. Implants were weighed and kept in a desiccators containing anhydrous calcium chloride. After three days, the implants were taken out and reweighed; the percentage moisture loss was calculated using the formula

$$\% \text{ Moisture Loss} = \frac{\text{Initial Weight - Final Weight x 100}}{\text{Initial Weight}}$$

The results of the study was as shown in **Table no. 2**

Surface pH:-

Dental implant were left to swell for 1 hour on the surface of the agar plate, prepared by dissolving 2 % (w/v) agar in warmed double distilled water with constant stirring and poured into the petridish to 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. The results of the study was as shown in **Table no. 2**

Drug content uniformity:-

Implant (size of 1 cm^2) was taken from different areas of implant and placed in a 10 ml volumetric flask; 10 ml of methanol was added and kept aside till the implant dissolve completely. From this solution, 1 ml was pipetted out and diluted to 10 ml with phosphate buffer pH 6.8. The absorbance of the solution was measured at 288.8 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 implant. The results of the study was as shown in **Table no. 2**

Tensile strength of the films:-

The tensile strength of the implant was determined by Brookfield's Texture Pro CT V1.4 CT3 Texture Analyser testing machine. It consists of two load cell grips. The lower one is fixed and the upper one is movable. The test implant of specific size was fixed between these cell grips and force was gradually applied till the implant breaks. The tensile strength of the implant was calculated. The results of the study was as shown in **Table no. 2**

***In- vitro* drug release:-**

Static dissolution method reported in the literature was adopted. implant of known weight and dimensions (1 cm^2) were placed separately into

vials containing 1 ml of pH 6.8 phosphate buffer. The vials were kept at 37 ^{0}C for 24 hrs. The buffer was drained off and replaced with fresh 1 ml phosphate buffer of pH 6.8 after 24 hrs. The concentration of drug in the buffer was measured at 288.8 nm using UV spectrometry. The procedure was continued every 24hr for 5 to 6 days.

***In- Vitro Antibacterial* Activity:**

In-Vitro antibacterial activity was performed on all formulations by placing the Dental implant (1 x 1 cm) on agar plates seeded with the bacteria *Streptococcus mutans*. After 48 hr of incubation at 37^{0}C, the implant were transferred to freshly seeded agar plates and incubated for an additional 48 h. This procedure was repeated until no inhibition of bacterial growth was detected on the agar plate. The growth inhibition zone on the agar plate was measured.

Kinetic Studies:-

To analyze the drug release rate kinetics and mechanism of drug release from the Dental implant, the *in-vitro* dissolution studies data was fitted into Zero order, First order, Higuchi matrix, Korsmeyer Peppas models. In this by comparing the r-values obtained, the best- fit model was selected. Result of kinetic study of F6 batch shown in **Table No. 3**

Table no.3: Drug release kinetics of Batch F6

Batch	Zero order (R^2)	First order (R^2)	Higuchi Model (R^2)	Korsmeyer-Peppas model (R^2)
F6	0.918	0.986	0.996	0.978

Accelerated Stability Studies:

The stability of the F6Dental implant was studied at 40ºC± 5°C with RH 75%± 5%. The films of size (1 cm^2) were weighed and wrapped in aluminum foil and placed in petriplates. These containers were stored for a period of one month. All the films were observed for any physical changes, such as color, appearance, flexibility. The drug content was estimated at an interval of each week. Result of Stability study of F6 batch shown in **Table no. 4.**

Table No. 4. Stability study of formulation F6

Week	Physical appearance	% Drug content
One	No change in color, smooth, flexible	93.97%
Two	No change in color, smooth, flexible	93.62%
Three	No change in color, smooth, flexible	94.01%
Four	No change in color, smooth, flexible	93.29%

RESULT

The FTIR studies (**Fig. 1**) confirmed the absence of any chemical interaction between the drug and the polymer. The physical properties such as thickness, uniformity of weight, % moisture loss, tensile strength, folding endurance, content uniformity, surface pH were given in **Table 2 & 3**. The fabricated Dental implant showed good film forming properties and reproducibility. The Dental implants were thin, flexible, elastic and smooth.

All Dental implantof measured thickness showed low standard deviation values ensuring the uniformity of Dental implant prepared by solvent casting technique. The Dental implant showed thickness between 0.13 mm to 0.16 mm. Uniformity of weight depends upon the thickness. Weights of all the formulations were in the range of 11.8 to 15.82. This indicated that all the implant were uniform in weight. The folding endurance values of all the implant were in the range of 142 - 177. It indicated that all the formulations had ideal properties. Percentage moisture loss values range from 2.83 to 3.86 %. Low moisture loss helps them to remain stable and from being completely dried and brittle.

The surface pH of all the formulations was determined as described elsewhere above. All the formulations were found to have pH between 6 –7.

