ELSEVIER

International Journal of Pharmaceutics 130 (1996) 169–177

international journal of pharmaceutics

Transdermal controlled administration of verapamil — enhancement of skin permeability

Girish K. Jain[a], A.K. Sharma[b], S.S. Agrawal[a,*]

[a]*College of Pharmacy, Pushp Vihar Sec-III, New Delhi-110017, India*
[b]*College of Pharmacy, SGSITS, 23 Park Road, Indoree, India*

Received 29 October 1993; revised 27 January 1995; accepted 1 June 1995

Abstract

Rapid permeation of verapamil hydrochloride (VHCl) across the skin using finite dose loading is documented. Transdermal drug delivery (TDD) systems of VHCl using hydrophilic polymers — polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP) and different concentrations of an enhancer, d-limonene were developed. In-vitro permeation profiles across the guinea-pig dorsal and human cadaver skins using a Keshary-Chien diffusion cell are reported. The permeation rate was enhanced and followed approximately zero order kinetics.

Keywords: Verapamil hydrochloride; d-Limonene; Guinea pig dorsal skin; Penetration enhancer; Transdermal delivery; Skin irritation

1. Introduction

Polymer matrices make good reservoirs for sustained release medications. Polyvinyl alcohol and polyvinyl pyrrolidone (of different grades) (Bhalla and Toddywalla, 1988; Viegas et al., 1988), silicone polymers (Viegas et al., 1988), eudragits (Bodde et al., 1989), polyvinyl acetate, polyethylene, ethylene-vinyl acetate (Govil, 1988), and polyacrylates (Yu et al., 1991), are commonly tried and used co-polymers. Drugs that have already been marketed are nitroglycerin, clonidine, scopolamine, oestradiol, isosorbide dinitrate, fentanyl and nicotine.

Table 1
Composition of different formulations

Ingredients	Formulations (Weight in g)					
	I	II	III	IV	V	VI
PVA	2	1.33	1.2	1.O	0.67	–
PVP	—	0.67	0.8	1.0	1.33	2.0
Glycerol	0.6	0.6	0.6	0.6	0.6	0.6
VHCl	0.2	0.2	0.2	0.2	0.2	0.2
Purified water	10	10	10	10	10	10

In each formulation, there were four formulae (A, B, C and D) which contained 0, 2, 5 and 20%respectively, of d-limonene by total weight of polymers.

* Corresponding author. D-404, Pragati Vihar Hostels (opp. Jawahar Lal Nehru Stadium), New Delhi-110003, India.

SSDI 0378-5173(95)04222-V

Penetration enhancers are substances that temporarily reduce the impermeability of the skin, hence promoting the passage of the drug through it. Various enhancers have been recognised like azone, pyrrolidones (Viegas et al., 1988), dimethyl sulphoxide (Barry, 1983), propylene glycol (Cooper, 1984), and d-limonene (Nagai, 1990). The latter was employed in the present study. d-Limonene is an oily, water insoluble but alcohol miscible liquid.

VHCl, a calcium channel blocker, is used in the management of essential hypertension. The low bioavailability (about 20%) due to extensive hepatic first pass metabolism associated with the oral route can be avoided by transdermal administration. The drug has a short half life and hence requires more frequent dosing by the oral route. A prolonged duration of action is possible with a single application of a transdermal patch. This will lead to better patient compliance.

Our aim was to develop a matrix type monolithic transdermal system for VHCl and to investigate the effect of penetration enhancer on the increase in the rate and amount of drug permeated across the skin.

2. Materials and methods

2.1. Materials

Guinea-pigs were purchased from A.I.I.M.S., New Delhi. Human cadaver skin from the chest was obtained after post-mortem of males in the age group 35-55 years. A Keshary-Chien diffusion cell designed with a volume of 15 ml and diffusional area of 1 cm^2 were employed. Polyvinyl alcohol (mol. wt. 14000, PVA), polyvinyl pyrrolidone (mol. wt. 14000, PVP) and glycerol were of AR grade. Alcohol and d-limonene were of U.S.P. grade.

