

# Formulation and Evaluation of Transdermal Films of Salbutamol Sulphate

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**ABSTRACT:** Transdermal drug delivery systems of salbutamol sulphate using eudragit RL100 and PVP were developed by solvent casting technique employing mercury as a substrate. Propylene glycol was used as a plasticizer. The prepared films exhibited satisfactory physico-chemical characteristics. *In vitro* permeation profiles across the guinea-pig dorsal skin using K-C diffusion cell are reported. Incorporating PEG-400 and tween 60 into the films enhanced the permeation across guinea-pig skin; permeation rate was greater with films containing PEG-400. The permeation followed zero order kinetics and mechanism was found to be matrix diffusion.

**Keywords:** Salbutamol sulphate, Guinea pig skin, Permeation enhancer

## INTRODUCTION

Transdermal drug delivery systems (TDDS) are adhesive drug-containing devices of defined surface area that delivers a predetermined amount of drug to the intact skin at a preprogrammed rate. The transdermal delivery has gained importance in recent years. The major advantages claimed for TDDS include avoidance of gastro-intestinal incompatibility and variable absorption; avoidance of hepatic first pass metabolism and consequent degradation and reduced bioavailability; reduced frequency of dosing with improved patient compliance and rapid termination of drug input by removal of the system from the skin.<sup>1</sup>

Salbutamol sulphate is a  $\beta_2$  adrenergic agonist with bronchodilatory effect and useful in treatment of asthma. As it undergoes hepatic first pass metabolism, its systemic bioavailability is 50%. In the present study transdermal films of salbutamol

sulphate were prepared and evaluated with a view to prevent its first pass metabolism and to achieve a controlled drug release with improved bioavailability.<sup>2,3</sup>

## MATERIALS AND METHODS

Salbutamol sulphate was obtained as a gift sample from Cipla Ltd., Mumbai, India. Eudragit RL100 was gifted by Intas Labs. Pvt. Ltd., Ahmedabad, India. Polyvinyl pyrrolidone K-30 (PVP), Polyethylene glycol (PEG-400), Glycerol and Tween 60 were procured from Otto Kemi Ltd., Mumbai, India.

**Preparation of Films.** The composition of transdermal films is listed in Table 1. The films were prepared by solvent casting technique employing mercury as a substrate. Propylene glycol and permeation enhancer (PEG-400, Tween 60) were mixed with dichloromethane using a magnetic stirrer. Eudragit RL100 and PVP were slowly added, until all the ingredients dissolved. Salbutamol sulphate was added and stirred well until a homogeneous solution

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was obtained. 10 ml of the solution was poured within a glass bangle (6.0 cm diameter) placed on a mercury surface. The rate of evaporation was controlled by inverting the cut funnel over the petridish. After drying at room temperature membranes were taken out, cut into 3.14 cm<sup>2</sup>, packed in aluminium foil and stored in desiccator until further use<sup>4</sup>.

### Evaluation of Transdermal Films

**(i) Physico-chemical properties.** The prepared transdermal films were evaluated for thickness (Micrometer; Mitutoyo, Japan), folding endurance (a measure of fragility), tensile strength (a measure of flexibility), percentage elongation at break and water vapour permeability.<sup>5-7</sup>

The drug content was determined by measuring the UV absorption of salbutamol sulphate extracted from the films. The film was dissolved in 5 ml of dichloromethane and volume was made to 10ml with phosphate buffer pH 7.4; dichloromethane was evaporated using rotary vacuum evaporator (Buchi type, MAC) at 45°C. The solution was filtered through a 0.45 µm membrane. The spectrophotometric absorbance of the filtrate was measured at 225 nm after suitable dilution and drug content was determined. The estimations were carried out in triplicate and average values were reported.

**(ii) *In vitro* permeation study.** Films measuring 3.14 cm<sup>2</sup> were subjected to *in vitro* permeation study using a Keshary-Chien Diffusion cell.<sup>8</sup> Guinea pigs were killed by cervical dislocation and dorsal skin was removed. After removing the epidermal hairs and subcutaneous fat, it was thoroughly washed and placed overnight in contact with the receptor phase (phosphate buffer pH 7.4).

