ORIGINAL ARTICLE

Formulation and Evaluation of Cefixime Strips for Chronic Periodontal Treatment

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Abstract

Aim: To develop a periodontal pocket drug delivery system of cefixime loaded ethyl cellulose (EC) strips using hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose K_4M (HPMC K_4M), and Eudragit RL-100 as copolymers with different concentrations. **Materials and Methods:** Casting/solvent technique was utilized to prepared strips. The prepared strips were evaluated for physicochemical parameters such as Fourier transform infrared spectroscopy (FT-IR), thickness, folding endurance, percentage moisture loss, content uniformity, *in-vitro* drug release, and *in-vitro* antibacterial activity. **Results and Discussion:** FT-IR data showed that drug and excipients were compatible with each other. The formulated strips were flexible, having uniform drug content, and exhibited acceptable physicochemical characteristics. The drug release was sustained for up to 5 days, even if the strips demonstrated initial burst effect. As formulation P_3 showed better drug release profile, was optimized among all other formulations. **Conclusion:** The present work proposes that the sustained release cefixime loaded EC strips with copolymer HPMC K_4M have a significant role in the treatment of chronic periodontitis.

Key words: Cefixime, ethyl cellulose, hydroxypropylmethyl cellulose K_4M, periodontal delivery, polymeric strips

INTRODUCTION

The inflammatory process and the immune response are involved in the periodontal infection. Periodontal destruction occurs mainly due to the presence of periodontal pathogens such as *Prevotella intermedia*, *Porphyromonas gingivalis*, and *Actinobacillus actinomycetemcomitans*. As the soft tissues surrounding, the teeth are affected by these pathogens and may lead to produce acute and chronic disorder. Finally, it may cause loss of supporting bones.[1] In general, periodontitis treatment involves scaling and planning, systemic antibiotic therapy.[2] Clinically and microbiologically, positive effects were demonstrated by some systemic antimicrobials, which additions to mechanical therapy.[3] Subinhibitory concentrations at the periodontal site may produce resistance in periodontal pathogens and create depressing impact toward these approaches. Periodontal pocket delivery systems acquire beneficial advantage because of this kind of negative effect. These delivery systems can locally provide inhibitory concentrations toward the periodontal pathogens of the drug for several days. Periodontal fibers,[4] strips,[5] and gels[6] were already studied. Certain biodegradable polymers were utilized as drug transporters such as polyester poly (caprolactone), cross-linked atelocollagen, poly (gylcolidecold-lactide), glycerol monooleate, and hydroxyl-propylcellulose.

In the present work, the goal was to formulate periodontal pocket delivery system containing cefixime, dispersed in ethyl cellulose (EC), and various copolymers mixtures in different concentrations. Formulated strips were cut into the specified shape and size to make easy insert into the periodontal pocket.

Dental dosage form using EC has been recently demonstrated to sustain the release of drugs.[7,8] EC has proved itself to use as modified release tablet matrix,[9] as a sustained release film former, and as a thickening agent,[10] and when the nonionic

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material is desired for oral as well as topical applications, as a stabilizer and suspending agent.[11] Hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose K_4M (HPMC K_4M), and Eudragit RL-100 copolymers have already been used as excipients of sustained release implant material in dentistry.[12] Cefixime is a third generation broad spectrum cephalosporin. It is used to treat infections of ear, sinuses, throat, chest, and lungs. In addition, it has been demonstrated to treat typhoid fever.[13]

MATERIALS AND METHODS

EC, V 10 mPa.s, Eudragit RL-100, M_r ~32,000, HPMC K_4M, M_r ~90,000, dichloromethane, M_r 84.93, and methanol, M_r 32.04, were purchased from Sigma-Aldrich, India; dibutylphthalate, M_r 278.34, and HPC, M_r 100,000 were purchased from Loba Chemicals, Mumbai, India; Cefixime, M_r 453.452, was granted by Zydus Cadila Health Care Ltd., Ahmedabad, India; Mutans-Sanguis Agar, pH 7.10-7.50, was purchased from HiMedia Laboratories, Mumbai, India; all reagents were of analytical grade.

