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EFFECT OF PENETRATION ENHANCERS ON TRANSDERMAL DELIVERY OF TIMOLOL MALEATE

Swarnlata Soni, Sanjay K. Jain and N.K. Jain

Department of Pharmaceutical Sciences,
Dr. H. S. Gour Vishwavidyalaya,
SAGAR (M.P.) 470 003 **INDIA**

ABSTRACT

In vitro skin permeation of Timolol maleate through human cadaver skin was studied using Franz diffusion cell. The results indicate that the drug penetrates poorly through human cadaver skin. However, skin penetration enhancers such as dimethyl sulfoxide (DMSO), oleic acid (OA) and lauryl chloride (LC) enhanced the permeability of Timolol maleate (TM) through human cadaver skin. The permeation enhancement of drug was maximum by lauryl chloride amongst the three enhancers. Moreover, lauryl chloride increases the permeation of drug through skin with increase in the time of application and concentration on skin. The change in lag time was also observed.

INTRODUCTION

Dermal therapy is generaly restricted to a limited number of drugs according to the main function of skin as a protective barrier towards entering compounds[1]. There is considerable interest in the percutaneous administration of drugs which are metabolised by first pass effect[2]. But, the stratum corneum presents a substantial barrier to skin permeation of hydrophilic

molecules. Since, many drugs are weak bases, it is common that they exist in a cationic form at physiological pH. Consequently, the percutaneous absorption of such drugs would be expected to be low. Therefore, these drugs require penetration facilitators to enhance their permeability across the skin[3,4].

Timolol maleate is the β-adrenoceptor blocking drug used as an antihypertensive[5]. It is extensively metabolised in the liver[6]. Delivery of this drug via transdermal route could be preferable, however, being a drug of hydrophilic nature, TM is not likely to permeate at a desired rate through skin[5].

In present study, the effect of three penetration enhancers, dimethyl sulfoxide (DMSO), oleic acid and lauryl chloride was studied on permeability of TM through human cadaver skin.

EXPERIMENTAL

A. Materials

Timolol maleate (Fairdeal Corporation Ltd., Bombay, India), Oleic acid, Dibutyl phthalate (Robert Johnson, India), DMSO, Disodium hydrogen phosphate, Potassium dihydrogen phosphate, Sodium chloride, Polyvinyl pyrrolidone [E. Merk (India) Ltd., Bombay, India], Ethyl cellulose (Central Drug House Pvt. Ltd., India), Lauryl chloride (Riedual Dehnacnay Seelze Hannover, West Germany).

B. Skin Preparation

Full thickness abdominal cadaver skin was washed with distilled water after removal of all subcutaneous fats. Skin was cut into about 15 cm^2 pieces for use in experiment. The skin pieces were soaked in saline phosphate buffer pH 7.4 and stored at -30°C until used. Just before the experiment, the skin pieces were taken out of the freezer and allowed to thaw at room temperature. Once they thawout, they were checked for any macroscopic damage using magnifying glasses. The penetration enhancers i.e.

DMSO, oleic acid and lauryl chloride, each 10% v/v were applied on stratum corneum of human cadaver skin for different time periods i.e. 15, 30, 45 and 60 min.

C. Drug Solution

A solution of 10 mg/ml TM in saline phosphate buffer pH 7.4 was used in donor compartment of Franz diffusion cell for in vitro skin permeability studies.

D. In vitro Skin Permeation Enhancement

The in vitro skin permeation studies were performed by using Franz diffusion cell (Crown Glass Company, New Jersey, U.S.A.) and prepared human cadaver skin was mounted between donor and receptor compartment of Franz diffusion cell. The skin was positioned in such a way that the stratum corneum side of the skin faced donor compartment and dermis side was continuously bathed with the content of the receptor compartment in the diffusion cell. The receptor compartment contained saline phosphate buffer of pH 7.4 [7]. The temperature of the receptor compartment was maintained at 37±1°C with use of a circulatory bath. The donor compartment was exposed to the ambient temperature (25±2°C). Samples (1.0 ml) were withdrawn periodically for 24 hrs and replaced with the same volume of saline phosphate buffer pH 7.4. These samples were analysed for drug content (Table 1 and 2).

