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Transdermal delivery of Prazosin HCL with non-ionic surfactants

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The effect of non-Ionic surfactants on the enhancement of skin permeation of prazozin HCl was studied *In vitro* using excised guinea pig skin. Among the Spans, Span 80 was found to produce the highest permeation of the drug. Among the Tweens, Tween 80 was found to produce the highest permeation of the drug. Tweens produced higher permeation than Spans. Adequate levels of transdermal permeation were observed.

PRAZOSIN HCl is a very potent and selective α_1 adrenergic receptor antagonist. Various studies have been reported on the suitability of prazosin HCl for transdermal delivery[1,2]. The present study was carried out to determine the effect of selected non-ionic surfactants on the transport of prazosin HCl across guinea pig skin *in vitro.* The concentration dependence of the surfactants on the enhancement of permeation of the drug was also determined.

Prazosin HCl (Sun Pharmaceutical Industries Ltd., Baroda), Ethylene vinyl acetate copolymer 2806 (Polyolefins Industries Ltd., Bombay), Spans 20, 40, 60, 80, Tweens 20, 40, 60 and 80 were used as received. All other chemicals used were of analytical grade.

The drug loaded and rate controlling membranes of ethylene vinyl acetate copolymer 2806 (EVA) were prepared using 'Glass substrate technique' by placing a glass plate over the mercury surface. Diethyl phthalate at 2% w/w of the polymer was used as the plasticizer. Rate controlling membranes were prepared at 50 and 100 um thickness. Drug-polymer matric was prepared by finely dispersing the drug particles in the solution of EVA. Opaque films of 100 um thick, containing 20 mg/sq. cm of prazosin HCl were prepared. The prepared films were kept in a vaccum desiccator for 24 h to remove the traces of toluene.

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Table 1
Cumulative release of prazosin HCl from transdermal patches containing 1% Span

S. No.	Sampling Interval	Cumulative drug release mcg/sq.cm			
	h	Span 20	Span 40	Span 60	Span 80
1.	6	51.9 ± 2.1	50.00 ±1.5	50.9 ±1.6	58.8 ±2.3
2.	12	115.8 ± 3.5	125.00 ±2.8	131.8 ±3.0	145.5 ±2.3
3.	24	236.8 ±4.8	220.50 ± 3.3	230.00 ±2.5	241.3 ± 3.8

Rate controlling membrane thickness : 50 u

Table 2
Cumulative release of prazosin HCl from transdermal patches containing 1% Tween

S. No.	Sampling Intervals	Cumulative drug release mcg/sq.cm			
	h	Tween 20	Tween 40	Tween 60	Tween 80
1.	6	49.5 ± 1.8	54.5 ± 2.3	60.0 ± 1.5	61.3 ± 1.3
2.	12	141.13 ± 2.0	145.8 ± 2.8	144.5 ± 2.8	150.8 ± 3.3
3.	24	252.50 ± 2.3	261.9 ± 3.8	268.1 ± 2.6	276.3 ± 1.5

Rate controlling membrane thickness : 50 u

The transdermal device was prepared by placing the drug loaded film on the backing laminate aluminum foil and the rate controlling membrane over it. The films were fixed to the backing laminate using a hot ring. The effective surface area of the device was 1.6 sq. cm. The most effective concentration of the permeation enhancer was determined by incorporating Tween 80 at different concentrations. All the surfactants were incorporated at the optimum concentration determined.

