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Research Article

SUSTAINED RELEASE DEVICE CONTAINING ORNIDAZOLE FOR PERIODONTITIS

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ABSTRACT
The purpose of this study was to develop a sustained release device containing ornidazole for insertion within periodontal pockets. Cast films of ethyl cellulose with dibutyl phthalate as plasticizer, containing ornidazole were prepared. The films were evaluated for thickness, folding endurance, weight variation, content uniformity, tensile strength and *in vitro* antibacterial activity. *In vitro* release of ornidazole from the film was measured using UV spectrophotometer. The release data obtained were subjected for release kinetics study. The study revealed that drug release was found to be diffusion controlled with sustained release of ornidazole over a period of nine days within the periodontal pocket.
KEYWORDS: Periodontitis, ethyl cellulose, ornidazole, films, release kinetics

INTRODUCTION

Periodontal diseases are a group of clinical conditions which affect the supportive structure of the teeth and are characterized by infection and inflammation. The development of periodontitis involves periodontal tissue breakdown and results from an interaction between the affecting organisms, e.g., *Bacteroides spp., Capnocytophaga spp.,* and *Actinobacillus actinomycetemcomitans* and the host defense mechanism. If untreated, will lead to increased tooth mobility and possibly results in tooth loss[1].

Conventional therapy, based on scaling, surgery and the use of systemic antibiotics or antimicrobials administration has been proposed[2]. However, the systemic route of antibiotic administration may not be ideal because of the concern over the development of bacterial resistance that may be induced over longer period of time. Systemic antibiotic therapy over a long period of time also raises the risk of undesirable side effects such as nausea, fever, abdominal pain and pseudomembranous colitis[3].

But local delivery of antimicrobial agents is becoming more prevalent since it leads to higher concentration of the drug at the intended site of action using a lower dose with an associated reduction in side effects related to systemic administration[4].

Ornidazole (OE) has shown a marked antibacterial and antiprotozoal activity under *in vitro* conditions. The antibacterial spectrum of ornidazole includes bacteria such as the *Peptostreptococcus species, Clostridium difficile, Clostridium species*, *Bacteroids species, Bacteroids fragilis*, *Provotella species, Porphyromonas species, Fusobacterium species, Actinomycetes, Propionibacterium species* and *Eubacterium species*[5].

Hence in the present study an attempt was made to develop a sustained release device (S.R.D.) in the form of polymeric films containing ornidazole and its physicochemical characterization.

MATERIALS AND METHOD

Materials

Ornidazole was obtained from Yarrow chem. Ltd Mumbai, India. Chitosan (85% deacetylated with viscosity of 8000-11000 cps) from Central Institute of Fisheries Technology, Kochi, India and all other chemicals used were of analytical grade.

Preparation of drug loaded ethyl cellulose films

Solvent casting technique was used for the preparation sustained release devices (S.R.D.) using chloroform and dichloromethane (1:1) mixture with slight modification[6]. Ethyl cellulose polymer (5%) with dibutyl phthalate as plasticizer (30%) was dissolved by slowly adding dry powder to 1:1 ratio of chloroform and dichloromethane, which was vigorously stirred. Ornidazole powder (0%, 10%, 20% and 30% w/w of the drugs) to the weight of polymer was added, after complete dissolution of the drug and polymer. The viscous dispersion was kept aside

for 30 min for complete expulsion of air bubbles. The films were casted by pouring the drug-polymer dispersion into the center of leveled glass moulds and allowed to dry at room temperature. After drying, films were cut into inserts of required size (7 x 2 mm), wrapped in aluminium foil separately and stored in desiccator until use.

Evaluation of ethyl cellulose films:

Compatibility studies were conducted using Fourier transform infrared (FTIR) spectroscopy of the drug alone, polymer alone and prepared films. Physicochemical properties such as thickness, content uniformity, weight variation, folding endurance and tensile strength of prepared films were determined.

Thickness: The thickness of polymeric films (4 × 4cm) was determined by using digital screw gauge (Mitutoyo 4026F, Japan) at different place of the films[7].

Weight variation: Twenty films of same size (7 × 2mm) were weighed on electronic balance and average weight was calculated[8].

Tensile strength: Tensile strength of the films 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 film of specific size (4 × 1 cm^2) was fixed between these cell grips and force was gradually applied till the film breaks. The tensile strength of the film was taken directly from the dial reading in kilograms[2].

Folding endurance Studies. This study was determined by repeatedly folding a 2 × 2 cm size films, at the same place, till it broke[2].

