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Formulation and Evaluation of Levofloxacin Dental Strips for Periodontitis Diseases

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ABSTRACT

Periodontitis is an inflammatory response to the overgrowth of anaerobic pathogenic organisms such as spirochetes and bactericides in the sub gingival plaque. If it is unchecked, results in the destruction of the bone and soft tissues supporting to the tooth, which leads to tooth loss. For treatment of these diseases we are preparing local drug delivery system of Levofloxacin dental strips. This helps to get local as well as sustained action against organism. Here we are used HPMC and ethyl cellulose as rate controlling polymer and dibutyl phthalate as plasticizers. Which shows tensile strength varies from 1.55-1.87 kg/cm^2,the thickness varies from 0.33±0.002mm to 0.38±0.008mm. The weight variation and drug content was found to be uniform in all the formulation and folding endurance was found to be more than 200 in all the strips. In vitro dissolution was carried out by using static dissolution method and in vitro anti-bacterial activity was carried out by *E.coli* and *S.aureus* the zone of inhibition was calculated. The stability study was carried out under accelerated condition to found out the stability of all the formulation.

Keywords: - Dental strip, Levofloxacin, In vitro antibacterial activity.

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INTRODUCTION

Periodontitis is an inflammatory response to the overgrowth of anaerobic pathogenic organisms such as spirochetes and bactericides in the subgingival plaque. If it is unchecked, results in the destruction of the bone and soft tissues supporting to the tooth, which leads to tooth loss. Periodontal disease includes conditions such as chronic periodontitis, aggressive periodontitis and necrotizing periodontitis.These conditions are characterized by destruction of the periodontal and the migration of the junctional epithelium along with the tooth surface.

Conventional therapy, based on scaling, surgery and the use of antimicrobials has been proposed. 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 Levofloxacin a fluoroquinolone anti-infective, Levofloxacin is available in the market as a conventional dosage and parenteral for the treatment of bacterial infections but not suitable means for the treatment of infection locally. The periodontal strips containing the following properties also.

1. Low incidence of undesirable side effects.
2. Easily applied in less time and effort with minimal pain and discomfort than conventional treatment.
3. Therapeutically effective to the same degree as conventional treatment.
4. Low in cost and high in patient acceptability.

Hence it was a challenge to develop periodontal strips containing Levofloxacin with rate controlling polymers, which has a prolonged action and shows the antibacterial activity directly at the site of infection without loss of dosage[1]

MATERIAL AND METHOD

Levofloxacin hemihydrate was obtained as gift sample Zydus cadila health limited, Goa, India), ethyl cellulose, Hydroxy propyl methylcellulose K4M Dibutylphthalate, PEG 400, Chloroform, Dichloromethane was procured from yarrow chemicals products limited Mumbai

Drug-polymer compatibility

The FTIR spectrum of the sample was recorded in a spectrometer (Jasco FTIR 4100), using potassium bromide (KBr) discs prepared from powdered samples mixed with dry potassium bromide in the ratio 1:300. This mixture were placed in sample holder and analyzed by FTIR to study the drug polymer compatibility.

Preparation of Cast strip containing Levofloxacin Hemihydrate

Periodontal strips were prepared by solvent casting technique. Ethyl cellulose alone and in combination with HPMC K4M were dissolved in chloroform and dichloromethane (1:1) mixture with dibutyl phthalate and Poly ethylene glycol 400 as a plasticizer in a beaker using magnetic stirrer to get different concentration of polymeric solutions. Into these solutions levofloxacin of required concentration was added. After complete mixing, the solution was poured into a clean glass mould of 14cm^2 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 hr. Table 1.

Table 1: Composition of the strips

Ingredient	Composition					
	F1	F2	F3	F4	F5	F6
Levofloxacin hemihydrate	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
HPMC K4M	100	80	60	40	20	-
Ethyl cellulose	300	320	340	360	380	400
Dibutyl phthalate(%w/w)	50	50	50	50	50	50
Chloroform	2.5ml	2.5ml	2.5ml	2.5ml	2.5ml	2.5ml
Dichloromethane	2.5ml	2.5ml	2.5ml	2.5ml	2.5ml	2.5ml

Evaluation of the strips

Strip Thickness[3]

The thickness of the implant was measured by micrometer screw gauge. An average of five values determined at 5 different points on the strip was calculated.