In vitro skin permeation experiments were performed at 32° with excised guinea pig skin using the Keshary-Chien cell. Distilled water was used as the dissolution medium. Samples were collected at 6, 12 and 24 h intervals. For control study, 25 mg of the

Table 3

Cumulative release of prazosin HCl from transdermal patches containing selected Spans and Tweens and varying thickness of rate controlling membrane at 24 h

S. No.	Members thickness um	Cumulative release of drug from release mcg/sq.cm			
		SPANS		TWEEN	
		Span 20 (1%)	Span 80 (1%)	Tween 60 (1%)	Tween 80 (1%)
1.	25	289.4 ± 3.9	253.1 ± 2.4	286.9 ± 2.6	293.8 ± 2.0
2.	50	236.8 ± 4.8	241.3 ± 3.8	268.1 ± 2.6	276.3 ± 1.5
3.	100	206.3 ± 2.3	197.5 ± 2.3	208.8 ± 1.5	214.5 ± 1.8

drug was directly placed on the excised guinea pig skin and its *in vitro* skin permeation was determined.

A calibration curve was prepared at a range of concentration of the drug in aqueous acid. (0.2% hydrochloric acid) The samples collected from dissolution experiments were diluted with an equal volume of 0.4% hydrochloric acid and analysed spectrophotometrically at 247 nm^3.

The cumulative amount of drug released from the transdermal patch containing no permeation enhancer was lower than control indicating that the transdermal patch exercised control over the release of the drug. Tween 80 was used at 0.5, 1.0 and 1.5% by weight of the matrix and the effect of permeation enhancer was found to be the highest at 1%.

Of the Spans used, Span 80 was found to produce the highest permeation enhancement with 241.3 mcg / sq. cm / day (Table 1), closely followed by Span 20 with 236.9 mcg / sq. cm / day. Of the Tweens used, Tween 80 was found to produce the highest permeation enhancement with 276.3 mcg / sq.cm / day, followed by Tween 60 with 268.1 mcg / sq. cm / day (Table 2). Two transdermal devices from each group which showed better *in vitro* permeation than the others, such as, the patches containing Tween 80 and 60 and Spans 80 and 60, were subjected to the study on the effect of varying the thickness of rate controlling membrane (Table 3). The result showed an inverse relationship of the permeation of the drug to the thickness of rate controlling membrane. However, the rate controlling membrane of 25 um thickness was too delicate to handle and so did not lend itself for further studies.

Based on the pharmacokinetic parameters[4], it was found that the device that could deliver between 1.68 mg and 8.4 mg of Prazosin HCl per day would maintain adequate therapeutic activity. All the permeation enhancers were found to produce *in vitro* drug permeation falling within the calculated levels. Of the transdermal devices formulated, the device containing Tween 80 at 1% and the rate controlling membrane thickness of 50 um is found to be the best. The study shows that this could deliver 2.76 mg / 10 sq.cm. / day which is well below the calculated maximum therapeutic drug blood level. This can be advantageous because the device delivers the drug at a level higher than that is necessary to maintain the minimum effective concentration and at the same time can reduce the adverse effects. This is particularly significant with Prazosin HCl which is known to

produce hypotension when high doses are given initially.

In conclusions, Tweens and Spans enhanced the transdermal permeation of prazosin HCl. The intra group variation among the Spans and Tweens were insignificant. Tweens were found to be better than Spans in the enhancement of permeation of the drug through excised guinea pig skin. Therapeutic levels of the drug could be achieved through transdermal permation.

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Bioactive Polymers; Synthesis, Characterisation, Release and Antimicrobial Property of Macromolecular Prodrug of Ampicillin

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The matrix of poly (methyl methacrylate-co-maleic anhydride) with surface containing functional anhydride group of different percentage was prepared by solution polymerization and characterized. A macromolecular prodrug of ampicillin was synthesized by linking the amino group of ampicillin to anhydride group of matrix via an amide bond. The amount of ampicillin covalently bound to the matrix was spectroscopically characterized and the *in vitro* release rate in weakly basic medium was established with its antimicrobiological activity. This prodrug allows a prolonged release (7-8 days) of the drug.

MUCH attention has been lately paid to the preparation and properties of pharmacoogically active polymers[1-6] which can serve as a carrier for low molecular weight drugs to form prodrugs. The controlled slow release of pharmacologically active components in the body can be achieved from prodrugs which can be considered as a special type of drug delivery system from which drug release is

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