Drug content and content uniformity: The drug loaded films of known weight of 2 × 7 mm dimension were crushed in 10 ml of 1% v/v acetic acid in water and shaken until it dissolved. The drug solution was suitably diluted with 1% v/v acetic acid and absorbance was measured at 319 nm.

***In vitro* drug release pattern by using static dissolution test apparatus:** A static dissolution method reported in the literature was adopted in this method. Sets of six films of know weight and dimension (7 × 2 mm) were placed in a small test tube containing 1ml of pH.6.6 phosphate buffer. The tubes were sealed and kept at 37 ^{o} C for 24 h. The buffer medium was collected and replaced with a fresh 1ml of pH 6.6 phosphate buffer. The concentration of drug in the buffer was measured at 319 nm. The same procedure was continued until complete drug release was observed[9].

Stability studies: The stability of the entire drug loaded polymer films were studied at different temperatures using the reported procedure[10]. The films of size (7 × 2 mm) were weighed in 3 sets (12 films in each set). The films were wrapped in aluminium 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 10 weeks. As a function of time, samples were analyzed for physical changes and drug content.

***In-vitro* antibacterial activity:** *In vitro* antibacterial activity was performed on all formulations by placing the strips, on agar plates seeded with oral bacteria, *streptococcus mutans*. After 48 h of incubation at 37˚ C, the films were transferred onto freshly seeded agar plates for an additional 48 h for incubation. This procedure was repeated until no inhibition of bacterial growth was detected on the agar plate. The growth inhibition area of microorganisms on the agar plate was measured[11].

RESULTS AND DISCUSSION

In the present study, periodontal films of ornidazole were formulated using the polymer ethyl cellulose with dibutyl phthalate as plasticizer. The prepared films were transparent and smooth surfaced with good tensile strength. The procedure developed to prepare the films was reproducible.

The results of FTIR studies are shown in Fig.1, confirmed the absence of any chemical interaction between the drug and the polymer. The physicochemical evaluation data presented in Table 2 indicates that the final size and thickness of the prepared films were satisfactory with the view of insertion to the periodontal pockets. All the films have uniform thickness which ranges from 0.125± 0.04 to 0.261± 0.05mm. The films of all the batches were found to be of uniform weight, ranging from 2.58 ± 0.00164 to 4.96 ± 0.00152 mg.

Folding endurance of the films was > 150 times indicate that the formulations have good film forming properties.

The tensile strength of plain and drug-loaded films were studied (Table 2). The tensile strength of the films ranged from 1.85 to 3.07 kg, tensile strength was minimum for plain film and maximum for film containing 30% of the drug. As the drug loading increases tensile strength of the film also increased, this may be due to the increased toughness and rigidity of the polymeric film.

Content uniformity studies of the films shows that the drug was uniformly dispersed and percentage of drug loading ranges from 83.52, 73.93 and 69.22, % for formulations OE 10%, OE 20% and OE 30% respectively (Table 2).

In vitro release studies of ornidazole was carried out in pH 6.6 phosphate buffer for 9 days which shows that there was an abrupt release observed in first two days, followed by slow and sustained release up to periods of 9 days for 10, 20, and 30% of the drug-loaded films, respectively as shown in Fig 2. The burst effect may be due to elution of drug from the outer surface and cut edges of the matrix. Average amount of drug release per day after 3rd day is found to be above the minimum inhibitory concentration of ornidazole.

In vitro drug release kinetic analysis showed that release mechanism for all the films fitted best to the Highuchi model, as the plots showed high linearity (R^2 = 0.914 to 0.936). The plot of cumulative drug release per unit area versus square root of time in days showed a near linear relationship from 3rd to 9th day respectively. This was confirmed by data based on Korsmeyer et al's equation, which showed good linearity (R^2 = 0.959 to 0.963) and with slope (n) values ranging from 0.203 to 0.261,

The *in vitro* antibacterial activity demonstrated a significant antibacterial profile on all the films, as shown in Fig 3. Film without the drug was also tested and it was found that the film was not effective against the microorganism. The stability studies carried out for a period of 10 weeks showed that there were no significant physical changes and the drug content.

CONCLUSION

The greatest advantage 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. On the basis of *in vitro* characterization it was concluded that ornidazole could be incorporated as a slow release device for the treatment of periodontitis. Periodontal films consisting of ethyl cellulose with dibutyl phthalate as plasticizers demonstrated sustained release of the drug. The drug remained intact and stable in the periodontal films during storage, with no significant chemical interaction between the drug and the excipients. Further, detailed investigation is required to establish *in-vivo* efficiency of these films.

