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Research Article

Antimicrobial activity of Novel Biodegradable Periodontal films containing Ciprofloxacin and Ornidazole

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Abstract: Local controlled drug delivery system of Ciprofloxacin and Ornidazole for the treatment of periodontitis is highly advantageous. For the present investigation, polycaprolactone strips containing Ciprofloxacin and Ornidazole in different ratios were prepared by solution casting method using acetone. All strips were cross-linked by exposing to the vapours of 2% v/v glutaraldehyde in water. The growth inhibition zone on the agar plate was measured by using oral bacteria *Streptococcus mutans*. The result showed that the crosslinked film with higher percentage of Ornidazole concentration retained the inhibition of growth for prolonged period of time.
Keywords: Ciprofloxacin, periodontitis, *Streptococcus mutans*

INTRODUCTION

Periodontitis is an inflammatory response to the overgrowth of anaerobic organisms such as spirochetes and bacteroides and in some cases, micro-aerophilic organisms in the subgingival plaque. Periodontal disease may result in the destruction of the bone and soft tissues supporting the tooth, which causes tooth loss. The clinical signs include changes in the morphology of gingival tissues, gingival bleeding as well as periodontal pocket formation. This pocket provides an ideal environment for the growth and proliferation of anaerobic pathogenic bacteria [1,2].

The oral cavity is colonized by more than 400 species of aerobic and anaerobic bacteria. Anaerobic bacteria outnumber their aerobic counterparts by a ratio of 10:1 to 100:1. These organisms inhabit the teeth, the gingival crevice, the mucous membranes, the dorsum of the tongue and saliva [3].

Conventional local application (as mouth rinse, gels, tooth paste) control only supragingival microbial plaques or mucosal infection, but not effective against periodontal disease involving pocket formation and also requires high initial concentration and multiple applications in order to provide sustained effectiveness [4,5].

Local application of antibiotics has been achieved either by subgingival irrigation or by incorporating the drug into different devices for insertion into periodontal pockets. In contrast to irrigation, the devices may secure antimicrobial effect for a prolonged period of time at the site. So a delivery system is developed by immobilizing antimicrobial agents with a carrier substance to provide controlled local release. Controlled local delivery of antibiotics has shown to reduce periodontopathogenic microorganisms with minimal side effects.

Controlled release local delivery devices, which may secure an antimicrobial effect for a prolonged period of time at the disease site, than that can be achieved by systemic or local topical application and also bypass systemic complication. These devices employ the control release technologies to assure therapeutic concentrations of the antimicrobials in the subgingival area for atleast three or more number of days following a single application. Hence a better, safer and effective low dose drug delivery device is highly desirable [6].

Many antibacterial agents have been tested for intra-pocket delivery, including tetracycline [7,8], doxycycline [4], chlorhexidine [9], metronidazole [10], ofloxacin, minocycline, and Ornidazole for their contribution to therapeutic response in periodontal disease [11].

The present work aims to prove the effectiveness from the selected formulation the one capable to with stand the prolonged antimicrobial activity and to determine the concentration ratio of the combination drug therapy which can release the dug at a controlled rate for effective treatment for prolonged period of time.

MATERIALS AND METHODS:

Ciprofloxacin and Ornidazole were obtained from Dr. Reddy's Laboratories, Hyderabad and Lincoln Pharmaceuticals Ltd, Ahmedabad. Other essential chemicals were obtained from Sigma Aldrich, st.Louis, USA; E-Merck (India) Ltd., Mumbai; S.D. Fine Chem Ltd., Mumbai.

Formulation Development

Preparation of Drug Loaded Polycaprolactone Films

Polycaprolactone (10% w/v) was soaked in acetone for 24 hours to get a clear solution. To the above solution different plasticizers were add. This dispersion was filtered through a muslin cloth to remove undissolved portion of the polymer . Required amount of the drugs were added and mixed for 15 minutes to dissolve the drugs in polycaprolactone solution. The viscous dispersion was kept aside for 30 minutes for complete expulsion of air bubbles. The films were casted by pouring the drug-polymer dispersion into the centre of levelled glass moulds of 5 x 3 cm^2 and allowed to dry at room temperature (30 ^oC) for 48 hours. After drying, films were cut into strips of 7 × 2 mm^2, wrapped in aluminium foil and stored in desiccator for further use [12].

Preparation of cross-linked polycaprolactone films:

The films were prepared as described above and subjected to cross-linking by exposing to glutaraldehyde vapours in a chromatography chamber.

Table 01: Formulation Table

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Ciprofloxacin	15mg	15mg	15mg	15mg	15mg	15mg	15mg	15mg	15mg	15mg	15mg
Ornidazole	15mg	15mg	15mg	15mg	15mg	15mg	15mg	15mg	15mg	15mg	15mg
Poly-Caprolactone	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
Glycerine	10%	20%	30%	---	---	---	---	---	---	---	---
Propylene Glycol	---	---	---	10%	20%	30%	---	---	---	---	---
PEG 400	---	---	---	---	---	---	10%	20%	30%	---	---
Dibutyl Pthalate	---	---	---	---	---	---	---	---	---	10%	20%
Acetone	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml
Observation	Brittle film	Brittle film	Brittle film	Brittle film	Brittle film	Brittle film	Brittle film	Brittle film	Brittle film	Brittle film	Flexible film

From the table no 1 it is clear that among the eleven formulation prepared by using different composition of plasticizers only F11 proved to have a good folding endurance property,thus selected for further studies. Further the different composition of drugs are taken and are prepared in different ratios to form uncrosslinked and cross linked films as shown in table 2.