2.2. Methods

2.2.1. Casting of matrices

PVA and PVP were dissolved in water by heating on a water bath at 90°C. Glycerol and VHCl were added, thoroughly mixed to form a continuous mixture and cooled. d-Limonene dissolved in alcohol was added gradually to the mixture with constant stirring. The solution was poured into glass plates especially designed to hold contents and heated in a hot-air oven at 60 $\pm$ 1°C for 10 h. The matrices were then removed, packed in aluminium foil and stored at 58% relative humidity (RH) in a humidity controlled cabinet, at room temperature.

2.2.2. Evaluation of matrices

2.2.2.1. Physico-chemical properties. Uniformity of weight was determined by weighing 20 matrices of 1 cm^2.

The moisture absorption/loss of the matrices was determined at 28, 58, 75 and 98% relative humidity (Kanig and Goodman, 1962).

The drug content of the matrices were determined by measuring the UV absorption of the drug extracted from matrices.

2.2.2.2. In vitro diffusion study. Matrices of VHCl measuring 1 cm^2 were subjected to in vitro diffusion testing using a Keshary-Chien Diffusion cell (Keshary and Chien, 1984). Guinea pigs were killed by cervical dislocation and dorsal skin was removed. After removing the epidermal hair and subcutaneous fat, it was thoroughly washed and placed overnight in contact with receptor phase (0.005% w/v sodium azide solution in distilled water).

Guinea pig skin was clamped between the donor and recipient compartments. The matrix was placed in a donor compartment over the skin and covered with Parafilm. The amount of drug diffused through guinea pig skin was determined by removing samples at predetermined time intervals. The samples were analysed for drug at 278 nm using a CECIL CE 594 Double Beam UV-Vis spectrophotometer (Moffat, 1986). The temperature of receptor phase was maintained at 37 $\pm$ 1°C throughout the experiment. The donor compartment was in contact with ambient conditions of the environment.

Matrices of VHCl showing promising results (formulations containing 5% and 20% d-limonene) were then evaluated using human cadaver skin.

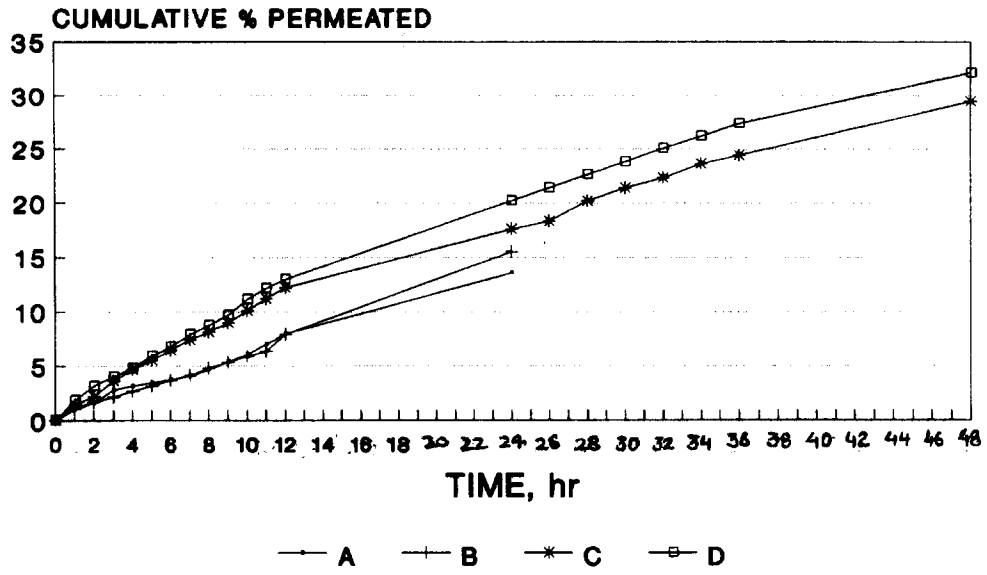

Fig. 1. Permeation of VHCl across guinea pig skin from formulation F-1.

