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## Preparation and Evaluation of Dental Implants containing Doxycycline Hydrochloride and Tinidazole in Biodegradable Carrier

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Dental implants of doxycycline hydrochloride and tinidazole were formulated using a biodegradable carrier, Poly ( $\epsilon$ -caprolactone), for the treatment of periodontitis. The *in vitro* drug release patterns and stability of these devices were studied. The formulations showed an initial burst release followed by more sustained release of the drugs throughout the period of study (42 days). The stability of the drugs were shown a marked improvement by formulating them in polymer matrix.

**P**ERIODONTITIS is a localised infection with a primary bacterial etiology in gingival crevices affecting the physiological structural organs supporting teeth. Treatment of periodontitis is aimed at controlling the population of microorganisms. High doses of antibacterial agents for a longer periods of time are required in the treatment, which eventually causes gastrointestinal disorders, development of resistance strains of bacteria and superinfection<sup>1,2</sup>. Dental implants of antiinfective agents in hydroxypropylmethyl cellulose, ethylcellulose and other non-biodegradable polymers have been reported<sup>3,4</sup>. In the present study, an attempt has been made to design dental implants containing doxycycline HCl and tinidazole in a biodegradable carrier, Poly ( $\epsilon$ -caprolactone), to avoid surgical removal of the polymer strip at the end of the therapy, patient non-compliance and other disadvantages.

Poly ( $\epsilon$ -caprolactone) of the mol. wt. 35,000, purchased from Poly Sciences Inc, Washington, PA, USA was used as a matrix polymer which is semicrystalline in nature (m.p. 63°) and, completely soluble in dichloromethane (A.R. grade obtained from E-Merck Ltd., Bombay). Carbopol (974 PNF, also purchased from Poly Sciences Inc, Washington, Pa, USA) is used as a mucoadhesive agent.

Poly ( $\epsilon$ -caprolactone) was dissolved in minimum quantity of dichloromethane. The drug and carbopol was

then dispersed uniformly by using a sonicator. The resultant viscous mass poured into a glass mould of 5 x 3 cm size lined with aluminium foil. The solvent was evaporated at room temperature. The dried film was then cut into pieces of 0.5x0.5 cm. Each film contained 1 mg of the drug. The drug, carbopol and polymer ratio was 1:3:15, respectively. Various physicochemical properties such as size (length and breadth), thickness, content uniformity and weight variation were determined on the prepared implants. The drug content uniformity and weight variation were found to be within the limits of  $\pm 5\%$ .

The drug content of the prepared implants was estimated using the following method. One implant containing either doxycycline HCl or tinidazole (separate formulations) was dissolved in 10 ml of dichloromethane. This was extracted with two successive quantities each of 10 ml of isotonic phosphate buffered saline, pH 7.2 (IPBS) in a separating funnel. The aqueous phases were separated and absorbance was determined at 375 nm for doxycycline HCl and at 316 nm for tinidazole, after suitable dilution using Shimadzu UV/Vis spectrophotometer. The extract of implant without drug/s was served as a blank.

*In vitro* drug release was performed by taking five implants with the drug/s (separate formulations) in a vial containing 5 ml of IPBS. One ml of the IPBS was withdrawn from 1st to 7th day, every day and thereafter weekly upto

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Table-1 : Stability data for Doxycycline Hydrochloride, Tinidazole and their Implants

Sample	Rate Constant values after three months ( $K \times 10^{-4} \text{ days}^{-1}$ )			
	Room Temperature	37°	82% RH+RT	Direct exposure to sun light for 1 month
Tinidazole Pure	3.838	5.118	14.074	102.355
Tinidazole Polycaprolactone implants	3.159	4.985	13.998	98.245
Doxycycline HCL Pure	2.245	3.959	5.117	114.180
Doxycycline HCl Polycaprolactone implants	1.679	3.385	4.536	107.213

6 weeks and immediately replaced with one ml of fresh IPBS. The drug content was estimated by measuring the absorbance after suitable dilution at 375 nm for doxycycline HCl and at 316 nm for tinidazole.

*In vitro* release studies were performed using IPBS showed an initial burst effect, which is expected to kill most of the periodontal microorganisms, followed by sustained release of the drugs for about 40 days, sufficient to inhibit the further growth of the microorganisms. From the doxycycline implants, 50% of the drug was released at the end of 7 days and 80% of the drug being released at 42 days. Whereas, tinidazole implants showed  $t_{50\%}$  equal to 6 days and  $t_{90\%}$  at 39 days (Fig. 1). Therefore, it is evident from these studies that consistent drug release pattern can be maintained for longer periods of time as required for the treatment of periodontitis.

Stability studies were conducted for the plain drugs and implants at room temperature, 82% RH, 37° and exposure to direct sunlight for 3 months. The drug content reduced markedly after exposing to sunlight. The rate of degradation is higher at 37° and 82% RH when compared to R.T (Table 1). The stability of the drugs were improved by formulating them in the polymer matrix, as indicated by their 'K' values. Thus it is possible to design suitable biodegradable dental implants of doxycycline and tinidazole capable of releasing the drugs in a predictable manner for longer periods of time as indicated in the effective treatment of periodontitis.

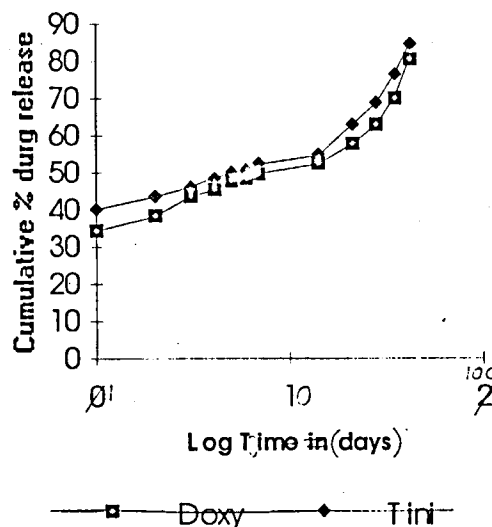


Fig. 1: Drug release from implants  
Cumulative % release of drugs from implants containing either doxycycline (□-□) or tinidazole (◆-◆)

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