

# Effect of enhancers on permeation kinetics of captopril for transdermal system

B G Desai, A R Annamalai<sup>1</sup>, B Divya, B M Dinesh

K.L.E. Society's College of Pharmacy, II block, Rajajinagar, Bangalore - 560 010,  
Department of Pharmacology, Annamalai University, Chidambaram, Tamilnadu, India

**T**ransdermal drug delivery system has seen a veritable explosion in the past decades. In the present scenario, very few transdermal patches are commercially available. The captopril being an antihypertensive drug requires chronic administration. Since the drug has an extensive first-pass metabolism, an attempt was made to develop transdermal drug delivery system for better patient compliance. In this study, flux and permeation enhancement trials of captopril were carried out using modified Franz diffusion cells through siloxane membrane for 8 h. Citral and dimethyl formamide as permeation enhancers showed the best permeability as compared to sodium tauroglycholate, sodium lauryl sulfate, etc. One longstanding approach for improving transdermal drug delivery uses penetration enhancers (also called sorption promoters or accelerants), which penetrate into skin to reversibly decrease the barrier resistance.

**Key words:** *Captopril, transdermal permeation studies*

## INTRODUCTION

The principle of transdermal drug delivery systems is to deliver drug across epidermis to achieve systemic effect over a prolonged period of time. Because of these attributes, transdermal drug delivery systems offer many advantages such as reduced side effects, improved patient compliance, elimination of first-pass metabolism, and sustained drug delivery.<sup>[1]</sup>

Captopril is classified as an antihypertensive. It has mean plasma half-life of 2 to 3 h, and only 40% of the orally administered drug reaches the circulation due to hepatic metabolism. The present research was directed to examine the release rate of captopril and see the enhancer effect on the flux and enhancement ratio. This study was aimed at developing a suitable film formulation containing captopril for transdermal use; the embedded drug should be released without any preferential binding to the polymer.<sup>[2,3]</sup>

There has been a giant leap by the pharmaceutical industry with respect to innovations in the new drug delivery arena in the past two decades. These innovations and changes in strategy present newer challenges and brighter opportunities for the application of new methodologies in the drug delivery process. Drug delivery through intact

skin is of utmost importance for controlled release of drugs for their extended and safe use, which is yet to be successfully accomplished for a large number of drugs. Formulations on skin can be classified into two categories according to the target site of action of the containing drugs. One has systemic action after drug uptake from the cutaneous microvascular network, and the other exhibits local effects in the skin. The current study focuses the drug release kinetics from the rate-limiting membrane by varying the type of solvent used, polymeric films, and drug loading in transdermal delivery systems.

## MATERIALS AND METHODS

Captopril was a gift sample from Micro Labs, Bangalore; dimethyl sulfoxide, sodium lauryl sulfate, dimethyl fluoride, citric acid sodium taurocholate, eugenol were obtained from S.D. Fine Chemicals, Mumbai. All the solvents and other reagents were of analytical or pharmacopoeial grade.

### Solubility measurement

The solubility of captopril was determined at several values of pH, viz., 6.2, 7.0, 7.4, and 8.0; excess of captopril was added to 5 mL of phosphate buffer solutions to form saturated solution. This solution was left for 24 h at 37°C. The suspensions were filtered using a 0.45 μ#. The concentration of captopril was determined spectrophotometrically by measuring at 205 nm.<sup>[4-6]</sup>

### Partition coefficient of drug in octanol/water

The partition coefficient of the drug was determined by

#### Address for correspondence:

Dr. B.M. Dinesh, K.L.E. Society's College of Pharmacy, II block,  
Rajajinagar, Bangalore- 560 010, India.  
E-mail: bmdine@yahoo.com

taking equal volumes of 1-octanol and aqueous solution in a separating funnel. Ten milligrams of drug was dissolved in 10 mL buffer solutions of pH 6.2, 7, 7.4, and 8.0 separately, to which 10 mL of octanol was added and kept in a separating funnel for 24 h. The aqueous layer was collected, and concentration of captopril was measured spectrophotometrically at 205 nm using buffer of the respective pH as blank.<sup>[7]</sup>

### Permeability study

The siloxane membrane was washed under running water for 3 to 4 h in order to remove glycerol, which is induced as a humectant. Removal of sulfur compounds can be accomplished by treating the siloxane membrane with a 0.3% w/v solution of sodium sulfide at 80°C for 1 min and washing with hot water (60°C) for 2 min, followed by acidification with a 0.2% v/v solution of sulfuric acid and then rinsing with hot water to remove the acid. This siloxane membrane will retain most proteins of molecular weight 12,000 or greater.