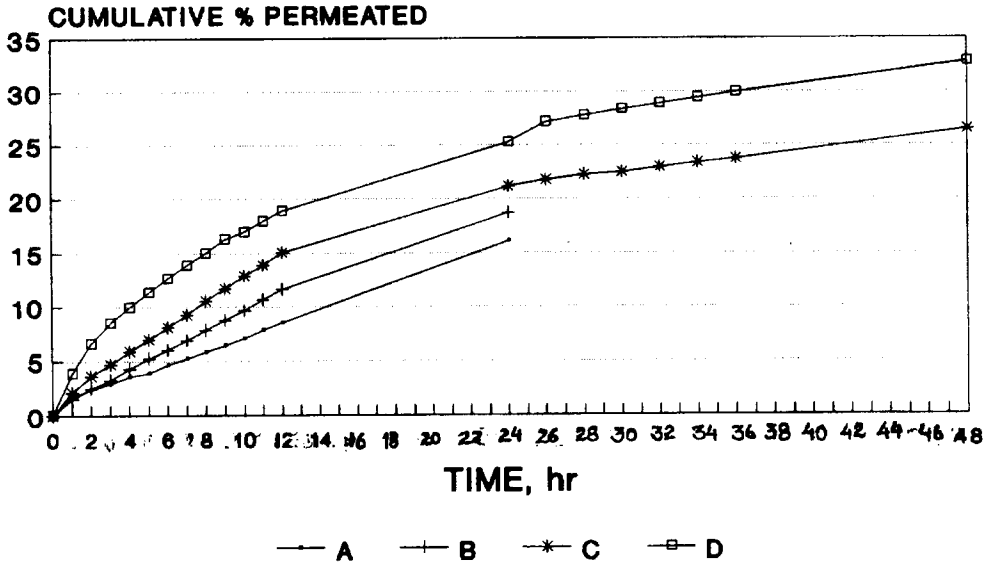

Fig. 2. Permeation of VHCl across guinea pig skin from formulation F-2.

Other parameters were kept the same as that for evaluation across guinea pig skin.

2.2.2.3. Primary skin irritation studies. Matrices were applied to the shaved skin on the back of 4 albino rabbits and secured using adhesive tape. On one side of the back, a control patch (without any drug) and on another side an experimental patch were secured. The animals were observed for any sign of erythema or oedema for a period of 7 days and scored as reported by (Draize et al., 1944).

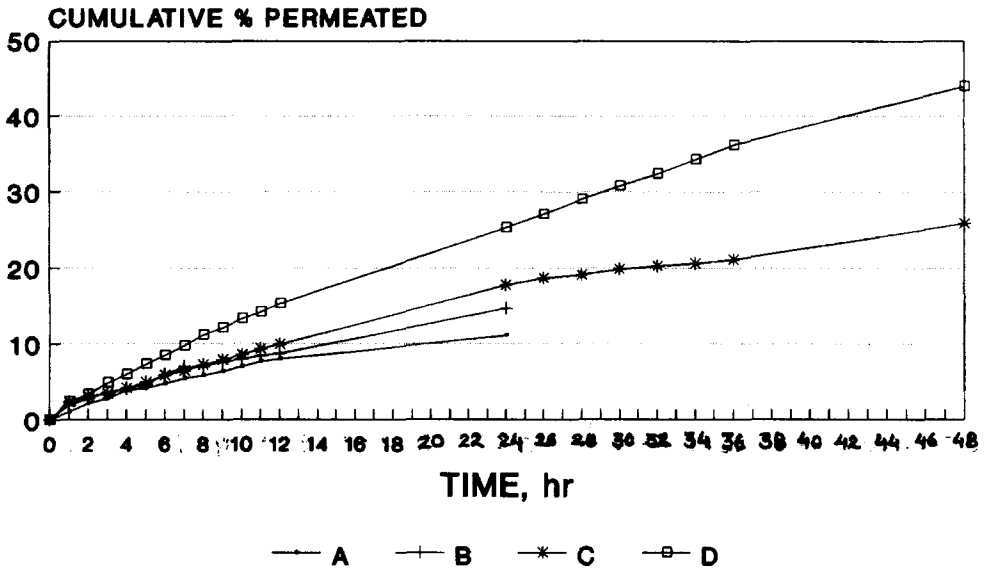

Fig. 3. Permeation of VHCl across guinea pig skin from formulation F-3.

