SHORT COMMUNICATIONS

Enhanced transdermal delivery of terbutaline sulphate *in vitro* using non-ionic surfactants

D. REJENDRAN*, G.L. PRABUSHANKAR, S.A. DHANARAJ, RAJEEV DUBE AND B. SURESH
Dept. of Pharmaceutics, J.S.S. College of Pharmacy, Ooctacamund - 643 001, Tamil Nadu.

Received 31st July 1995

Feasibility studies were carried out to develop a transdermal delivery system for terbutaline sulphate. Eight non-ionic surfactants were used as permeation enhancers. The flux of terbutaline sulphate from transdermal patches containing any of the selected non-ionic surfactants or without surfactants were determined using Keshary - Chein cell. Among the Spans used, Span 80 produced the highest permeation of the drug. Of the Tweens used, Tween 80 produced the highest permeation of the drug. Adequate levels of transdermal permeation were observed.

TRANSDERMAL route has been recognised as one of the highly potential routes of systemic drug delivery. Extensive studies have been carried out to provide drugs through this route. (Chien, 1987; Pai et al., 1994). The major limitations of this route are difficulty of permeation of drug through human skin and skin irritation (Chien, 1987; Behel **et al.**, 1982). Studies have been carried out to find safe permeation enhancers to improve the transdermal flux of drugs (Rojanasakul, and Hsieh, 1994). Non-ionic surfactants, especially polysorbates, have been found to be safe permeation enhancers for the transdermal pemeation enhancement of variety of drug (Shahi and Zatz, 1978).

Terbutaline sulphate is a bronchodilator. It is extensively metabolised in the liver (Barry and Bennett, 1987; Benet **et al.**, 1991). The drug is being tried for transdermal delivery (Jain, **et al.**, 1992). The present study investigated a modified matrix system for the *in vitro* delivery of terbutaline sulphate through excised guinea pig skin, using non-ionic surfactants as permeation enhancers.

* **For correspondence**

Terbutaline sulphate (Astra - IDL, Bangalore) and Ethylene vinyl acetate copolymer 2806 (Polyolefin Industries Ltd., Bombay), were received as gift samples. Spans 20, 40, 60 and 80 and Tweens 20, 40, 60 and 80 were used as received. All other chemicals used were of analytical grade.

The drug loaded membranes and drug free rate controlling membranes of Ethylene vinyl acetate copolymer 2806 (EVA) were prepared using 'Glass substrate technique' by placing glass over mercury surface. Diethyl phthalate at 2% was used as the plasticizer. Rate controlling membranes were prepared at 50 μ thickness. Drug - polymer matrix was prepared by finely dispersing the drug particles in the solution of EVA. Transluscent films of 100 μ thick, containing 10 mg / sq. cm of terbutaline sulphate were prepared. The prepared films were kept in a vaccum desiccator for 24 hours to remove the traces of tolune.

The transdermal device was prepared by placing the drug loaded film on the backing laminate aluminium foil and the rate controlling membrane over it. The films were fixed to the backing laminate using

Table 1: Cumulative release of terbutaline sulphate from transdermal patch containing no permeation enhancer

S. No.	Sample Interval	Cumulative drug release^n mcg / sq. cm
1	6 h	171.9 ± 2.4
2	12 h	421.9 ± 4.9
3	24 h	783.8 ± 2.5

$n = 2$

a hot ring. The effective surface area of the device was 1.6 sq. cm.

The selected permeation enhancers were separately incorporated at 1% by weight of matrix polymer in to the transdermal patches.

In vitro skin permeation experiments were performed at 32° using Keshary - Chein cell. Guinea pig skin obtained from the abdominal region freed from adhering fat and other visceral debris was washed throughly with physiological saline and cut into four pieces. Two pieces were used immediately and the other two pieces were packed in polythene bags and kept frozen until used the next day. Excised guinea pig skin was mounted on the diffusion cell with the dermis side in contact with the dissolution medium. The transdermal device was placed on the skin and clamped with the cap. The receptor compartment was filled with saline solution containing 20% of Polyethylene Glycol 400 as co-solvent. Samples were collected at 6, 12 and 24 h intervals by removing all the quantity of the dissolution medium of receptor compartment and replacing it with fresh dissolution medium. *In vitro* skin permeation studies were done in duplicate.