E. Analytical Method[7]

Timolol maleate was estimated in the samples using the spectrophotometric method reported in British Pharmacopoeia 1988 by measuring the absorbance at 295 nm.

RESULTS AND DISCUSSION

The effect of penetration enhancers (DMSO, oleic acid and lauryl chloride) on transdermal permeation of timolol maleate was studied in human cadaver skin. Timolol maleate is a polar

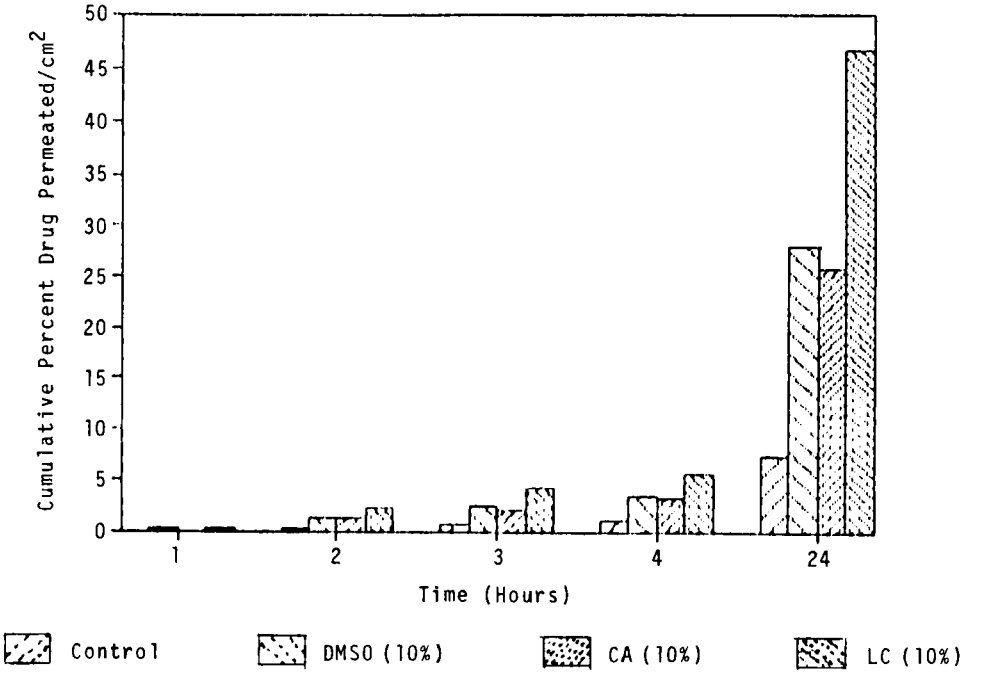

Figure 1

Effect of penetration enhancers on permeability of Timolol maleate through human cadaver skin.

hydrophilic molecule[6]. The permeation of TM was remarkably enhanced by the application of penetration enhancers (DMSO, OA or LC) as shown in Fig. 1 and Table 1. The total amount of TM permeated through skin in 24 hrs after the application of DMSO, OA and LC (10% v/v each) was noted to be 27.87±3.12, 25.87±2.37 and 46.79±1.75 per cent/cm^2 respectively. It is clear from the data presented in Table 1 that overwhelming enhancement on human cadaver skin was observed with LC (10% v/v) among the penetration enhancers used. It is observed that on increasing the concentration of lauryl chloride from 6 to 10% v/v, the total TM permeation increased from 12.25±2.10 to 46.79±1.75 per cent/cm^2 and below 6% v/v LC showed negligible effect on skin permeation enhancement (Fig. 2).

TABLE I.

Cumulative percent Timolol maleate permeated/cm^2 through human cadaver skin after application of various enhancers on skin for 30 min.