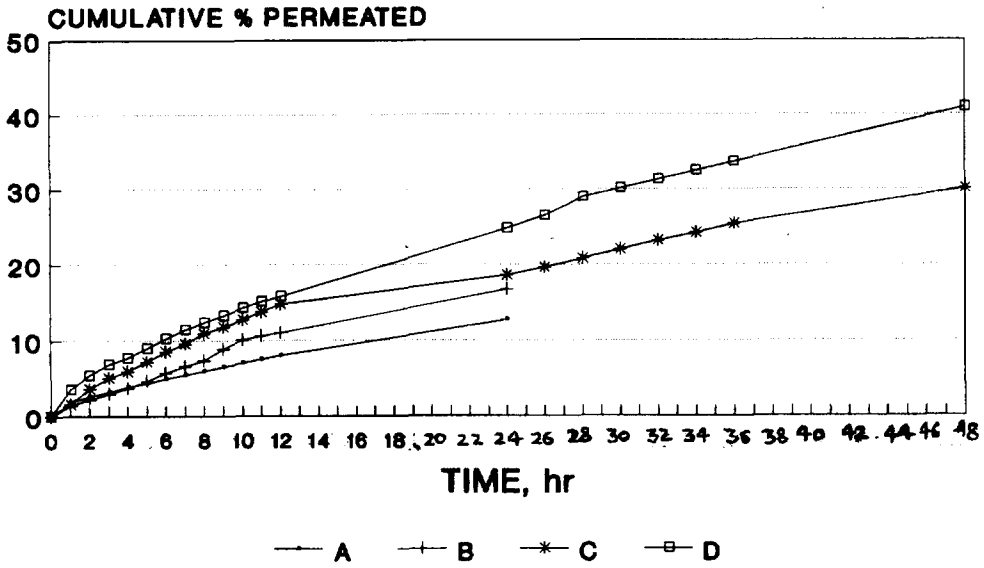

Fig. 4. Permeation of VHCl across guinea pig skin from formulation F-4.

2.2.2.4. In vitro diffusion study across cadaver skin. Matrices of VHCl showing promising results (formulations containing 5% and 20% d-limonene) were then evaluated using cadaver skin. Other parameters were kept the same as in Section 2.2.2.2 above.

3. Results and discussion

3.1. Physico-chemical properties

The matrices of VHCl showed satisfactory physico-chemical properties except that of formulation VI (Table 1). Matrices stored at 75 and 98% RH showed increase in weight while matrices

