INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com ISSN 2230 – 8407

Research Article

FORMULATION AND *IN-VITRO* EVALUATION OF CLARITHROMYCIN PERIODONTAL STRIPS FOR PERIODONTITIS

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Article Received on: 06/06/12 Revised on: 18/07/12 Approved for publication: 30/07/12

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ABSTRACT

Periodontitis is an inflammatory response to the overgrowth of anaerobic organisms in the sub gingiva and if unchecked, results in the destruction of the bone and soft tissues supporting the tooth. Studies suggest that clarithromycin can attain higher concentration in the inflammed gingiva and it also produces anti-inflammatory effect. The systemic drug administration has been useful in treating periodontitis but the disadvantage that, the drug is diluted several thousand folds before it reaches the site. This problem can be overcome by administering the drug directly to the intended site of action with lesser dose. In present study periodontal strips were prepared by using solvent casting technique. Formulations were designed by taking Ethyl cellulose alone and with copolymers (HPMC K4M, Eudragit RS- 100, PVP K30) was dissolved in chloroform and dichloromethane (1:1) solution, using dibutyl phthalate and PEG-400 as plasticizers.

KEY WORDS: Clarithromycin, implant, controlled release and in vitro release.

INTRODUCTION

Periodontitis is an inflammatory response to the overgrowth of anaerobic organisms in the sub gingiva and if unchecked, results in the destruction of the bone and soft tissues supporting the tooth.[1,2] The bacterial toxins and certain enzymes produced by the body to fight the infection actually breaks down the bone and the connective tissue holding the teeth. Periodontitis is characterized by the inflammation of gingiva followed by the formation of periodontal pocket and absorption of the alveolar bone. This results in the loosening of the tooth. Conventionally scaling, root planning and surgical procedures were proposed to treat the periodontitis. But due to the mechanical limitations and the inefficacy of these procedures, use of antibiotics in conjunction to the conventional therapy is proposed. Clarithromycin is chemically 6-O-methylerythromycin. It is a semi synthetic broad spectrum macrolide antibiotic with a biological half life of 3 – 4 hours. The main adverse effects of clarithromycin are diarrhoea, nausea, vomiting and dyspepsia. It is available in the market as conventional dosage forms such as tablets, capsules, and parenterals for the treatment of bacterial infections but not present as controlled dosage form for the treatment of infection locally.

Studies suggests that clarithromycin can attain higher concentration in the inflammed gingiva and it also produces anti-inflammatory effect.[3] The systemic drug administration has been useful in treating periodontitis but the disadvantage that, the drug is diluted several thousand folds before it reaches the site and exposes the rest of the body to potential side effects. This problem can be overcome by administering the drug directly to the intended site of action with lesser dose. In the context to above mentioned principles clarithromycin is chosen as a model drug for the present study. The purpose of the present study is to formulate periodontal strips, which could be easily placed into the periodontal pocket, and be capable of delivering therapeutic concentration of clarithromycin for prolonged period of time with a much lower dose, hence obviating untoward side effects.

MATERIALS AND METHODS

Clarithromycin was obtained as gift sample from Regain Laboratories Pvt. Ltd., Hissar. Hydroxy propyl Methyl Cellulose (HPMC K4M), Eudragit RS 100, Poly-vinyl-pyrrolidine K30 (PVP K30), PEG 400 were obtained from CDH Pvt. Ltd, New Delhi. All other reagents and solvent used were of analytical grade.

PREPARATION OF CAST STRIPS CONTAINING CLARITHROMYCIN

Periodontal strips were prepared by using solvent casting technique. For the purpose glass moulds of area 15cm^2 were used. Formulations were designed as shown in table 1. Ethyl cellulose alone and with copolymers (HPMC K4M, Eudragit RS 100 and PVP K-30) was dissolved in chloroform and dichloromethane (1:1) solution, using dibutyl phthalate and PEG-400 as plasticizers. Clarithromycin was added into the polymeric mixture and mixed homogenously using magnetic stirrer in a closed beaker. After complete mixing the solution was kept aside to remove entrapped air bubbles. The solution was then taken and poured into the clean leveled glass moulds. The solvent was allowed to evaporate slowly by inverting a glass funnel with a cotton plug closed into the stem of the funnel at room temperature for 24 hours. After complete evaporation of solvent, cast strips were obtained, which were then cut into pieces of 7×4 mm, wrapped in an aluminum foil and stored in a desiccator at room temperature in a dark place for further evaluation studies.