Time (hr)	Control	DMSO (10% v/v)	Oleic acid (10% v/v)	Lauryl chloride (% v/v)					
				4	6	7	8	9	10
1	0.00	0.37±0.82	0.00	0.00	0.00	0.08±0.25	0.09±0.62	0.10±0.32	0.33±0.25
2	0.35±1.12	1.34±1.00	1.20±1.00	0.37±1.00	0.37±1.00	0.62±0.40	0.69±0.28	0.85±0.90	2.24±0.80
3	0.67±0.88	2.51±1.22	2.16±1.00	0.67±0.90	0.80±0.40	1.21±0.60	1.61±0.30	1.82±0.75	4.21±1.20
4	1.06±0.75	3.36±2.17	3.17±2.21	1.07±0.85	1.60±0.50	1.77±0.55	2.37±0.33	2.62±1.00	5.60±2.00
24	7.29±2.37	27.87±3.12	25.87±2.37	7.89±2.00	12.25±2.10	19.90±2.21	27.50±1.12	35.67±2.22	46.79±1.75

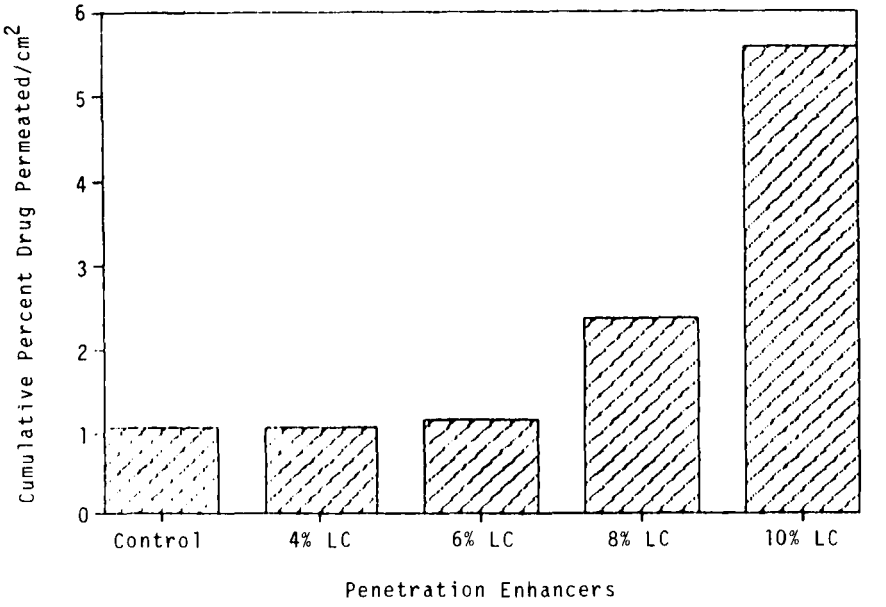

Figure 2

Effect of concentration of Lauryl chloride on permeability of Timolol maleate through human cadaver skin.

TABLE 2

Cumulative percent Timolol maleate permeated/cm^2 through human cadaver skin after application of 10% v/v LC on skin for different time

Time (min)	Control	Time of application of lauryl chloride			
		15 min	30 min	45 min	60 min
10	0.00	0.00	0.00	0.00	0.00
20	0.00	0.00	0.00	0.00	0.00
30	0.00	0.00	0.00	0.00	1.06±0.50
40	0.00	0.00	0.00	0.28±0.22	1.97±0.55
50	0.00	0.00	0.00	0.60±0.50	2.54±0.55
60	0.00	0.00	0.33±0.42	0.93±0.55	3.14±0.65
120	0.35±1.12	0.93±0.50	2.24±0.40	2.75±0.65	5.43±0.72
180	0.67±0.88	1.75±0.75	4.21±0.25	4.55±0.70	7.02±0.60
240	1.06±0.75	2.43±0.57	5.60±0.65	6.35±0.65	8.53±0.30