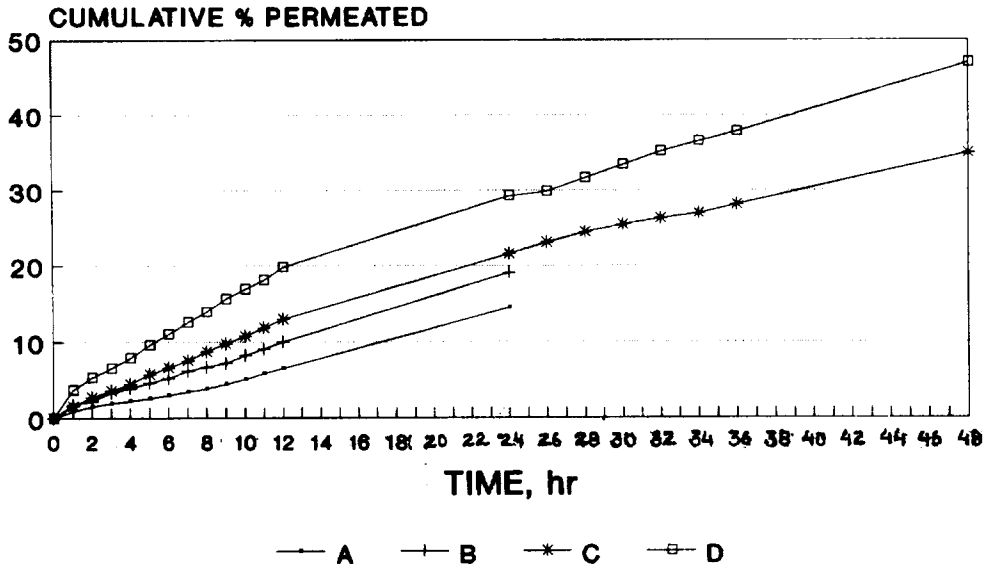

Fig. 5. Permeation of VHCl across guinea pig skin from formulation F-5.

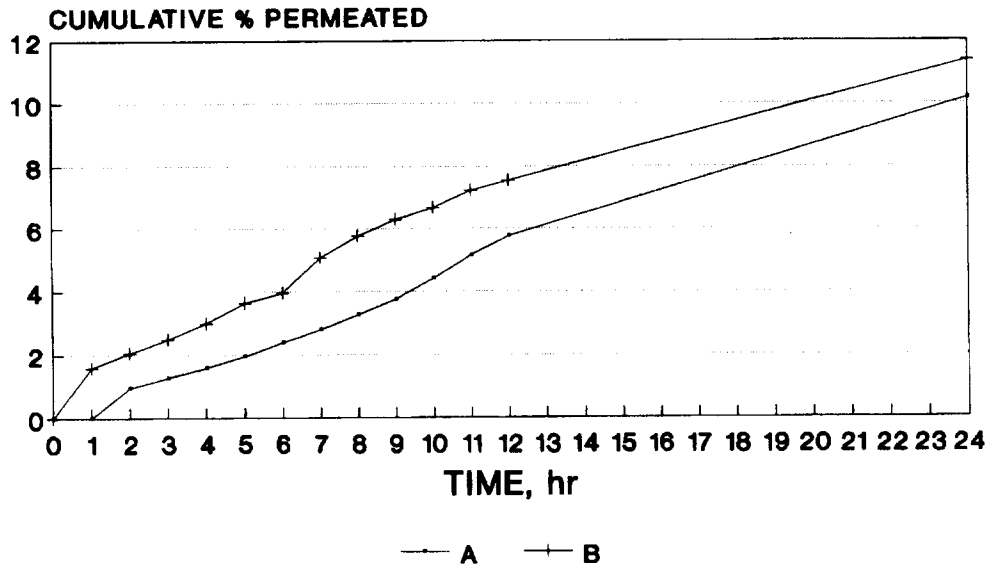

Fig. 6. Permeation of VHCl across guinea pig skin from formulation F-6.

stored at 20% RH showed decrease in weight. Change in weight of matrices was negligible when stored at 58% RH.

3.2. *In vitro release profile*

Permeation of VHCl across the guinea pig and cadaver skin for different formulations is shown in Figs. 1–9. The permeation profile followed almost zero order release kinetics. The permeability flux for different formulations are shown in Table 2 and Table 3 along with the R^2 value which shows the straightness of the plot between cumulative amount permeated vs. time.