EVALUATION OF THE PREPARED FORMULATIONS:

Uniformity of Thickness: Five strips were taken from each batch and their individual thickness was measured using micrometer screw gauge.

Uniformity of Weight: Five strips were taken from each batch and their individual weights were determined by using electronic balance.

Uniformity of Drug Content: Five strips were taken from each batch and individually dissolved in 5 ml of phosphate buffer pH 6.8 solution in a beaker and filter it. 0.2 ml of the filtered solution was diluted to 10ml with chloroform in a volumetric flask. To this 10ml of solution taken in a separating funnel 5ml of conc. HCl was added followed by the addition of 10ml of acetone, was shaken for 5 mins. for the formation of stable coloured complex. The upper orange-red coloured layer was separated out and the absorbance was measured using UV-Vis spectrophotometer at λ_{max} 487 nm.

Tensile Strength of the Strips: Tensile strength of the strips was determined by Universal strength testing machine. It consists of two load cell grips, the lower one is fixed and upper one is movable. The test strip of specific size (4 × 2 cm) 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.

Folding Endurance: The folding endurance of the strips was determined by repeatedly folding the strip at the same place up to 300 times till it broke or folded, which is considered satisfactory to reveal good strip properties. This test was carried out on all the strips.[4]

***In vitro* Drug Release:** Static dissolution method reported in the literature was adopted. Strips of known weight and dimensions (size of 7×4 mm) were placed separately into 6 sets of small test tubes containing 2 ml of pH 6.8 phosphate buffer. The test tubes were sealed with aluminum foil and kept at 37°C for 24 hours. 1 ml of buffer was taken out and replaced with fresh 1 ml of pH 6.8 phosphate buffer after every 24 hours. The concentration of drug in this 1 ml of buffer was measured using UV-Vis spectrophotometer at λ_{max} 487 nm. The procedure was repeated for 8 days.[5, 6]

RESULTS AND DISCUSSION:-

Periodontal strips were prepared by using solvent casting technique. Formulations were designed as shown in table I. Ethyl cellulose alone and with copolymers (HPMC K4M, Eudragit RS- 100, PVP K30) was dissolved in chloroform and dichloromethane (1:1) solution, using dibutyl phthalate and PEG-400 as plasticizers.

The weight of all the strips was found to be in the range of 9.8 ± 0.064 to 10.7 ± 0.008. The uniformity of weight of the strip indicates good distribution of the drug, polymer and plasticizer. The physicochemical evaluation data for uniformity of weight and thickness is presented in table II. The prepared strips were evaluated for the thickness using micrometer screw gauge. The average of three readings was taken; the mean thickness and standard deviation were calculated. The low standard deviation of the measured thickness of all the 4 formulations may indicate uniform distribution of drug and excipients in prepared implants. It was found to be in the range of 0.415 ± 0.026 to 0.451 ± 0.008.

For various formulations, the % drug content was found to vary between 91.31 ± 0.022 to % 96.76 ± 0.034. Tensile strength was found to range between 1.54 ± 0.056 to 1.88 ± 0.028. Folding endurance values ranged from 188.33 ± 0.57 to 214.33 ± 1.52.

The release profile of the formulations is shown in the figure I. The periodontal implants prepared with Ethyl cellulose (F1) releases the drug completely in 6 days. The release of the drug from the formulation F1 was found to be 94.36% at the end of 6 days. The formulation with Ethyl cellulose and HPMC K4M (F2) showed complete release in 4 days. The release of drug from formulation F2 was found to be 93.91% at the end of 4 days. The formulation with Ethyl cellulose and PVP K30 (F3) showed complete release in 7 days. The release of drug from formulation F3 was found to be 95.12% at the end of 7 days. The formulation with Ethyl cellulose and Eudragit RS 100 (F4) showed complete release in 8 days. The release of drug from formulation F4 was found to be 98.66% at the end of 8 days.