Table 02: Polycaprolactone strips containing drugs – parameters for preparation.

	Strip code	% of drug	
		Ciprofloxacin	**Ornidazole**
Uncross-linked films	F11(A)	7.5%	7.5%
	F11(C)	10%	5%
	F11(E)	5%	10%
Cross-linked films	F11(B)	7.5%	7.5%
	F11(D)	10%	5%
	F11(F)	5%	10%

***In Vitro* Antibacterial Activity**

In vitro antibacterial activity was performed on all formulations by placing the film (0.5 x 0.5 cm) on agar plates seeded with the oral bacteria *Streptococcus mutans*. After 48 h of incubation at 37 ^oC, the films 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 [12].

***In Vitro* Drug Release**

In vitro drug release was performed by placing films of known weight and dimension (7 × 2 mm^2) into small vials containing 2 ml of phosphate buffer solution, pH 6.6. The vials were sealed and kept at 37 ^oC for 24 hours. One ml of buffer was withdrawn and immediately replaced with a fresh 1 ml phosphate buffer solution, pH 6.6 after 24 hours [13]. The concentrations of drugs in the buffer were measured at

274.8 nm and 318 nm. The procedure was continued for 6 days and 16 days for uncrosslinked and crosslinked films respectively.

RESULTS AND DISCUSSIONS:

The drug release profile obtained from the dissolution of the selected formulations were determined for the maximum time point for the drug release. The datas are mentioned in the Table 3, it clarifies that the drug release from the crosslinked films were (F11-B,F11-D,F11-F) controlled release for a period of 16 hrs. The remaining uncrosslinked films showed a relatively rapid drug release than the crosslinked ones. The study can be compared with the the antimicrobial study that was conducted shown in table .The study concluded that the crosslinked films showed more bacterial resistance for prolonged time period than the uncrosslinked films from the zone of inhibition studies as shown in figure 1. The reason may be the probable student dumping of the drugs at a faster rate than the ones which are crosslinked. The crosslinked system served as the diffusion control type which released the drug for the prolonged period of the time thus the antimicrobial activity was able to persist for prolonged period. Thus the presence of crosslinking process that affected the dissolution process also affected the antimicrobial activity.

Among the various crosslinked formulations F11(F) was found to be more resistant aganst the microbes. The probable reason lies hidden in the composition of the drug , it proves that the higher percentage of the Ornidazole helps in enhancing the antimicrobial activity. Comparatively the case among the uncrosslinked films F11(E) was found to be effective as it contained the higher ratio of Ornidazole. So as per the above studies it can be concluded that F11(F) can be selected for the best film for the treatment against the Periodontitis.

Table 03: Antibacterial activity of polycaprolactone films against *S. mutans*.

Time (days)	F11(A)	F11(B)	F11(C)	F11(D)	F11(E)	F11(F)
1	40	39	48	36	38	36
2	35	37	37	29	32	33
3	26	36	24	28	26	30
4	R	29	20	27	21	28
5	R	24	R	25	20	26
6	R	21	R	19	R	22
7	R	12	R	15	R	16
8	R	10	R	12	R	14
9	R	R	R	11	R	11
10	R	R	R	R	R	R

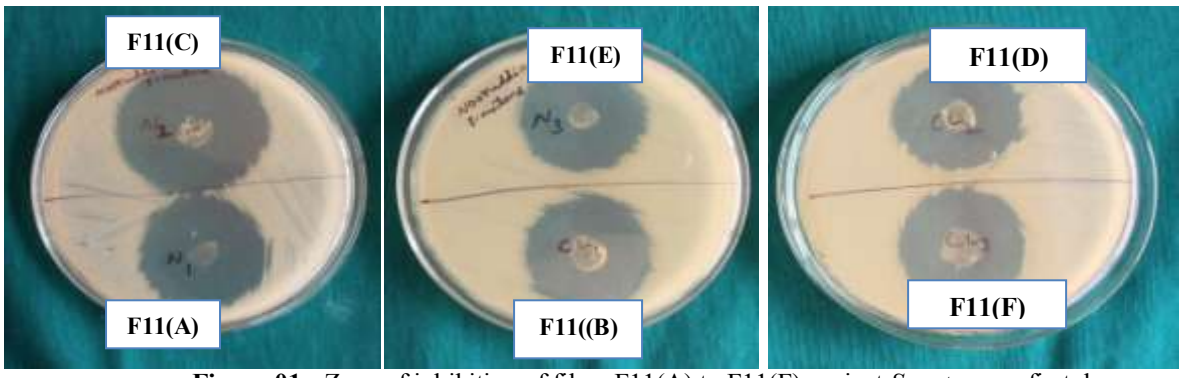

Figure 01: Zone of inhibition of films F11(A) to F11(F) against *S.mutans* on first day.

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