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## Formulation and Evaluation of Topical Drug Delivery Systems containing Ciprofloxacin and Tinidazole

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Different topical formulations containing ciprofloxacin and tinidazole in lanolin petrolatum base, emulsion (water washable) base and PEG (water soluble) base were prepared and evaluated for drug release in phosphate buffer (pH 6.0). Antimicrobial activity of these formulations were compared against marketed formulation containing 1% w/w silver sulfadiazine USP. It was found that release of ciprofloxacin and tinidazole from the PEG base was maximum through sigma membrane in phosphate buffer (pH 6.0) and also observed that the release of tinidazole was more than that of ciprofloxacin. The formulations exhibited significant antimicrobial activity both against aerobic and anaerobic bacteria compared to the marketed formulation. The antimicrobial activity of formulation containing PEG was found to be higher than other formulations.

Infection is a life threatening complication of burn injury. the morbidity and mortality arising out of a major burn injury is a result of bacterial infection of wounds. Infection of burn injury is responsible for 50% to 75% of the hospital deaths. Burn patients are prone for infection more readily than other patient groups<sup>1</sup>. Extensive burn injuries are particularly susceptible to infections as a result of the disruption of the normal skin barrier and accompanying depression of immune response. The moist thermally coagulated burn wound with its constantly replenished supply of diffusing serum nutrients and it's warm surface temperature provides an environment suitable for rapid microbial growth. As the local microbial growth increases, the potential for invasion of adjacent viable tissue and penetration into the circulation also increases<sup>1-3</sup>. During the past decades anaerobic bacteria have been established as causative organisms of infections in around 15% of the burn infected patients. Imidazole derivatives such as Metronidazole and tinidazole are the drugs of choice even today to control the anaerobic infections of burns to various degrees. Thus it is a practice

to administer either of these drugs orally or intravenously depending on the severity, to patients, with burn wounds that have been infected with anaerobic bacteria<sup>4-5</sup>.

Antibacterials such as ciprofloxacin and norfloxacin are administered for the treatment of many infections in the form of tablets, capsules and injections. So far, the preparations of above antibacterials for topical use are not common. ciprofloxacin remains the most potent fluoroquinolone antibacterial against Enterobacteriaceae and *Pseudomonas* and is more potent than norfloxacin, ofloxacin and amifloxacin against *Mycobacterium tuberculosis* and more potent than ofloxacin against intracellular mycobacterium. Ciprofloxacin is unique among the fluoroquinolones in being bactericidal for stationary phase bacteria<sup>6,7</sup>.

In the present study, a topical drug delivery system containing ciprofloxacin and tinidazole were formulated and evaluated with the view to develop localized drug delivery system for the treatment of burn wounds.

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## MATERIALS AND METHODS

Ciprofloxacin hydrochloride was procured from Cipla Ltd, Bangalore and tinidazole from Cheminor Drugs Ltd, Hyderabad. Silver sulfadiazine Cream USP was obtained from Universal Impex, Mumbai. Polyethylene glycol 4000 and polyethylene glycol 40 were purchased from SD Fine Chemicals Ltd., Boisar. All other materials used in the formulations are of laboratory grade.

### Preparation of Formulations

Three semisolid topical formulations were prepared by standard pharmacopoeial methods. Formulation I contained water soluble base formulation II contained water washable hydrophilic base and formulation III contained lanolin petrolatum base. One per cent (w/w) ciprofloxacin hydrochloride and 1%w/w tinidazole were incorporated in the above formulations by levigation method.

Water soluble base contained 50% w/w each of polyethylene glycol(PEG) 4000 and PEG 400. Water washable hydrophilic base is made up of white petrolatum-25%w/w, stearyl alcohol-25% w/w, propylene glycol-12%w/w, sodium lauryl sulfate-1% w/w, methyl paraben-0.025%w/w, and propyl paraben-0.015%w/w. Lanolin petrolatum base consisted of white petrolatum -50%w/w, wool fat-30%w/w, hard paraffin-4% w/w, and liquid paraffin-16%w/w.