In vitro release studies shows that the drug release was more sustained in case of strip F4 followed by F3 > F1 > F2. The regression values of strips F1 to F4 are higher with first order and therefore the release kinetics followed first order from all the strips. The release data of clarithromycin strips (F1 to F4) were given in table IV and fig II & III.

Hixson Crowell cube root law and Higuchi's model were applied to test the release mechanism. The R^2 values are higher for Higuchi's model compared to Hixson Crowell cube root law for all the strips. Hence clarithromycin release from all the strips followed diffusion rate controlled mechanism as shown in table IV.

CONCLUSION

Various batches of Clarithromycin periodontal strips were prepared by solvent casting method and characterized. The formulations F3 (Clarithromycin, Ethyl cellulose and PVP K30) and F4 (Clarithromycin, Ethyl cellulose and Eudragit RS 100) satisfied required pharmaceutical characteristics of periodontal implant and was found promising. The Clarithromycin periodontal implants would be able to offer benefits such as increasing residence time, prolonging drug release, reducing frequency of administration, and thereby may help to improve patient compliance. The results indicate formulation F3 and F4 has better drug release over an extended period of 7 and 8 days respectively.

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Table I. Composition of Different Clarithromycin Periodontal Strips

Ingredients	F1	F2	F3	F4
Drug (mg)	120	120	120	120
Ethyl Cellulose (mg)	1200	1000	1000	1000
HPMC K4M(mg)	-	200	-	-
PVP K30(g)	-	-	200	-
Eudragit RS 100 (mg)	-	-	-	200
Dibutyl phthalate (ml)	0.3	0.3	0.3	0.3
PEG 400 (ml)	0.1	0.1	0.1	0.1

Table II. Physicochemical characteristics of strips containing Clarithromycin

Strips	Weight (mg) ± SD	Thickness (mm) ± SD	Tensile strength (kg) ± SD	Drug content % ± SD	Folding Endurance
F1	10.5 ± 0.042	0.427 ± 0.024	1.32 ± 0.032	93.56 ± 0.062	198.33 ± 1.52
F2	9.8 ± 0.064	0.415 ± 0.026	1.54 ± 0.056	91.31 ± 0.022	188.33 ± 0.57
F3	10.1 ± 0.032	0.451 ± 0.008	1.51 ± 0.016	94.54 ± 0.024	214.33 ± 1.52
F4	10.7 ± 0.008	0.449 ± 0.036	1.88 ± 0.028	96.76 ± 0.034	210.33 ± 0.57

Table III. In vitro release profile of Clarithromycin strips.

Time (Days)	% Drug Release			
	F1	F2	F3	F4
0	0	0	0	0
1	31.27	38.21	34.69	33.46
2	54.31	63.29	51.24	53.44
3	72.17	82.99	68.53	66.25
4	79.11	93.91	76.71	77.09
5	88.69	-	86.58	89.65
6	94.36	-	90.88	92.93
7	-	-	95.12	96.16
8	-	-	-	98.66

Table IV. Comparison of R^2 values for F1-F4.

Strip Code	Regression Coefficient (R^2) Values			
	Zero Order	First Order	Higuchi's Model	Hixson- Crowell Model
F1	0.892	0.9385	0.9956	0.9704
F2	0.7877	0.981	0.9652	0.9438
F3	0.8513	0.9598	0.9816	0.9744
F4	0.8288	0.9184	0.9816	0.9744