The drug solution was prepared as per the dose. Fifteen milligrams of drug per 2 mL of buffer (7.4 pH) was taken in the donor compartment. The siloxane membrane was mounted in the space between the donor and the receptor compartments. The receptor cell contained phosphate buffer of pH 7.4 as the medium. The samples were withdrawn every hour. The medium was magnetically stirred for uniform drug distribution and was maintained at a temperature of 37°C ± 1°C. The amount of drug diffused was estimated spectrophotometrically at 205 nm. The release details are given under 'RESULTS.'

The enhancers considered for the study were sodium lauryl sulfate (SLS), dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), hyaluronidase and sodium tauroglycolate (STG), citral, citric acid, and eugenol. The donor compartment contained a suspension of the drug and 1% w/w concentration of different enhancers. Siloxane membrane was used as the barrier. All other experimental conditions and analytical techniques followed were similar to those reported in permeability study section.<sup>[8-17]</sup>

## RESULTS AND DISCUSSION

### Effect of pH on solubility

The values of solubility of captopril at different values of pH of phosphate buffer solution were determined, and they were found to be 8.764, 17.580, 24.219, and 30.198 mg/mL in 6.2-, 7-, 7.4-, and 8.0-pH buffers respectively. As the pH of the buffer increased, the solubility of captopril was also found to increase.

### Effect of pH on partition coefficient

The partition coefficient of captopril was determined in phosphate buffers of pH 6.2, 7.0, 7.4, and 8.0, and the partition coefficients were found to be 1.0452, 1.418, 3.859, and 1.414 respectively.

### Permeation studies

The permeation studies were carried out using a passive diffusion cell, and the membrane used was siloxane membrane [Figure 1]. The permeability coefficient and flux of captopril were found to be 4.35 cm/h and 65.31 µg/cm<sup>2</sup>/h respectively.

The enhancement ratio of the drug with different enhancers was studied using passive diffusion cell through dialysis membrane. The permeability coefficient, flux, and enhancement ratio of captopril [Figure 2] [Table 1] with dimethyl sulfoxide (1% DMSO) were found to be 13.80 cm/h, 207.14 µg/cm<sup>2</sup>/h, and 3.172% respectively. The permeability coefficient, flux, and enhancement ratio of captopril with sodium lauryl sulfate (1% SLS) were found to be 5.09 cm/h, 76.43 µg/cm<sup>2</sup>/h, and 1.170% respectively. The permeability coefficient, flux, and enhancement ratio of captopril with dimethyl fluoride (1% DMF) were found to be 5.377 cm/h, 80.66 µg/cm<sup>2</sup>/h, and 1.236% respectively. The permeability coefficient, flux, and enhancement ratio of captopril with sodium tauroglycolate (1% STG) were found to be 7.06 cm/h,