Preparation of cefixime strips

To obtain periodontal strips of fixed area (20 cm^2), casting/solvent technique using methanol and dichloromethane (1:1) mixture, was utilized. To optimize polymer, copolymer, and plasticizer concentrations, total 24 preliminary batches [Table 1] were formulated using 2^3 factorial design. In this, the polymer (EC, X_1), Copolymers (HPC, X_2, HPMC K_4M, X_3 and Edragit RL-100, X_4) and plasticizer (dibutyl phthalate, X_5) were selected as independent variables. On the basis of folding endurance results, finally total six formulations [Table 2] were prepared.

To formulate dental implants, dissolving polymer and copolymer in methanol and dichloromethane (1:1) mixture, dibutylphalate (50% v/w of that polymer) was added as a plasticizer, using magnetic stirrer in a closed beaker. Into this, accurately 40 mg

Table 1: Preliminary formulations

Variables level of 2^3 factorial design for cefixime dental strip

Variable level (%)	–1 (low)	+1 (high)
EC (X_1)	1.6	1.8
HPC (X_2)	1.2	1.6
DBP (% V/W)# (X_5)	50	60
EC (X_1)	1.6	1.8
HPMC K_4M (X_3)	0.05	0.1
DBP (% V/W)# (X_5)	50	60
EC (X_1)	1.6	1.8
Eudragit RL-100 (X_4)	0.05	0.1
DBP (% V/W)# (X_5)	50	60

Ingredients (%)	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8
EC	1.6	1.6	1.8	1.8	1.6	1.6	1.8	1.8
HPC	1.2	1.2	1.2	1.2	1.6	1.6	1.6	1.6
DPT (% V/W)#	50	60	50	60	50	60	50	60
Cefixime	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Ingredients (%)	**B_1**	**B_2**	**B_3**	**B_4**	**B_5**	**B_6**	**B_7**	**B_8**
EC	1.8	1.8	1.6	1.6	1.8	1.8	1.6	1.6
HPMC K_4M	0.05	0.05	0.05	0.05	0.1	0.1	0.1	0.1
DPT (% V/W)#	50	60	50	60	50	60	50	60
Cefixime	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Ingredients (%)	**C_1**	**C_2**	**C_3**	**C_4**	**C_5**	**C_6**	**C_7**	**C_8**
EC	1.6	1.6	1.8	1.8	1.6	1.6	1.8	1.8
E RL-100	0.1	0.1	0.1	0.1	0.05	0.05	0.05	0.05
DPT (% V/W)#	50	60	50	60	50	60	50	60
Cefixime	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4

EC: Ethyl cellulose, HPC: Hydroxypropyl cellulose, HPMC K_4M: Hydroxypropylmethyl cellulose, E RL-100-Eudragit RL-100, DPT: Dibutylphtalate, DBP: Dibutylphthalate. #Based on polymer and copolymer weight. In each formulation, 20 ml of methanol: Dichloromethane (1:1). From this, 10 ml was poured into the clean glass Petri dish (Anumbra® - area 60.6 cm^2 approximately) to cast strips

Table 2: Final formulations

Ingredients	Composition (%)					
	P_1	P_2	P_3	P_4	P_5	P_6
EC	1.8	1.6	1.6	-	-	1.6
HPC	-	1.2	-	1.8	-	-
HPMC K_4M	-	-	0.05	-	0.5	-
Eudragit RL-100	-	-	-	-	-	0.05
DBP (% V/W)#	50	50	50	50	50	50
Cefixime	0.4	0.4	0.4	0.4	0.4	0.4

#Based on polymer and copolymer weight. In each formulation, 20 ml of methanol: Dichloromethane (1:1). From this, 10 ml was poured into the clean glass Petri dish (Anumbra® – area 60.6 cm^2 approximately) to cast strips. EC: Ethyl cellulose, HPC: Hydroxy propyl cellulose, DBP: Dibutylphthalate, HPMC: Hydroxy propyl methyl cellulose

of cefixime was added. After absolute mixing, 10 ml of solution was poured into a clean glass Petri dish (Anumbra® - area 60.6 cm^2 approximately), to be found on a horizontal plane and set aside at 30°C, by inverting glass funnel with a cotton plug closed in the stalk of funnel on Petri dish, for at least 24 h to permit total evaporation of solvent. Casted strips were cut with sharp knife into pieces of 0.5×0.4 cm^2, enfolded with aluminum foil, accrued in desiccators at room temperature in dark place for further use. With the help of gas chromatography, solvent residues were determined for methanol.