This reveals that the prepared films would not alter the pH of the gingival fluid in the periodontal pocket. Tensile strength of drug loaded Dental implant was found to be good. With increase in the HPMC and Eudragit RL100 proportion the tensile strength of implant also increased. The tensile strength values of the implants ranged from 17.91 to 26.75 kg/cm^2. The % drug content in various formulations ranged from 90.9 % – 94.5 % . It was observed from the drug content data that there was no significant difference in the uniformity of the drug content. However, when compared with the theoretical drug content the estimated drug content was slightly less; it is the indication of drug loss during fabrication of the implants. *In*- Vitro Drug Release Out of the nine formulations, the formulation (F6) containing EC and Eudragit RL 100 showed complete and controlled release with 93.6 % at the end of 144 hours. All physical parameters are satisfactory and it shows good reproducibility results.

Table No. 4. Indicate that the regression values are higher with First order release kinetics. Therefore all the Moxifloxacin HCl films follow first order release kinetics and R^2 values are higher for Higuchi's model compared to Korsmeyer Peppa's model for F6 implant. Hence Moxifloxacin HCl release from all the implants followed diffusion rate controlled mechanism. The optimized formula F6 showed the antibacterial activity for 6 days. The study indicates that the formulated polymeric implants containing Moxifloxacin HCl retained their antibacterial activity. The implants were studied for stability studies for 1 month and there were no changes in physical parameters. There was no change in physical appearance and drug content hence it was concluded that the formulation F6 was stable.