Guinea pig dorsal skin was clamped between the donor and recipient compartments. The film was placed in donor compartment over the skin and covered with parafilm. The temperature of receptor phase was maintained at 37±1°C throughout the experiment. The compartment was in contact with ambient condition of environment. The amount of drug permeated through guinea pig skin was

determined by withdrawing samples of 1 ml at predetermined time intervals and replacing an equal volume of pre-warmed buffer (37 ± 1°C). The samples were analysed for drug at 225 nm using a double beam UV-Vis spectrophotometer (Thermo-spectronic-1).

**(iii) Skin irritancy studies.** The guinea pigs were divided into 5 groups (n=3). On the previous day of the experiment, the hairs on the backside area of guinea pigs were removed. The animals of group I was served as normal, without any treatment. One group of animals (Group II, control) was applied with adhesive tape USP (Leucoplast<sup>TM</sup>). Transdermal systems (blank, without drug and drug loaded) were applied onto nude skin of animals of III and IV groups. A 0.8% v/v aqueous solution of formalin was applied as a standard irritant (group V). The animals were applied with new patch/formalin solution each day upto 7 days and finally the application sites were graded according to a visual scoring scale.<sup>9</sup>

## RESULTS AND DISCUSSION

The transdermal films of salbutamol sulphate were prepared by solvent casting technique and were characterized for thickness, tensile strength, percentage of elongation at break, folding endurance, water vapour permeability, content uniformity, *in vitro* permeation studies and skin irritancy studies. The physico-chemical characteristics of the films are shown in Table 2.

Film thickness was uniform in all the formulations and it was found to vary between 246.66 to 256.66 µm. The percent elongation at break and tensile strength was measured using the instrument as described by Seth *et al.*<sup>9</sup> The formulation F<sub>3</sub> showed the maximum elongation where as the least value was found with F<sub>5</sub>. The elongation at break was found to vary between 63.66 to 90.83 %. Tensile strength measures the ability of film to withstand rupture. The presence of tween 60 decreased the tensile strength of the films. The incorporation of PEG-400 markedly increased the tensile strength of the films. In present study,

formulations F<sub>1</sub>, F<sub>2</sub>, F<sub>3</sub>, were better than F<sub>4</sub>, F<sub>5</sub> with respect to folding endurance; as the concentration of tween 60 increased folding endurance value decreased. For the various formulations drug content

was found to be between 3.89 to 4.10 mg per film. The low coefficient of variation (C.V.<2%) indicated content uniformity in the prepared formulations.

**Table 1. Composition of transdermal films.**

Code	Eudragit RL100 (in parts)	PVP	Propylene Glycol (% w/w)*	PEG-400 (% w/v)	Tween 60 (% w/v)	Salbutamol sulphate (%w/v)
F <sub>1</sub>	6	2	40	-	-	0.972
F <sub>2</sub>	6	2	40	0.5	-	0.972
F <sub>3</sub>	6	2	40	1.0	-	0.972
F <sub>4</sub>	6	2	40	-	0.5	0.972
F <sub>5</sub>	6	2	40	-	1.0	0.972

\*based on polymer weight.

**Table 2. Physico-chemical characteristics of transdermal films of salbutamol sulphate.**

Code	Thickness ( $\mu$ m)	Folding Endurance	Tensile Strength (kg/mm <sup>2</sup> )	Elongation at Break (%)	Moisture vapour transmission (gm/cm <sup>2</sup> .h)	Drug Content (mg/film)	Permeability Rate (mg/cm <sup>2</sup> .hr)
F <sub>1</sub>	253.33 $\pm$ 11.54	290.00 $\pm$ 7.81	0.839 $\pm$ 0.08	81.16 $\pm$ 4.53	0.098 $\pm$ 0.001	4.08 $\pm$ 0.07	1.05
F <sub>2</sub>	250.00 $\pm$ 10.02	379.66 $\pm$ 5.52	1.031 $\pm$ 0.04	83.33 $\pm$ 3.81	0.146 $\pm$ 0.008	3.94 $\pm$ 0.05	1.92
F <sub>3</sub>	256.66 $\pm$ 5.77	389.96 $\pm$ 4.04	1.148 $\pm$ 0.27	90.83 $\pm$ 2.88	0.178 $\pm$ 0.005	4.10 $\pm$ 0.06	2.54
F <sub>4</sub>	246.66 $\pm$ 15.27	228.33 $\pm$ 3.05	0.775 $\pm$ 0.03	78.00 $\pm$ 2.29	0.119 $\pm$ 0.002	3.94 $\pm$ 0.07	1.96
F <sub>5</sub>	246.66 $\pm$ 5.77	195.33 $\pm$ 8.07	0.671 $\pm$ 0.18	63.66 $\pm$ 4.36	0.125 $\pm$ 0.007	3.89 $\pm$ 0.04	2.14