Characterization of strips

With the help of Fourier transform infrared (FT-IR) spectroscopy compatibility of drug and excipients were carried out. Various physicochemical properties such as thickness, folding endurance, percentage moisture loss, content uniformity, *in-vitro* drug release, and *in-vitro* antibacterial activity were determined.

Infrared absorption spectroscopy (IR)

Samples of pure cefixime powder, cefixime, and all excipients were triturated with KBr in equal quantity and compressed with the help of hydraulic pressure to prepare discs for IR analysis. To obtain spectra, these discs were scanned using IR-spectrophotometer (Bruker Optics, Germany) over 400-4000 cm^{-1}.

Measurement of strip thickness

According to American Academy of periodontology, chronic form of periodontitis contains 3-4mm pocket depth. So, for compatibility reason, it was necessary to formulate appropriate thickness containing strip. Therefore, electronic outside micrometer (Model IP54, Beijing C&C Trade Center, China) was used to carry outstrips thickness. Randomly selected three points from the strips were considered to determine thickness. Mean of three times measurements was considered as the result.

Uniformity of weight

Single pan balance was utilized to measure weight of individual 20 strips (0.6×0.5 cm^2) from all the formulations. The average weights of these strips were calculated, and the standard deviation was taken.

Folding endurance

To handle and during inserting dental strip into the periodontal pocket, appropriate folding endurance is required. The low value of it may create problems as well as the high value may cause increases in brittleness. To determine folding endurance, repeatedly folding a strip (2×2 cm^2) at the same place till it broke.[14] The total number of times, without breaking, the strip was folded at the same place, represent the folding endurance value.

Percentage moisture loss

Weighed pieces of the strip were kept in a desiccator containing anhydrous calcium chloride at room temperature in dark place. After three successive days, the strips were taken out and re-weighed. The % moisture loss was calculated from the weight decrease, as follows:

$$\% \text{ moisture loss} = (W_1-W_2)/W_1\times 100$$

Where, W_1 and W_2 are the weight of the strip before and after kept in desiccator, respectively.

Content uniformity

Cefixime content determined by dissolving three weighed strips separately in 10 ml of dichloromethane.[15]. The drug was extracted with two consecutive quantities, each of 10 ml isotonic saline phosphate buffer pH 6.8 using separating funnel. The separation of the aqueous phase was done, and suitable dilution was made. Using UV-spectrophotometer (UV-1800, Shimadzu, Japan), absorbance was measured at 288.8 nm for cefixime.

In-vitro release studies

Cefixime release form the strips was determined by utilizing glass vial using 1 ml isotonic saline phosphate buffer pH 6.8 as dissolution medium at 37°C. 1 ml dissolution medium was withdrawn at every 24 h interval and to maintain "sink conditions" immediately replaced it with fresh 1 ml dissolution medium.[16] UV-spectrophotometric analysis at 288.8 nm was carried out to determine the amount of drug release, with suitable dilution of dissolution medium.

In-vitro antibacterial activity

To determine *in-vitro* antibacterial activity of all formulations, strip was cut into 0.5×0.5 cm^2. This cut strip was placed on Mutans-Sanguis Agar plates, seeded with the facultative anaerobic organisms, *Streptococcus mutans* at 37°C in biological oxygen demand incubator (Alliance Enterprise, Vadodara). Zone of inhibition was measured after 48 h. From this plate, strip was taken out and placed on another Mutans-Sanguis Agar plates having fresh seeding of organisms and incubated for 48 h at 37°C. This procedure was repeated till no inhibition was obtained.[17,18]

RESULTS AND DISCUSSION

The FT-IR data showed that drug and all excipients were compatible with each other, as there is no any interaction occurs (Figure 1). Folding endurance of preliminary formulations A_1, B_3, and C_5 were found to be in acceptable limit (between 150 and 300). So, finally total 6 formulations were formulated.