### Evaluation of Drug Release

*In vitro* release of ciprofloxacin and tinidazole from different formulations were carried out employing a glass cylinder with both ends open, 10 cm height, 3.7 cm outer diameter and 3.1 cm inner diameter, used as a permeation cell. A Sigma dialysis membrane(soaked in distilled water for 2 hours before use) was fixed to one end of the cylinder with the aid of a rubber band to result in a permeation cell. Two grams of formulations was taken in the cell (donor compartment) and the cell was immersed in a beaker (150ml) containing 100 ml of phosphate buffer (pH 6) as receptor compartment. The cell was immersed to a depth of 1 cm below the surface of the receptor solvent. The medium in the receptor compartment was agitated continuously using a magnetic stirrer and a temperature of  $37\pm 1^\circ$  was maintained. Samples (10 ml) of the receptor compartment were taken at various intervals of time over a period of 8 h and each time fresh

Table I - antimicrobial activity of different formulations

Formulations	Zone of inhibition in mm $\pm$ S.D	
	<i>Ps. aeruginosa</i>	<i>P. gingivalis</i>
Market Formulation	11.50 $\pm$ 1.50	0.00 $\pm$ 0.00
Formulation I	32.00 $\pm$ 2.65	36.00 $\pm$ 5.29
Formulation II	20.00 $\pm$ 3.46	32.00 $\pm$ 4.36
Formulation III	15.50 $\pm$ 2.18	20.00 $\pm$ 6.06
Results are mean of three trials		

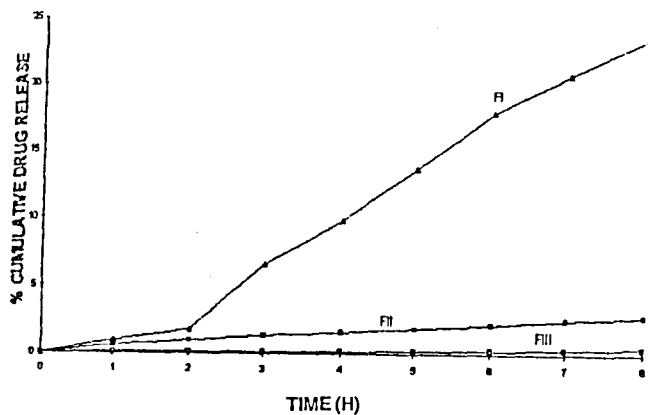
buffer is replaced. The samples withdrawn were estimated spectrophotometrically. Amount of ciprofloxacin and tinidazole release at various interval of time was calculated and plotted against time<sup>8,9</sup>. (Figure-1,2).

### Evaluation of Antimicrobial Activity

Antimicrobial activity of the formulations was evaluated according to the classical Kirby-Bauer disc diffusion method. For antiaerobic studies the organism used was *Pseudomonas aeruginosa* and the medium used was Muller-Hinton agar medium. For anti anaerobic studies the organism used was *Porphyromonas gingivalis* and the medium used was Wilkins-Chalgren agar. The diameter of the zones of inhibition was measured and compared with that obtained with a marketed formulation (MF, 1% w/w silver sulfadiazine) (Table-1).

## RESULTS AND DISCUSSION

In the *in vitro* release studies, the release profile of ciprofloxacin and tinidazole through a dialysis membrane was studied in phosphate buffer (pH 6.0). These studies were primarily aimed at obtaining release pattern of the formulations. The release of ciprofloxacin and tinidazole from different formulations are shown in figure-1 and 2. The release was higher from formulation I than formulation II which is greater than that from formulation III [FI>FII>FIII]. The reason for this can be explained as follows : PEG water soluble base (Formulation I) is anhydrous and non occlusive and may hinder percutaneous absorption due to dehydration of the stratum corneum. However, in case of *in vitro* release, the membrane was fully hydrated at all the time due to receptor medium. The base in the donor compartment partially solubilised there by increas-