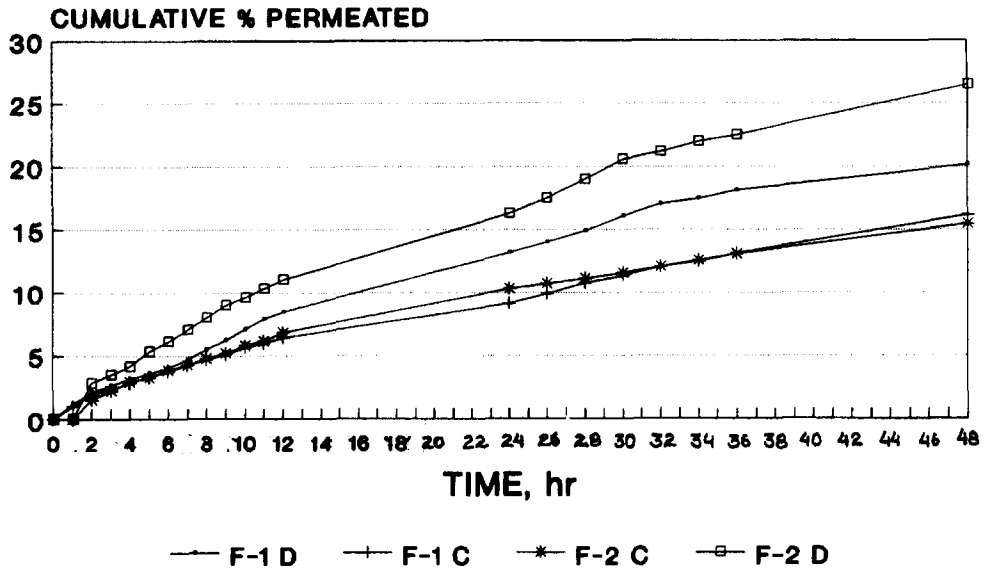

Fig. 7. Permeation of VHCl across human cadaver skin from formulations F-1 and F-2.

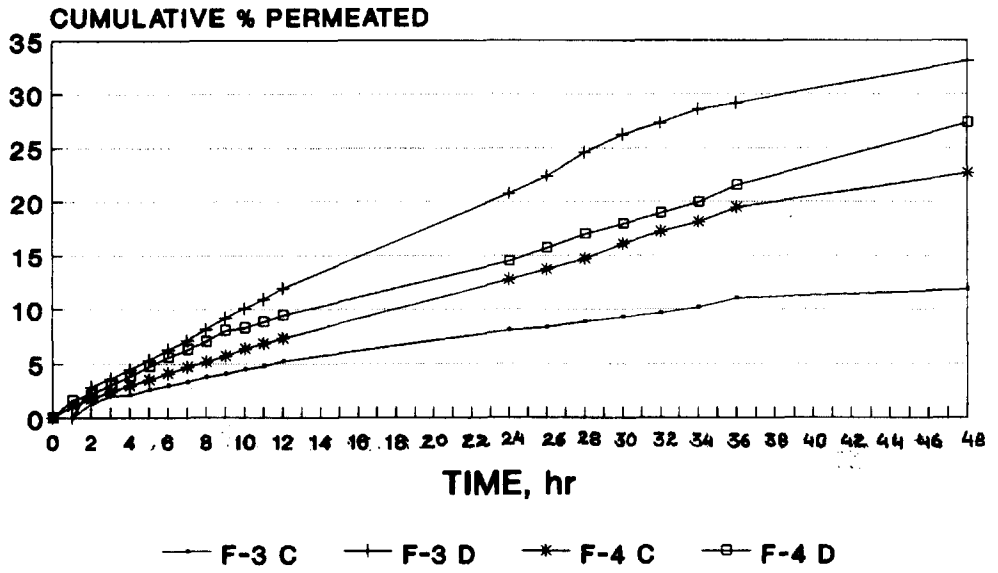

Fig. 8. Permeation of VHCl across human cadaver skin from formulations F-3 and F-4.

The amount of drug permeated across cadaver skin was much less when compared to guinea pig dorsal skin. These observations confirm the fact that cadaver skin is less permeable than guinea pig skin as reported by several authors.

3.3. Primary skin irritation studies

No erythema or oedema was noticed on the skin of albino rabbits. Thus, the primary skin irritation studies did not reveal any irritation after application of the patches for 7 days on the skin of rabbits.