A calibration curve was prepared with a range of concentration of the drug in dissolution medium. The standard and sample solution were analysed spectrophotometrically at 211 nm.

The cumulative amount of drug release from the transdermal patch containing no permeation enhancer was 783.75 mcg/ sq.cm / day (Table 1). Significant enhancement of permeation was observed with the incorporation of non-ionic surfactants. Of the Spans used, Span 80 provided the highest permeation enhancement with 2800 mcg / sq. cm / day representing an increased in flux of 3.57 times (Table 2). Of the Tweens used, Tween 80 was found to provide the maximum permeation enhancement with 2818.75 mcg/ sq. cm / day representing an increase in flux of 3.6 times (Table 3). The *in vitro* profile shows that Spans were better than Tweens in enhancing the permeation of terbutaline sulphate through skin. However, the difference between the maximum permeation provided by Spans and Tweens was found to be insignificant. All the formulations were found to provide an overall drug release between first and zero order. The steady state diffusion was found to be near zero order. Based on the pharmacokinetic parameters, it was found that the transdermal device that would deliver about 2 mg / day of the drug to the systemic circulation could maintain adequate therapeutic activity. Among the transdermal patches incorporating various permeation enhancers, only the transdermal device containing Tween 20 failed to achieve a permeation of above 2 mg / sq.cm / day. Satisfactory skin permeation was achieved with all the other non-ionic surfactants used.

ACKNOWLEDGEMENT

The authors thank Mr. S. Ravisankar, Scientist-in-charge, Instrumental Analysis, J.S.S. College of Pharmacy, Ootacamund for his services in successful completion of this work.

Table 2: Cumulative release of terbutaline sulphate from transdermal patches containing selected Spans at 1% level

S. No.	Sampling	Cumulative drug release (mcg / sq. cm^n			
		Span 20	Span 40	Span 60	Span 80
1	6h	762.5 ± 6.3	700.0 ± 4.6	750.0 ± 5.5	768.8 ± 6.8
2	12h	1662.5 ± 3.0	1543.8 ± 3.0	1675.0 ± 7.3	1706.3 ± 4.5
3	24h	2771.9 ± 2.6	2528.1 ± 2.4	2706.3 ± 3.0	2800.0 ± 2.3

n = 2

Table 3: Cumulative release of terbutaline sulphate from transdermal patches containing selected Tweens at 1% level

S. No.	Sampling Interval	Cumulative drug release (mcg/ sq. cm^n			
		Tween 20	Tween 40	Tween 60	Tween 80
1	6h	428.1 ± 4.5	440.6 ± 5.9	718.8 ± 4.9	777.0 ± 5.3
2	12h	990.6 ± 2.9	1221.9 ± 3.3	1515.6 ± 5.5	1681.3 ± 4.5
3	24h	1778.1 ± 2.9	2190.6 ± 4.5	2578.1 ± 3.6	2818.8 ± 6.0

n = 2

REFERENCES

1. Benet, L.Z., Williams, R.L., Gilman, A.G., Rall, T.W., Nies, A.S., and Taylor, P., (eds.) The Pharmacological basis of therapeutic, Eighth edition, Volume II, Pergamon Press, New York, 1991, 1709.
2. Barry, B.W., and Bennett, S.L., **J. Pharm. Pharmacol.**, 1987, 39, 535.
3. Behel C.R., Barret, M., Flynn, G.L., Kurihara, T., Walters, K.A., Gatmaiton, O.G., Harper, N., Higuchi, W.I., and Pierson, C.L., **J. Pharm. Sci.**, 1982, 71, 229.
4. Chien, Y.W., Transdermal Controlled Systemic Medications, Volume 31, Marcel Dekker, Inc., New York., 1987, 25.
5. Rojanasakul Y., and Hsieh, D.S. (ed.) Drug Permeation Enhancement: Theory and Applications, Volume 62, Marcel Dekker, Inc. New York, 1994, 405.
6. Jain S.K., Vyas, S.P., and Dixit, V.K., **J. Controlled Release.**, 1992, 22, 177.
7. Pai, R., Desai, M.S., Babitwale, A.D., and Shrivastava, R., Drug develop. **Indus. Pharm.**, 1994, 20(11), 1905.
8. Shahi, V., and Zatz, J.L., **J. Pharm. Sci.**, 1978, 67, 789.