The physical parameters such as thickness, folding endurance, percentage moisture loss, and content uniformity were described in Table 3. The casted strips showed excellent strip forming properties as well as reproducibility. Formulated strips have flexibility, elasticity, and smooth surface.

Formulation P_5 contains HPMC K_4M in low concentration may cause less thickness of strips, whereas remaining formulations were represented thicknesses in the range of 135-178.4 mm. Weight uniformity of all the formulations was obtained in the range of 20.17-20.58 mg. Data represent the uniformity in weight uniformity and thickness of dental strips having less standard deviation values, proved uniformity of formulations by casting/solvent evaporation technique. All formulations have more than 200 folding endurance except P_5 has 178, as it contains only HPMC K_4M. All formulations have more than 200 folding endurance except P_5 has 178, as it contains only HPMC K_4M. All formulations contain different concentrations of polymer and copolymers. So, the values of tensile strength were obtained in the range of 24.2±0.06-27.6±0.03 kg/cm^2, as the concentrations of copolymer increases the tensile strength value was decreased.

All formulations have percentage moisture loss between the ranges of 1.21-2.18. Formulation P_5 contains HPMC K_4M alone, which has moisture loss property on storage. So, it exhibited high percentage moisture loss. In case of formulation P_1, has low percentage moisture loss due to hydrophobic nature of EC. Drug content of all formulated strips was in the range of 96.6-97.9. This clearly stated that uniform distribution of drug in all the formulations. Highest drug content uniformity showed in P_3, whereas lowest drug content uniformity in P_5 (Table 3).

Figure 2 represents that in first 24 h, all strips showed rapid release of drug. It has been due to burst effect, as because of the outer surface of strips have quick elution and sharp cut edge of the strips matrix. After completion of burst effect, slowly sustained release of drug was seen up to 5 days. To recognized drug release profile as well as release mechanism, the *in-vitro* dissolution data were treated according to cumulative percentage of drug remaining versus time (Zero order), log cumulative percentage of drug remaining versus time (First order), cumulative percentage of drug release versus square root of time (Higuchi's equation) and Peppas equation. From the kinetic analysis of *in-vitro* drug release, Peppas model was best fitted to release mechanism of all the strips due to high linearity of plots. Comparison of regression coefficients and slopes was made in Table 4.

Figure 3 shows a comparison of zone of inhibition of all cefixime strips. Longer period antibacterial activity was obtained through formulation P_1, P_2, P_3, and P_6 (6 days) then formulation P_4 and P_5 (4 days), as they have not contained EC. This might be due to less numbers of pore channels.

CONCLUSION AND FUTURE PERSPECTIVES

Periodontal pocket drug delivery system has a great advantage against systematic drug therapy is that the

Table 3: Physicochemical evaluation data of cefixime strips

Formulation code	Mean thickness (mm) (n=3)	Average weight (mg) (n=20)	Content uniformity (n=3)	% moisture loss (n=3)	Folding endurance (n=3)
P_1	143.2±0.05	20.28±0.22	97.5±0.11	1.21±0.028	263±0.55
P_2	178.4±0.04	20.58±0.12	96.7±0.13	1.28±0.042	292±0.66
P_3	149.2±0.05	20.17±0.15	97.9±0.76	1.86±0.044	266±0.23
P_4	135.0±0.03	20.32±0.14	97.7±0.17	1.62±0.038	258±0.48
P_5	108.5±0.05	20.49±0.16	96.6±0.10	2.18±0.046	178±0.38
P_6	168.4±0.04	20.51±0.18	97.1±0.46	1.45±0.041	274±0.18

All values are mean±Standard deviation of 3, 20, 3, 3, and 3, respectively

inhibitory concentration is achieved in lesser amount of drug. Ultimately, this reduces the development of organism resistance. In addition, this delivery has less time-consuming in comparison to mechanical debridement. Compatibility studies by FT-IR showed no any chemical reaction between drug and excipients. Formulated strips have fine flexibility, possessed good folding endurance, and exhibited acceptable physicochemical properties. Strips showed sustained release of drug for up to 5 days followed by initial burst release of drug. From all the formulations, P_3 formulation containing 1.6% EC and 0.05% HPMC K_4M showed release of drug and *in-vitro* antibacterial activity up to 120 and 144 h, respectively. The amount of residual methanol was found to be acceptable limit (689.5 ppm = < 3,000 ppm).