F I Water soluble base F II Water washable hydrophilic base F III Lanolin petrolatum base

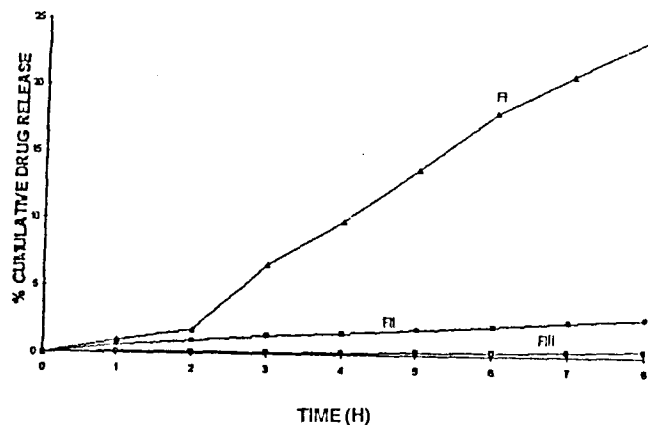
Fig. 1 : *In vitro* release profiles of ciprofloxacin from different topical formulations

ing the amount of drug available for penetration<sup>11</sup>.

Lower release of drugs was observed with formulation II and formulation III. This may be attributed to the biphasic nature of the base. The drugs get partitioned into the two phases and migration of drugs becomes slower<sup>8,11</sup>. In all *in vitro* studies across the dialysis membrane, the release of tinidazole was comparatively higher than ciprofloxacin. This could be attributed to the solubility of tinidazole in phosphate buffer (pH 6.0) which is higher compared to that of ciprofloxacin<sup>6</sup>.

Microbiological studies were carried out to assess the antibacterial potential of different formulations with that of the marketed formulation. Formulation I exhibited highest antimicrobial effect against both aerobic (*Ps. aeruginosa*) and (*P. gingivitis*) bacteria as compared to that of other formulations, this may be attributed to the hydrophilic (water washable) nature of the base. Marketed formulation did not show any antibacterial activity against anaerobic bacteria under the present study conditions (Table-1)<sup>8,11</sup>.

Thus, based on the results obtained from both release and antimicrobial studies, it is possible to conclude



F I Water soluble base F II Water washable hydrophilic base F III Lanolin petrolatum base

Fig. 2 : *In vitro* release profiles of tinidazole from different topical formulations

that the formulations prepared in this investigation can be considered as suitable localised drug delivery systems for the treatment of infected burn wounds.

## REFERENCES

1. Ramakrishnan, K.M., Rao, D.K., Doss C.R. Mathicanan, T., Manokaran, G and Thyagarajan, S.P. *Burns*, 1985, 11, 404.
2. Wang, W.D, Li, N., Guang, X and Pin, Z.Y., *Burns*, 1985, 11, 192.
3. Muller, M., *Surgery*, 1983, 93, 165.
4. Rice, T.T., *Rehabil. Nurs.*, 1992, 17, 244.
5. Ramakrishnan, K.M, Jayaraman., V., Ramachandran, K. and Madhivanan, T., *Burns*, 1986, 12, 270.
6. Webster, J.R. and Leslie, T. In; *Goodman and Gilman's The Pharmacological basis of Therapeutics*, 8th Ed. Vol.2 Pergamon press, USA, 1990, 999.
7. Prabhavathi B, Fernandes and Daniel, T.W.C., *Annual Reports in Med. Chem.*, Academic Press Inc, Jovanovich, 1987, 22, 119.
8. Chowdhary, K.P.R. and Kumar. P.A., *Indian J. Pharm. Sci.*, 1996, 58, 47.
9. Reddy, S.G.K., Bhatia, M.S. and Trivedi, P., *Indian Drugs*, 1997, 34, 190.
11. Lawrence, H.B. In: *Remington's Pharmaceutical Sciences*, Gennaro, A.R. Ed 18th Ed, Mack Publishing Company, Pennsylvania. 1990, 1602.