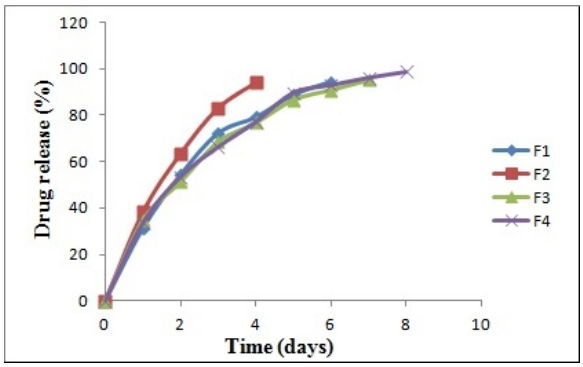

Fig I. In vitro release profile of Clarithromycin strips

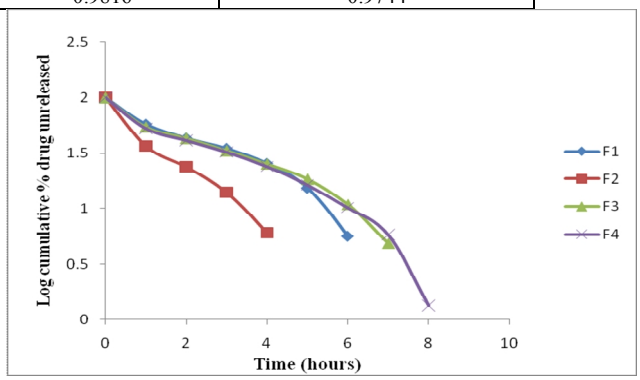

Fig. III. First order release profile of F1-F4

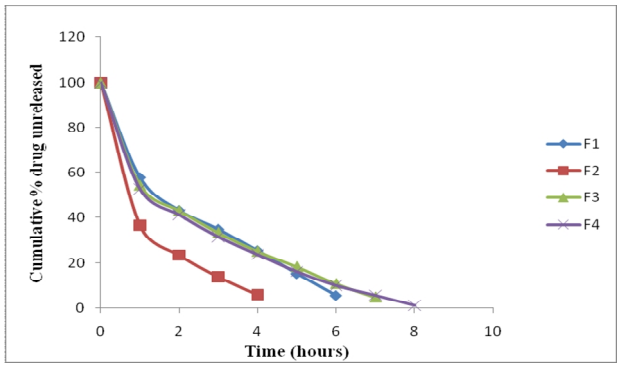

Fig. II. Zero order release profile of F1-F4

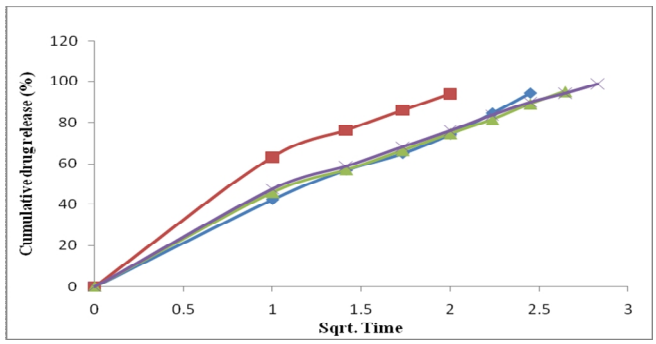

Fig. IV. Higuchi's model for F1-F4

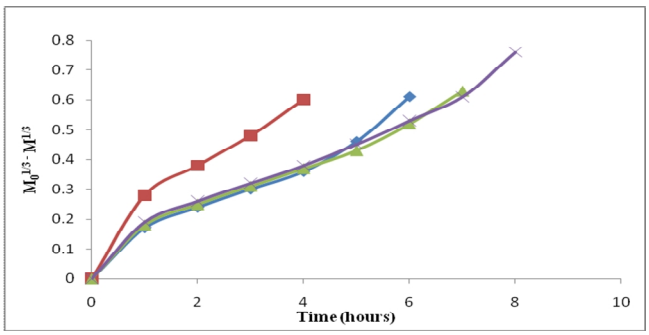

Fig. V. Hixson-Crowell model for F1-F4

Source of support: Nil, Conflict of interest: None Declared