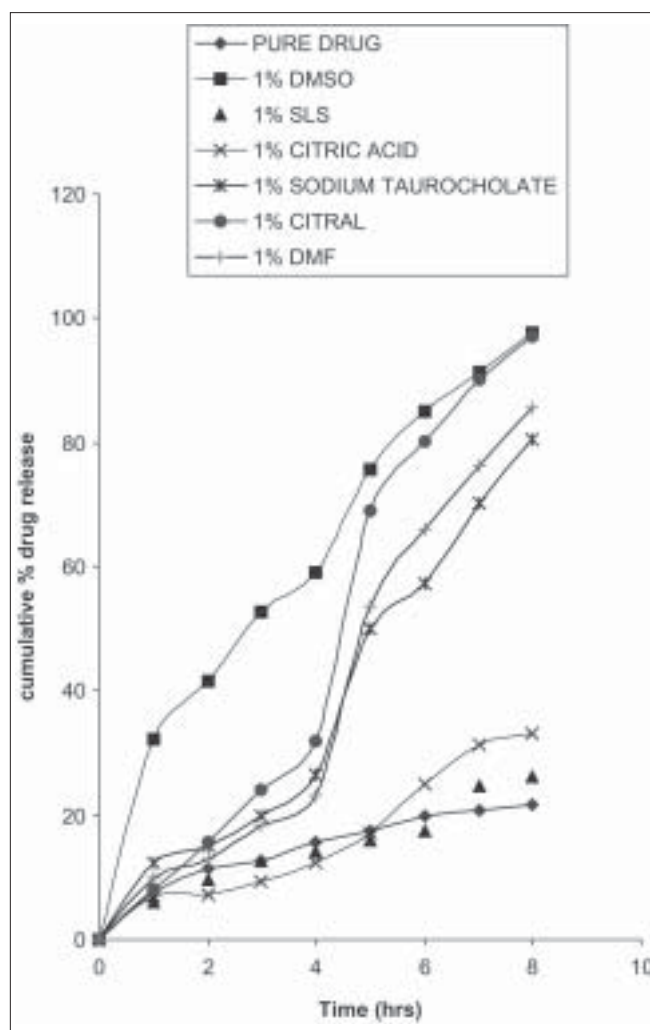
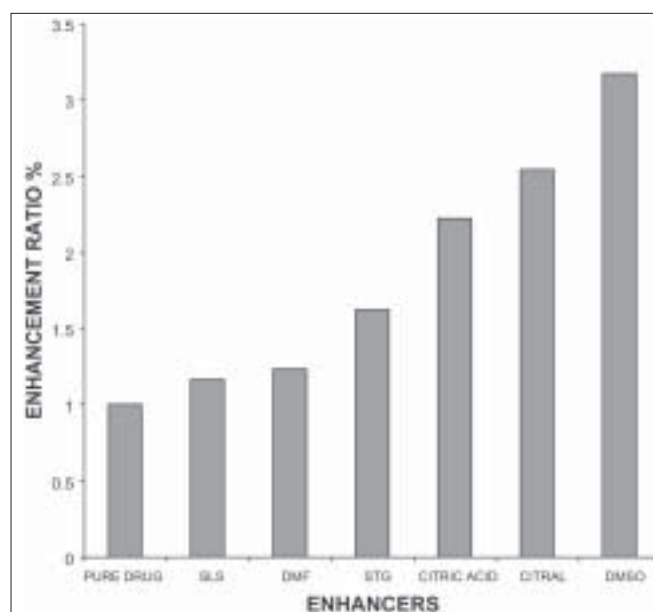


Figure 1: Study of pre-formulation screening of captopril with different enhancers (n = 3)

**Table 1: Data for permeability coefficient, flux, and enhancement ratio of drug alone and of drug with different enhancers (n = 3)**

Enhancer 1%	Permeability coefficient (cm/hr)	Flux (J) $\mu\text{g}/\text{cm}^2/\text{hr}$	Enhancement ratio (%)
Pure drug	4.35	65.31	1
SLS	5.09	76.43	1.170
DMF	5.377	80.666	1.236
STG	7.06	105.9	1.622
Citric acid	9.67	145.15	2.222
Citral	11.07	166.05	2.544
DMSO	13.80	207.14	3.172



**Figure 2:** Bar graph wing enhancement ratio of captopril with different enhancers (n = 3). Equations for calculating permeability coefficient (P), flux (J), enhancement ratio: Permeability coefficient (P) is the velocity of drug passage through the membrane in  $\mu\text{g}/\text{cm}^2/\text{h}$ . The permeability coefficient was calculated from the slope of the graph of percentage of drug transported versus time as

$$P = \text{Slope} \times Vd/S \quad (1)$$

where Vd = volume of donor solution; S = surface area of tissue

Flux (J): Flux is defined as the amount of material flowing through a unit cross-sectional barrier in unit time. It is calculated by

$$\text{Flux (J)} = P \times CD \quad (2)$$

where CD = concentration of donor solution; P = Permeability

Enhancement ratio: Enhancement ratio was used to evaluate the effect of permeation enhancer on diffusion and permeation of selected drug molecules. It is calculated by

$$\text{Enhancement ratio (\%)} = \frac{\text{Permeability coefficient of drug with enhancer}}{\text{Permeability coefficient of drug alone}} \quad (3)$$