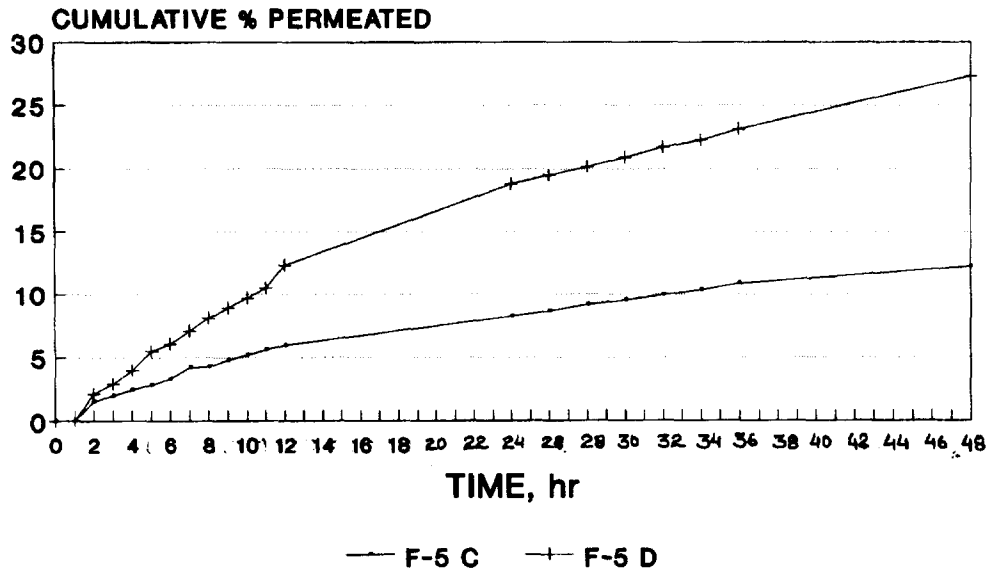

Fig. 9. Permeation of VHCl across human cadaver skin from formulation F-5.

Table 2
Permeability of VHCl across guinea pig skin

Formulation		*n*	J = ± S.E. (mg/cm²/h)		R^2	
			24 h	48 h	24 h	48 h
I	A	5	0.057 ± 0.002	—	0.99	—
	B	5	0.063 ± 0.002	—	0.99	—
	C	8	0.079 ± 0.005	0.063 ± 0.002	0.99	0.98
	D	5	0.087 ± 0.004	0.063 ± 0.004	0.95	0.94
II	A	9	0.064 ± 0.002	—	0.99	—
	B	10	0.081 ± 0.003	—	0.98	—
	C	6	0.107 ± 0.003	0.059 ± 0.004	0.99	0.92
	D	4	0.109 ± 0.010	0.069 ± 0.005	0.88	0.90
III	A	5	0.051 ± 0.004	—	0.95	—
	B	5	0.061 ± 0.003	—	0.95	—
	C	5	0.072 ± 0.002	0.056 ± 0.002	0.99	0.97
	D	6	0.093 ± 0.002	0.107 ± 0.004	0.99	0.98
IV	A	9	0.053 ± 0.003	—	0.96	—
	B	5	0.076 ± 0.004	—	0.96	—
	C	4	0.087 ± 0.008	0.061 ± 0.003	0.89	0.94
	D	4	0.102 ± 0.006	0.085 ± 0.003	0.95	0.97
V	A	5	0.054 ± 0.003	—	0.95	—
	B	5	0.076 ± 0.004	—	0.99	—
	C	10	0.093 ± 0.003	0.076 ± 0.002	0.90	0.98
	D	5	0.096 ± 0.003	0.125 ± 0.003	0.98	0.96
VI	A	4	0.044 ± 0.001	—	0.99	—
	B	4	0.049 ± 0.003	—	0.92	—

VI C and VI D were not studied as results of VI A and VI B were not favourable.