Folding endurance[3]

The folding endurance is expressed as the number of folds. 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 strip showed breakage or cracks in center of strip. The total folding operations were named as folding endurance value.

Tensile Strength[3]

Tensile strength of the strips was determined by Universal strength testing machine. It consists of two load cell grips, the upper one is fixed and lower one is movable. The test strip of specific size (5×1 cm^2) was fixed between these cell grips and force was gradually applied till the strip breaks. The tensile strength of the strip was taken directly from the dial reading in kilograms/cm^2

Drug Content[6]

Drug content uniformity in strips was determined. 7mm×2mm implant was placed in volumetric flask containing 10 ml of dichloromethane and chloroform (1:1); the flask was vigorously shaken

to extract the drug from the Implant. 5 ml of resulting solution was taken and diluted to 10 ml with phosphate buffer pH 6.8. The absorbance of the solution was measured spectroscopically at 287 nm. The polymeric solution without drug served as blank. The drug content was studied in triplicate and the mean reported.

Weight variation[3]

Uniformity in the weight the implant was determined. Five strips of 7mm×2mm each were weighed on an electronic balance and the mean weight was recorded.

Antimicrobial activity study of the prepared dental strips[5]

Nutrient agar was prepared and sterilized by autoclave under aseptic condition. the medium was transferred to sterile Petri plates. After the solidification of nutrient agar medium, they were inoculated with microorganism i.e. *S.aureus* and *E.coli* and strips ($14mm^2$) were placed in these plates and incubated for 24 hours at 37 ºC. The zone of inhibition was measured after incubation.[10]

In-vitro drug release profile of the prepared Antibacterial dental strips[2]

Static dissolution (vial method)

Static dissolution method reported in the literature was adopted. Strips of known weight and dimensions ($14mm^2$) were placed separately into vials containing 1 ml of pH 6.8 phosphate buffer. The vials were kept at 37 ºC for 24 hrs. The buffer was drained off and replaced with fresh 1ml phosphate buffer of pH 6.8 after 24 hrs. The concentration of drug in the buffer was measured at 287nm wavelength using UV spectrometry. The procedure was continued every 24hr for 2 to 4 days.

Stability studies[2]

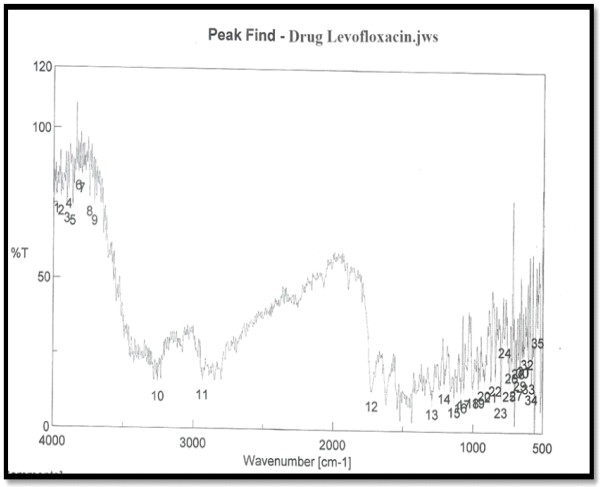
The stability of all drug loaded polymer strips were studied at different temperatures. Patches (7 mm × 2 mm) were wrapped individually in aluminum foil and maintained temperature at (40 ± 2 ^oC) and 75 ± 5% RH for 1 month as per ICH guidelines. Apart from this the patches were also exposed to room conditions (27± 2^oC) for 1 month. Changes in the appearance and drug content of the stored patches were investigated after storage. The data presented are the mean of three determinations.

RESULTS AND DISCUSSION

Drug-polymer compatibility[6]

The FTIR spectra of Levofloxacin alone and in combination with polymer were shown and it's showed characteristic peaks at 3254cm^{-1}, 2935 cm^{-1}, 1723cm^{-1}, 1294 cm^{-1}, 1087 cm^{-1} due to its

functional group. It shows that there was no chemical interaction between the drug and polymer used. Figure 1,2 and 3. Physicochemical parameters of dental strips like Weight variation, Thickness, Folding endurance, Tensile strength, Drug content are carried out according to the standard procedure (Table 2).