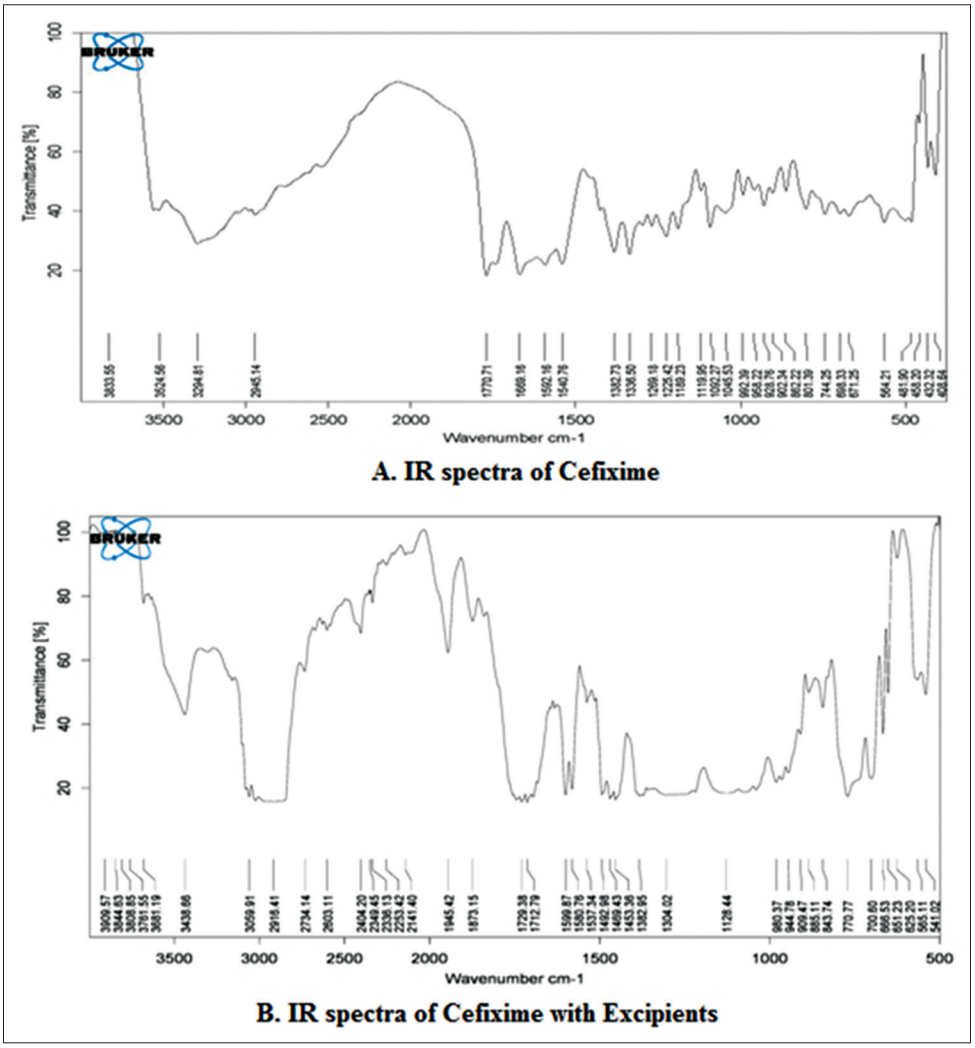

Figure 1: Cefixime-Excipients compatibility A. IR spectra of cefixime - Characteristics bands at 3300-3500 Cm^{-1} (NH_2 – Primary amine), 1680-1750 Cm^{-1} (C=O), 1630-1690 Cm^{-1} (Cyclic amide), 1540-1590 Cm^{-1} (C-H=) B. IR spectra of Cefixime with Excipients - Characteristics bands at 3438.66 Cm^{-1} (NH_2 – Primary amine), 1729.38 Cm^{-1} (C=O), 1599.87 Cm^{-1} (Cyclic amide), 1580.76 Cm-1 (C-H=)