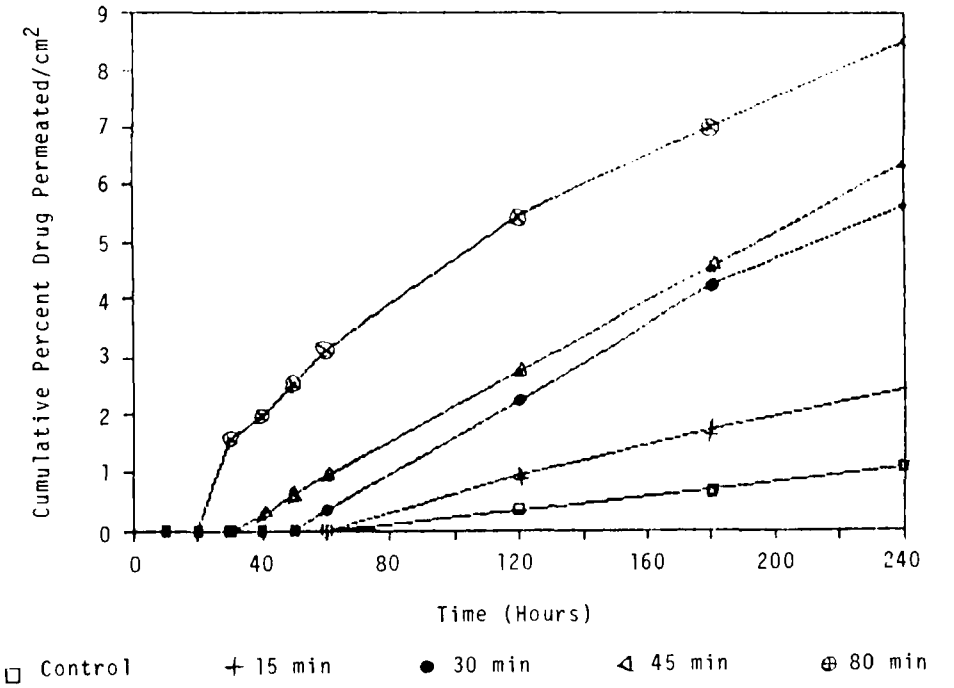

Figure 3

Effect of 10% Lauryl chloride on permeability of Timolol maleate with time of application on human cadaver skin.

The application time of enhancer was optimised by applying 10% (v/v) LC for various time periods i.e. 15, 30, 45 and 60 mins. It is noted that on increasing the time of application of LC on skin, the permeation of TM through skin was increased whereas the lag time was decreased (Table 2 and Fig. 3).

The mechanism of enhancement effect of penetration enhancers is established for DMSO and oleic acid, but the mechanism of lauryl chloride as enhancer is not established yet. The permeation enhancement effect by DMSO is due to changing reversible configuration of protein structure of stratum corneum or by increasing thermodynamic activity of drug[8]. DMSO enhances the permeation of drug through skin by swelling of stratum corneum to induce formation of channels which lowers diffusional

resistance[9]. The enhancement effect of OA is due to increasing lipophilicity of stratum corneum and transepidermal water loss[10].

Lauryl chloride is a C_{12} alkyl halide C_{12} compounds have generally proved to be the most active in biological systems when a series of surfactant with similar hydrophilic portions are studied[11]. C_{12} compounds interact at a lower concentration than those with a C_{18} Chain[12]. But, the mechanism of lauryl chloride as penetration enhancer is yet to be established.

It is therefore concluded that by optimising the time and concentration of enhancer, the skin permeability rate of TM can be improved. This study clearly establishes the utility of lauryl chloride as penetration enhancer. It may afford a promising means for transdermal enhancement of water soluble drugs. In order to elucidate the mode of action of LC further study should be performed similar to the action of C_{12} surfactant.

Lauryl chloride holds a promise as skin penetration enhancer.

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