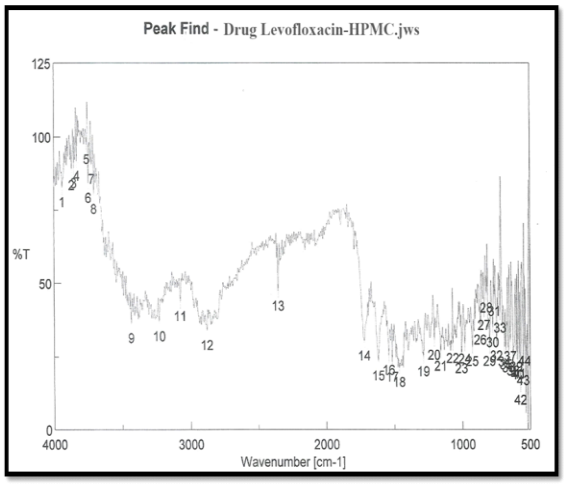


Figure 1: Pure drug of Levofloxacin hemihydrates Figure 2: Pure drug+HPMC

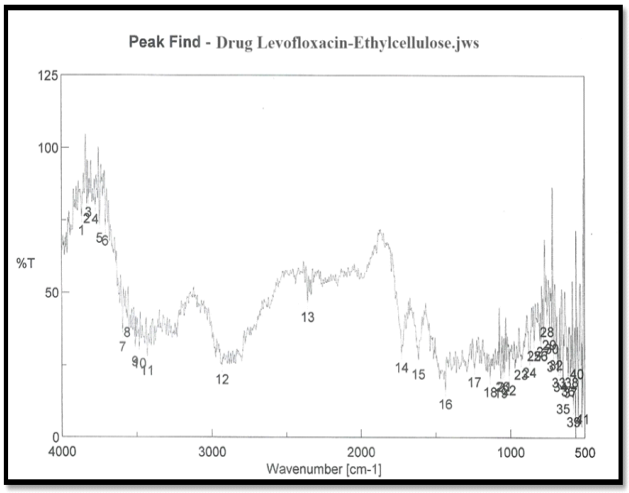


Figure3: Pure drug of Levofloxacin hemihydrates + ethyl cellulose

Table 2: Physicochemical parameters of dental strips containing Levofloxacin hemihydrates

Formulation	Thickness in mm(n=5)	Weight in mg (n=10)	Drug content in %	Folding Endurance	Tensile Strength (kg/cm2)
F1	0.38±0.008	4.3±0.016	97.22±1.5	>200	1.55
F2	0.36±0.007	4.15±0.012	99.34±1.3	>200	1.61
F3	0.35±0.004	4.26±0.014	98.54±2.05	>200	1.65
F4	0.36±0.004	4.25±0.011	99.56±1.08	>200	1.71
F5	0.35±0.003	4.08±0.008	98.45±1.01	>200	1.78
F6	0.33±0.002	4.25±0.011	99.22±1.09	>200	1.87

Table 7 Interpretation of Levofloxacin HCL

Functional group	Reported frequency	Observed frequency in pure drug
F	1400-1000	1300(13 in FTIR)
C=O	1725-1680	1725(12 in FTIR)
N-H	3500-3310	3300(11 in FTIR)
O-H	3550-3450	3500(10 IN FTIR)

Table 3:*In vitro* Dissolution profile of dental strips

Time in hours	% Drug Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
24	60.76±2.03	59.67±1.22	51.98±1.21	45.55±1.88	38.33±1.23	33.56±1.89
48	87.98±1.66	81.12±1.32	66.56±1.11	60.11±1.89	57.09±1.44	55.78±1.98
72	99.23±1.22	97.23±1.44	89.44±1.55	84.67±1.22	81.44±1.54	78.58±1.09
96			99.23±0.99	98.34±2.32	91.9±1.58	89.45±1.78
120					99.56±2.45	97.45±1.67

Table 4: Comparison of release mechanism based on regression coefficient for static dissolution