Table 4: Kinetic data of the strips

Formulations code	Zero order		First order		Higuchi's		Peppa's	
	R^2	K_0(mg/h)	R^2	$K_1(h^{-1})$	R^2	KH	R^2	N
P_1	0.5909	1.652	0.9954	0.068	0.9089	12.904	0.9996	0.139
P_2	0.2853	1.022	0.9653	0.046	0.8329	10.091	0.9998	0.152
P_3	0.2933	1.069	0.9901	0.053	0.8381	10.557	0.9990	0.159
P_4	0.2560	1.000	0.9455	0.043	0.8179	9.884	0.9998	0.138
P_5	0.3331	1.044	0.9232	0.042	0.7964	9.732	0.9997	0.120
P_6	0.2156	0.983	0.9839	0.046	0.8565	10.285	0.9992	0.176

n=0.5, Fickian diffusion (Higuchi Matrix), *n*=0.5<*n* < 1- Anomalous trasport

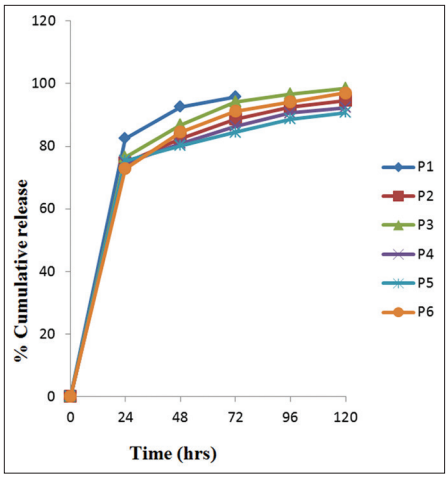

Figure 2: % cumulative drug release profile Plot of *In-vitro* cumulative percentage drug release Vs. Time Formulation P_1 to P_6 showing brust release of drug on day one and sustained for the rest five days. EC with DBP-P_1-- ♦, EC and HPC with DBP-P_2 --■, EC and HPMC K4M with DBP-P_3--▲ HPC with DBP-P_4-- ×, HPMC K4M with DBP-P_5-- +, EC and Eudragit RL-100 with DPC-P_6--● Ethyl Cellulose (EC), Hydroxy Propyl Cellulose (HPC), Hydroxy Propyl methyl cellulose K4M (HPMC K_4M), Dibutylphthalate (DBP)

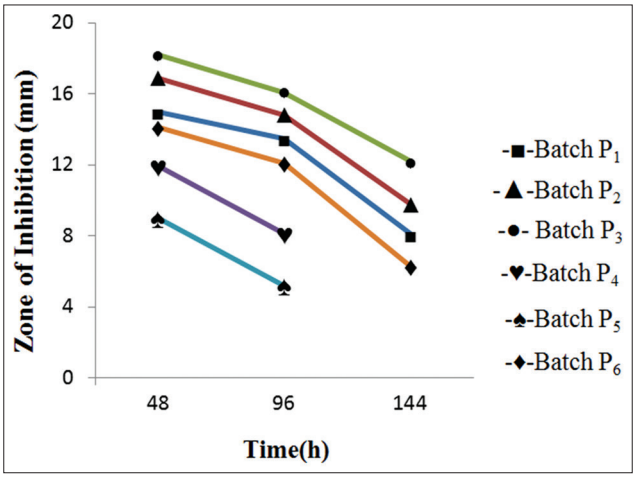

Figure 3: Plot of Zone of inhibition produced by cefixime strips Vs Time EC with DBP-P_1-- ■, EC and HPC with DBP-P_2 --▲, EC and HPMC K4M with DBP-P_3--● HPC with DBP-P_4-- ♥, HPMC K4M with DBP-P_5--♠, EC and Eudragit RL-100 with DPC-P_6--♦ Ethyl Cellulose (EC), Hydroxy Propyl Cellulose (HPC), Hydroxy Propyl methyl cellulose K_4M (HPMC K_4M), Dibutylphthalate (DBP)

Finally, it is concluded that local therapy of periodontitis with the help of cefixime loaded EC strips has a remarkable role. In addition to this, it is cost-effective and will not interfere with a daily routine habit of patients. Incorporation of cross-linking of strips with support of suitable agent may increase the sustain release property of drug for several number of days.