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Table 1: Percentage drug loading in ethyl cellulose periodontal films

Strip code	% drug Loading
ECP	0
OE-10	10
OE-20	20

OE-30	30

ECP-Ethyl cellulose Plain Strips, **O**-Ornidazole

Table 2: Data for drug content of ethyl cellulose films containing ornidazole.

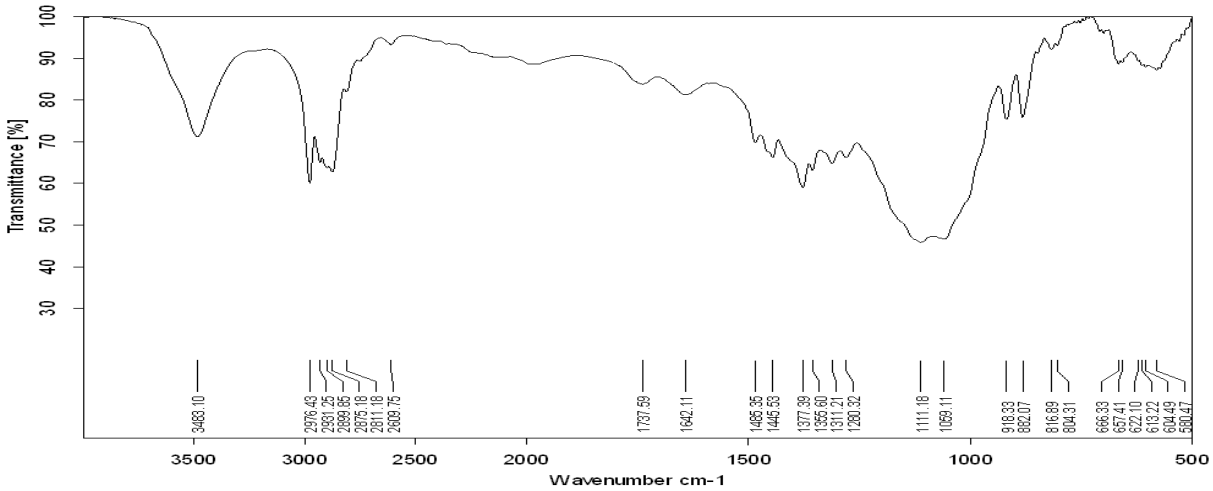
Strip Code	Drug content* (µg)	Theoretical drug loading(µg)	% of drug loading
EC	-	-	-
OE-10	182.716 ± 0.009	218.75	83.527
OE-20	323.456 ± 0.003	437.50	73.932
OE-30	454.320 ± 0.005	656.25	69.229

Table 3: Physical characteristics of ornidazole loaded ethyl cellulose films

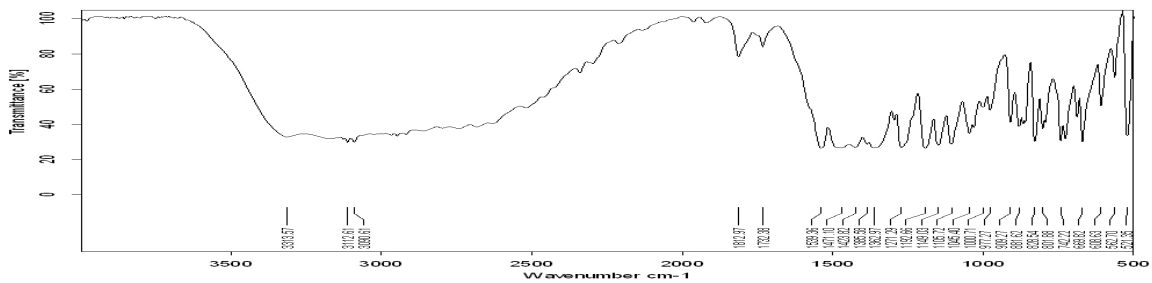
Strip code	Tensile strength (kg)	Folding endurance	Weight variation (mg)	Thickness (mm)
ECP	1.85± 0.024	200± 2.85	2.58± 0.02	0.125± 0.004
OE-10	2.18± 0.060	185± 2.13	4.28± 0.27	0.190± 0.009
OE-20	2.54± 0.030	180± 2.63	4.39± 0.27	0.218± 0.010
OE-30	3.07± 0.041	175± 7.34	4.96± 0.44	0.261± 0.030