105.9  $\mu\text{g}/\text{cm}^2/\text{h}$ , and 1.622% respectively. The permeability coefficient, flux, and enhancement ratio of captopril with citric acid (1%) were found to be 9.67 cm/h, 145.15  $\mu\text{g}/\text{cm}^2/\text{h}$ , and 2.222% respectively. The permeability coefficient, flux, and enhancement ratio of captopril with citral (1%) were found to be 11.07 cm/h, 166.05  $\mu\text{g}/\text{cm}^2/\text{h}$ , and 2.544% respectively.

## REFERENCES

- Hadgraft J, Lane ME. Skin permeation: The years of enlightenment. *Int J Pharm* 2005;305:2-12.
- Bruton LL, Laza JS, Parker KL. Goodman Gilman's: The pharmacological basis of therapeutics. New York: McGraw Hill Medical Publishing Division; 2006. p. 801-10.
- Martindale: The complete drug reference. The enhancement effect of surfactants on the penetration of lorazepam through rat skin. 33<sup>rd</sup> ed. London: Pharmaceutical Press; 2007. p. 853-4.
- Nokhodchi A, Shokri J, Dashbolaghi A, Hassan-Zadeh D, Ghafourian T, Barzegar-Jalali M. The enhancement effect of surfactants on the penetration of lorazepam through rat skin. *Int J Pharm* 2003;250:359-69.
- Sutariya V, Mashru R, Sankalia MS. Transbuccal delivery of lomotrigine across porcine buccal mucosa *in vitro* determination of routes of buccal transport. *J Pharm Sci.*, 2005;8:54-62.
- Mashru R, Sutariya V, Sankalia M, Sankalia J. Transbuccal delivery of lamotrigine across porcine buccal mucosa: *In vitro* determination of routes of buccal transport. *J Pharm Pharma Sci* 2005;8:54-62.
- Shah JC, Ross JS. Reduction in skin permeation of n,n-diethyl-m-toluamide by altering the skin/vehicle partition co-efficient. *J Control Release* 2000;67:211-21.
- Pugh WJ, Hadgraft J. Prediction of human skin permeability coefficients. *Int J Pharm* 1994;103:163-78.
- Hadgraft J, Lane ME. Skin permeation: The years of enlightenment. *Int J Pharm* 2005;305:2-12.
- Nanayakkara GR, Bartlett A, Forbes B, Marriott C, Whitfield PJ, Brown MB. The effect of unsaturated fatty acids in benzyl alcohol on the percutaneous permeation of three model penetrants. *Int J Pharm* 2005;301:129-39.
- Ghafourian T, Zandasrar P, Hamishekar H, Nokhodchi A. The effect of penetration enhancers on drug delivery through skin: A QSAR study. *J Control Release* 2004;99:113-25.
- Hadgraft J. Skin deep. *Eur J Pharm Biol* 2004;58:291-9.
- Kanikkannan N, Singh M. Skin permeation enhancement effect and skin irritation of saturated fatty alcohols. *Int J Pharm* 2002;248:219-28.
- Akimoto T, Kawahara K, Nagase Y, Aoyagi T. Polymeric transdermal drug penetration enhancer: The enhancing effect of oligodimethylsiloxane containing a glucopyranosyl end group. *J Control Release* 2001;77:49-57.
- Copoví O, Díez-Sales JV, Herráez-Domínguez, Herráez-Domínguez M. Enhancing effect of alpha-hydroxyacids on "*in vitro*" permeation across the human skin of compounds with different lipophilicity. *Int J Pharm* 2006;314:31-6.
- Nokhodchi A, Shokri J, Dashbolaghi A, Hassan-Zadeh D, Ghafourian T, Barzegar-Jalali M. The enhancement effect of surfactants on the penetration of lorazepam through rat skin. *Int J Pharm* 2003;250:359-69.
- Hadgraft J. Passive enhancement strategies in topical and transdermal drug delivery. *Int J Pharm* 1999;184:1-6.

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