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REFERENCES

1. Sunil A, Venkatesh M, Udupa N. Controlled drug delivery systems for periodontitis. Pharm Rev 2004;2:61-82.
2. Goodson JM. Antimicrobial strategies for treatment of periodontal diseases. J. Periodontol 1994;5:142-68.
3. Herrera D, Sanz M. Systematic review on the effect of systematic antimicrobials as an adjunct to scaling and root planning in periodontitis patients. J Clin Periodontol 2000;53:604-10.
4. Awen BZ, Katakam P, Rao CB. Design and *in-vitro* evaluation of controlled release cephalexin subgingival films using natural biodegradable polymer. Recent Res Sci Technol 2010;2:06-11.
5. Addy M, Hassan H, Moran J, Wade W, Newcombe R. Use of antimicrobial containing acrylic strips in the treatment of chronic periodontal disease. A three month follow-up study. J Periodontol 1988;59:557-64.
6. Bansal K, Rawat MK, Jain A, Rajput A, Chaturvedi TP, Singh S. Development of satranidazole mucoadhesive gel for the treatment of periodontitis. AAPS PharmSciTech 2009;10:716-23.
7. Golomb G, Friedman M, Soskolne A, Stabholz A, Sela MN. Sustained release device containing metronidazole for periodontitis use. J Dent Res 1984;63:1149-53.
8. Soskolne A, Golomb G, Friedman M, Sela MN. New sustained release dosage form of chlorhexidine for dental use. II. Use in periodontal therapy. J Periodontal Res 1983;18:330-6.
9. Chandran S, Asghar LF, Mantha N. Design and evaluation of ethyl cellulose based matrix tablets of ibuprofen with pH modulated release kinetics. Indian J Pharm Sci 2008;75:596-602.
10. Sadashivaiah R, Dinesh BM, Uma AP, Desai BG, Raghu KS. Design and *in-vitro* evaluation of haloperidol lactate transdermal patches containing ethyl cellulose-povidone as film formers. Asian J Pharm 2008;2:43-9.
11. Melzer E, Kreuter J, Daniels R. Ethyl cellulose: A new type of emulsion stabilizer. Eur J Pharm Biopharm 2003;56:23-7.
12. Mastiholimath VS, Dandagi PM, Gadad AP, Patil MB, Manvi FV, Chandur VK. Formulation and evaluation of ornidazole dental implants for periodontitis. Indian J Pharm Sci 2006;68:68-71.

13. Matsumoto Y, Ikemoto A, Wakai Y, Ikeda F, Tawara S, Matsumoto K. Mechanism of therapeutic effectiveness of cefixime against typhoid fever. Antimicrob Agents Chemother 2001;45:2450-4.
14. Semalty M, Semalty A, Kumar G. Formulation and characterization of mucoadhesive buccal film of glipizide. Indian J Pharm Sci 2008;70:43-8.
15. Lakshmi PK, Sreekanth J, Sridharan A. Formulation development of fast releasing oral thin films of levocetrizine dihydrochloride with Eudragit® Epo and optimization through Taguchi orthogonal experimental design. Asian J Pharm 2011;5:84-92.
16. Ahmed MG, Harish NM, Charyulu RN, Prabhu P. Formulation of chitosan-based ciprofloxacin and diclofenac film for periodontitis therapy. Trop J Pharm Res ;8:33-41.
17. Rawlins EA. Bentley's Textbook of Pharmaceuticals. 8th ed. London: Bailliere Tindall; 2002. p. 447.
18. Steinzberg D, Friedman M, Soskolne A, Sele MN. A new degradable controlled release device for treatment of periodontal disease: *In-vitro* release study. J Periodontol 1990;61:393-8.

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