ECP-Ethyl cellulose Plain Strips, **OE**-Ornidazole and Ethyl cellulose

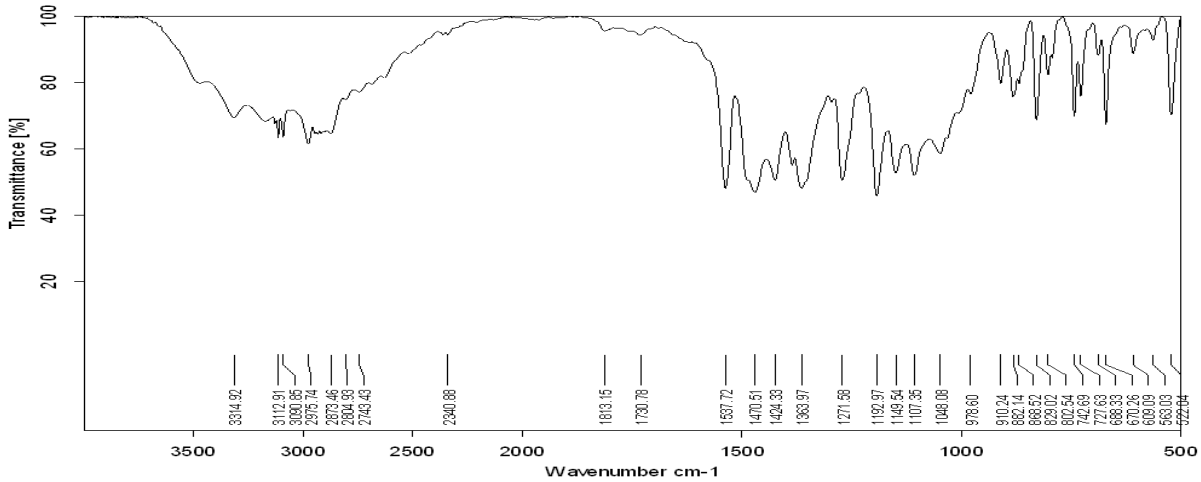
*Each value is a mean and standard deviation of six determinations



(a) Ethyl cellulose



(b) Ornidazole



(c) Ethyl cellulose film containing ornidazole

Fig 1: (a) FT-IR of pure ethyl cellulose (b) FT-IR of pure sample of ornidazole (c) FT-IR of ethyl cellulose film containing ornidazole

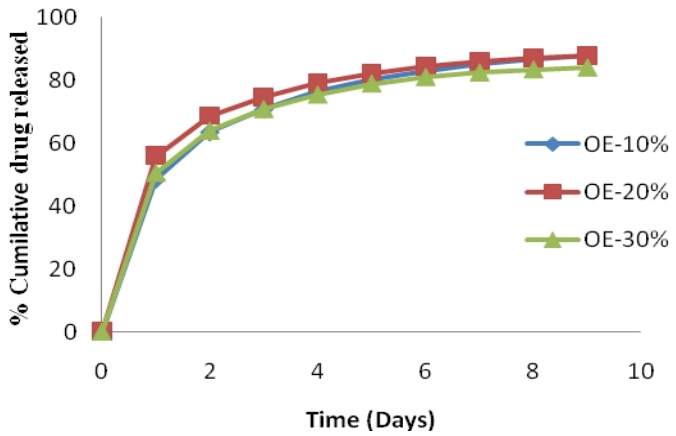


Fig 2: Drug release profile of ethyl cellulose films containing ornidazole

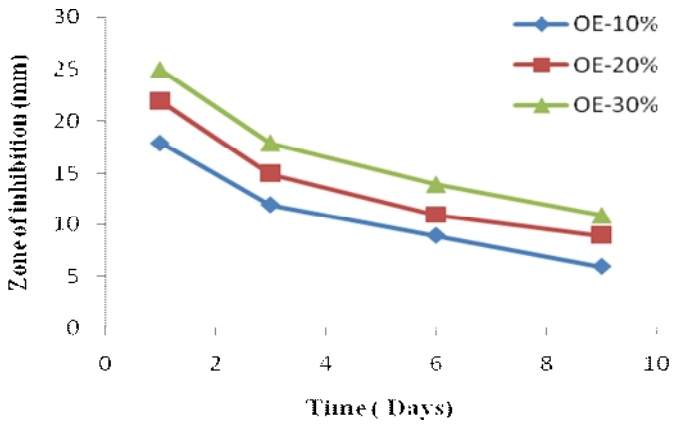


Fig 3: *In-vitro* antimicrobial activity of ethyl cellulose films containing ornidazole.

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