Figure No. 1(A): FTIR of Moxi

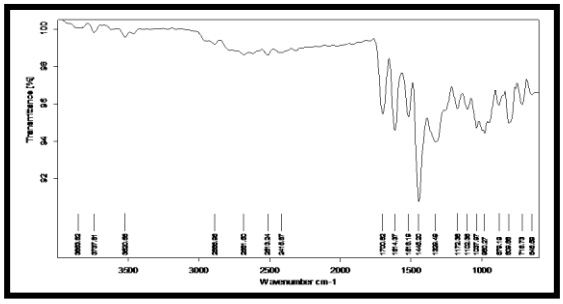


Figure No. 1(B): FTIR of Moxi and EC

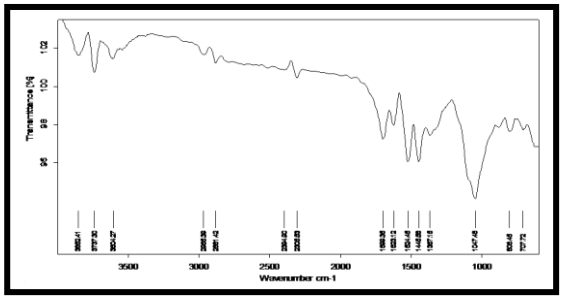


Figure No.1(C) FTIR of Moxi & HPMC K100M

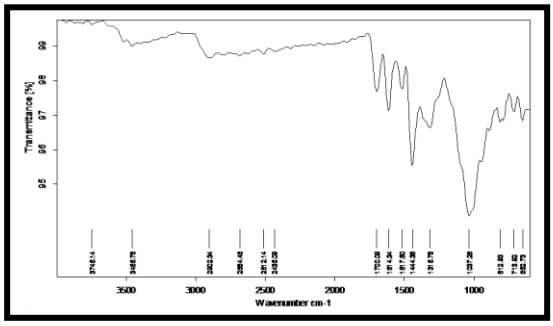


Figure No.1 (D). FTIR of Moxi & ERL100

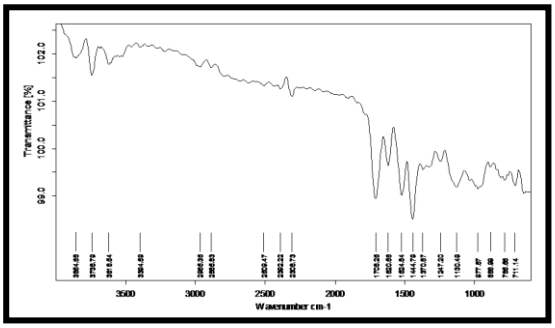


Figure no.1 (E) FTIR of Moxi and HPC Figure no. 1

(F) FTIR of Moxi, EC, HPMCK 100M, ERL100 & HPC

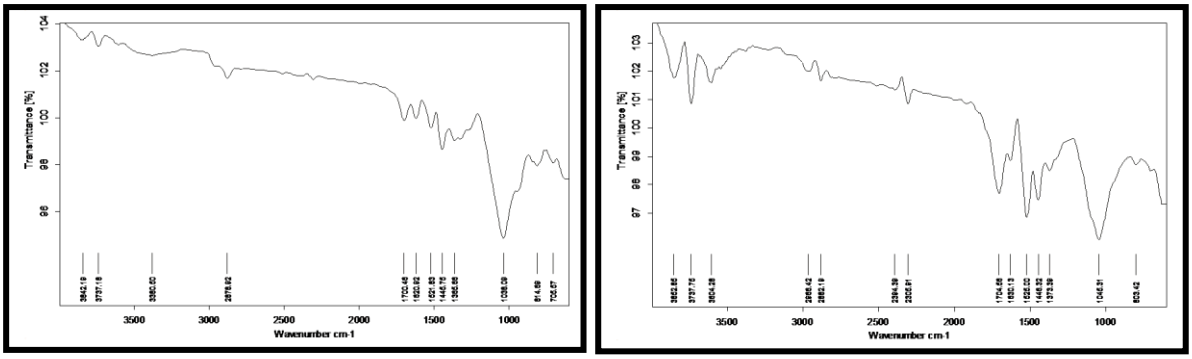
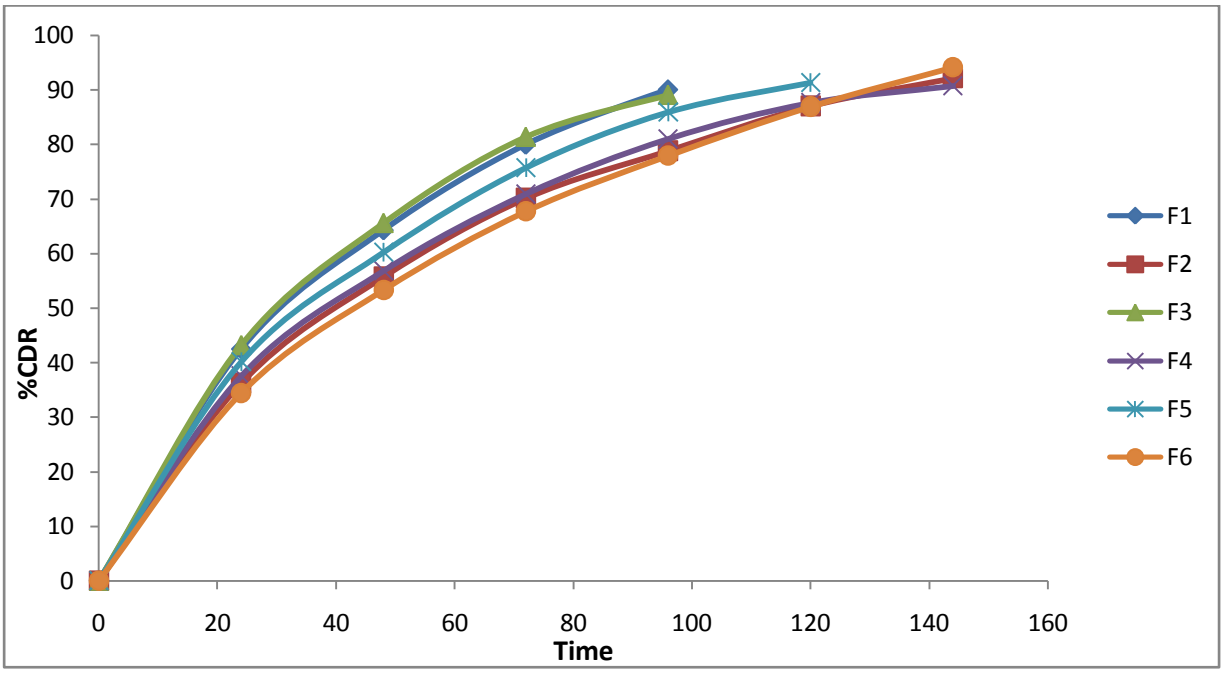


Figure No. 3: *In Vitro*cumulative % drug release plot



CONCLUSIONS

The greatest advantages associated with the use of subgingival local delivery systems over systemic delivery are that the administration is less time consuming than mechanical debridement and a lesser amount of the drug is sufficient to achieve effective concentration at the site. In the present work periodontal film of Moxifloxacin HCl were prepared by Solvent casting technique by using Ethyl cellulose, Eudragit RL100, HPMC K100M and HPC. From this ethyl cellulose and Eudragit RL100 polymers are used in combination. F6 batch showed best results. All batches were subjected to weight variation, thickness uniformity, drug content, In Vitro drug release study, short term stability study, etc studies.

Tensile strength of F6Dental implant was found to be 26.75 gm/cm^2, thickness was 0.16 mm and folding endurance 177. Weight variation of F6 film was found to be 14.7 mg (0.6 SD) and % drug content were found to be 94.5% (1.3SD) uniform in all formulations. I.R. spectra revealed that, there was no interaction between polymers and drug. All the polymers used were compatible with the drug. In Vitro drug release of F6Dental implant was found to be 93.6 % at the end of 6 days. The prepared formulations found to demonstrate significant In Vitro antibacterial activity. All the Dental implants were found to be stable over the storage period and conditions tested. Overall study suggests that among the implants prepared F6 was found to show the best results. Thus the

specific objectives listed in this dissertation were achieved namely Formulation and evaluation of Dental implants of Moxifloxacin HCl for the treatment of periodontitis, certainly these finding can be applied for controlled delivery of drugs for localized treatment of periodontitis.

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