Table 3
Permeability of VHCl across human cadaver skin

Formulation		n	J ± S.E. (mg/cm²/h)		R^2	
			24 h	48 h	24 h	48 h
I	C	4	0.040 ± 0.003	0.030 ± 0.002	0.93	0.94
	D	4	0.057 ± 0.002	0.042 ± 0.002	0.97	0.95
II	C	4	0.047 ± 0.003	0.025 ± 0.003	0.95	0.73
	D	4	0.075 ± 0.005	0.053 ± 0.003	0.94	0.93
III	C	4	0.036 ± 0.002	0.027 ± 0.001	0.95	0.96
	D	4	0.090 ± 0.003	0.075 ± 0.003	0.98	0.97
IV	C	4	0.054 ± 0.002	0.045 ± 0.002	0.98	0.96
	D	4	0.064 ± 0.004	0.050 ± 0.003	0.95	0.94
V	C	4	0.039 ± 0.003	0.024 ± 0.002	0.91	0.90
	D	4	0.086 ± 0.003	0.024 ± 0.003	0.97	0.92

3.4. Effect of penetration enhancers

There was improvement in drug permeability across the guinea pig skin in the formulations containing the penetration enhancer. d-Limonene in low concentrations of 2% and 5% did not affect permeation significantly, but in higher concentration (20%) the effect was significant.

It was also observed that the formulations containing enhancer had lower lag times. This effect was more pronounced in formulations containing higher concentrations of enhancer.

4. Conclusions

The incorporation of d-limonene as penetration enhancer in sustained-release polymers shows definite improvement in drug permeation across the skin. The VHCl permeation across the skin has increased extensively by incorporation of PVA and PVP instead of using PVA or PVP alone.

Acknowledgements

GKJ was supported as Senior Research Fellow of Council of Scientific and Industrial Research, New Delhi, India. Sample of VHCl was supplied kindly by Torrent Laboratories Ltd., Ahmedabad, India.

References

Barry, B.W., Properties that influence percutaneous absorption, In: *Dermatological formulations - Percutaneous Absorption*, Marcel Dekker Inc., New York, 1983, pp. 127-233.

Bhalla, H.L. and Toddywalla, R.D., Transdermal films of ephedrine, *Drug Dev. Ind. Pharm.*, 14(1) (1988) 119-131.

Bodde, H.E., Van Aalten, E.A.C. and Junginger, H.E., Hydrogel patches for transdermal drug delivery: in-vivo water exchange and skin compatibility, *J. Pharm. Pharmacol.*, 41 (1989) 152-155.

Cooper, E.R., Increased skin permeability for lipophilic molecules, *J. Pharm. Sci.*, 73 (1984) 1153-1158.

Draize, A.H., Woodward, G. and Calvery, H.O., Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes, *J. Pharmacol. Exp. Ther.*, 82 (1944) 377-390.

Govil, S.K., Transdermal drug delivery devices, In: *Drug Delivery Devices-Fundamentals and Applications*, Vol. 32, Tyle, P. (ed.), Marcel Dekker Inc., New York, 1988, pp. 384-419.

Kanig, J.L. and Goodman, H., Evaluative procedures for film forming materials used in pharmaceutical appplications, *J. Pharm. Sci.*, 51(1) (1962) 77-83.

Keshary, P.R. and Chien, Y.W., Mechanisms of transdermal controlled nitroglycerin administration (I): development of finite-dosing skin permeation system, *Drug Dev. Ind. Pharm.*, 10 (1984) 883-913.

Moffat, A.C., *Clarke's Isolation and Identification of Drugs in Pharmaceuticals, Body Fluids and Post-mortem Material*, 2nd edn, The Pharmaceutical Press, London, 1986, pp. 1060.

Nagai, T., Plenary lecture on Formulation approach to enhancement and control of bioavailability of drugs, In: *International Symposium on Innovations in Pharmaceutical Sciences and Technology*, Oct 27-29, 1990, at Sh. B.V. Patel PERD Centre, Ahmedabad, India.

Viegas, T.X., Hikal, A.H. and Cleary, R.W., Formulation of penetration enhancers in polymers, *Drug Dev. Ind. Pharm.*, 14(6) (1988) 855-866.

Yu, J.W., Chien, T.-Y. and Chien, Y.W., Transdermal dual-controlled delivery of testorene and estradiol: (II) enhanced skin permeability and membrane-moderated delivery, *Drug Dev. Ind. Pharm.*, 17(14) (1991) 1905-1930.