Formulation	Regression coefficient (R^2)		
	Zero order	First order	Higuchi's model
F1	$R^2 = 0.893$	$R^2 = 0.882$	$R^2 = 0.995$
F2	$R^2 = 0.902$	$R^2 = 0.899$	$R^2 = 0.998$
F3	$R^2 = 0.912$	$R^2 = 0.902$	$R^2 = 0.995$
F4	$R^2 = 0.948$	$R^2 = 0.925$	$R^2 = 0.988$
F5	$R^2 = 0.937$	$R^2 = 0.907$	$R^2 = 0.987$
F6	$R^2 = 0.947$	$R^2 = 0.933$	$R^2 = 0.982$

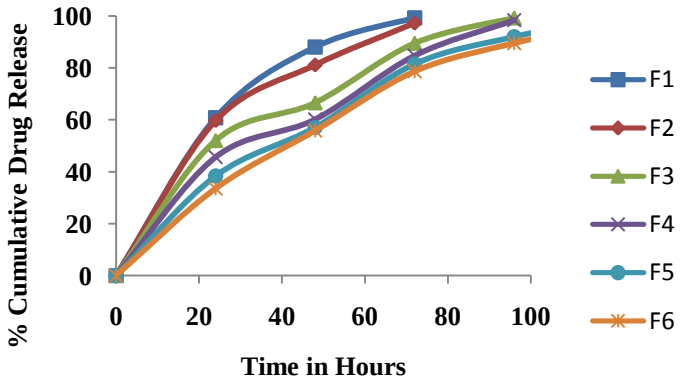


Figure 4: *In vitro* release of levofloxacin dental strips in pH 6.6 phosphate buffer

In vitro dissolution

In vitro dissolution was carried out by using phosphate buffer of pH 6.8 for 5 days in static method. Here release was controlled mainly due to the presence of polymer used in the formulations. The release study shows that drug release in formulation F5 is controlled compare

to the other all formulation Table 3 and figure 4. The regression values of all formulated strips are higher with zero order with higuchi model. Therefore the release kinetics of all strips follows zero order. The data of regression value were given in Table 4.

Antimicrobial activity study of the prepared dental strips

In vitro anti-bacterial activity strips were carried out by following the procedure mentioned in methodology using *S.aureus and E.coli* organism. The zone of inhibition was higher at first24 hour and decrease as time proceeds. This shows that Levofloxacin hemihydrate retains its anti-bacterial after formulation of the strips. Table 5

Table 5: Comparison of *in vitro* anti-bacterial activity strips using *S.aureus and E.coli*

Sl.No	Zone of inhibition in mm							
	S.aureus				***E.coli***			
	1day	3day	5day	7day	1day	3day	5day	7day
F1	42mm	36mm	31mm	27mm	45mm	38mm	32mm	26mm
F2	44mm	37mm	33mm	28mm	43mm	36mm	31mm	25mm
F3	41mm	37mm	32mm	26mm	44mm	39mm	32mm	25mm
F4	46mm	40mm	35mm	29mm	46mm	39mm	33mm	23mm
F5	44mm	36mm	30mm	25mm	41mm	35mm	29mm	24mm
F6	45mm	38mm	31mm	24mm	44mm	36mm	30mm	25mm

Stability studies

Stability study was carried out on all the formulation coded F1 to F6. Decreases in the drug content were seen ranging from 0.25% to 1.65%. This shows stability of the strips after storage of one month. The formulations were also observed for its physical changes, this was also not changed during this one month of study. Table 6

Table.6: Stability studies data of F1 to F6

Days	% Drug content					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	99.2	98.0	99.8	98.6	98.5	99.7
7	99.2	97.9	99.0	98.6	98.4	99.2
14	99.0	97.8	99.0	98.4	98.4	99.0
21	99.0	97.5	98.8	98.0	98.0	98.3
28	98.8	97.0	98.6	97.6	97.8	98.1

CONCLUSION

Form this study we can conclude that the Levofloxacin hemihydrate could incorporate sustained release strips to treat periodontitis. These strips consist of ethyl cellulose, HPMC can be used as rate controlling polymer and Dibutyl phthalate was used as plasticizer. The FTIR study shows that there is no incompatibility between drug and polymer. Formulation shows stability after one month of the storage.

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