The *in vitro* permeation study was performed across hairless guinea pig skin using K-C diffusion cell. It was found that only 40.19% of the drug permeated through hairless guinea pig skin from F<sub>1</sub> (without permeation enhancer) at the end of 12 hours. The transdermal films (F<sub>2</sub> and F<sub>3</sub>) containing PEG-400 as permeation enhancer showed a significant increase in permeation rate. Hence, the combination of propylene glycol and PEG-400 in the films increased the drug permeability. The synergistic effect may be due to functioning of glycols in combination as co-solvents to produce saturated or nearly saturated solution of active medicament in the formulation thereby maximizing the thermodynamic activity of the penetrant. The drug permeated from film F<sub>4</sub> at the end of 12 hours was found to be 73.86%. The permeation of the drug from formulation F<sub>5</sub> containing tween 60 (1% w/v) was found to be 80.94% at the end of 12 hours, which was greater than F<sub>1</sub>, F<sub>2</sub>, and F<sub>4</sub> but lesser than F<sub>3</sub>. The permeation promoting activity of non-ionic surfactant

(tween 60) may be due to the reduction in surface tension, improvement in the wetting of skin and enhanced distribution of the drug. The formulations can be arranged in order of permeation rate as: F<sub>3</sub> > F<sub>2</sub> > F<sub>5</sub> > F<sub>4</sub> > F<sub>1</sub>.

From the *in vitro* permeation profile (Figure 1) it is evident that kinetics of permeation from transdermal films is zero order as the plots between cumulative % drug permeated versus time showed good linearity ( $R^2 > 0.98$ ). The coefficient of determination values were much closer to 1 for the Higuchi plot, thus indicating that the drug release from transdermal films followed a diffusion-controlled mechanism (Figure 2).

The result of skin irritation test showed no erythma associated with the prepared TDDS application. The absence of edema indicated that these polymeric films of salbutamol sulphate were compatible with skin and hence can be used for the transdermal application.

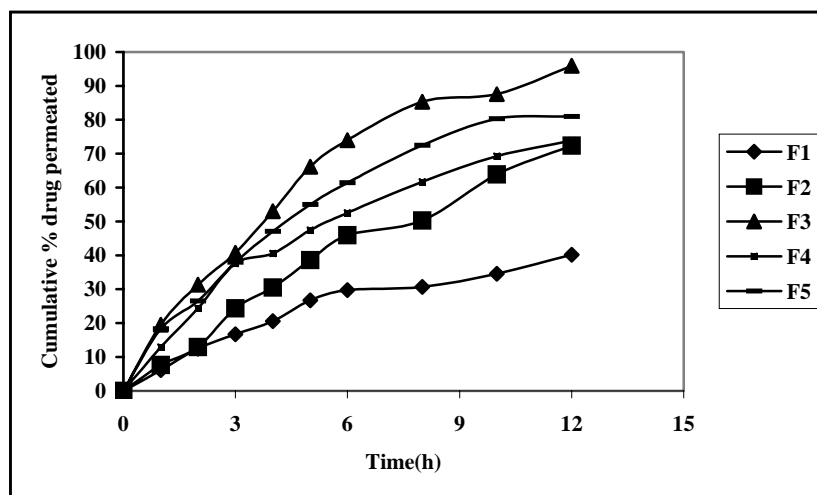


Figure 1. Permeation of salbutamol sulphate across guinea pig skin from different formulations.

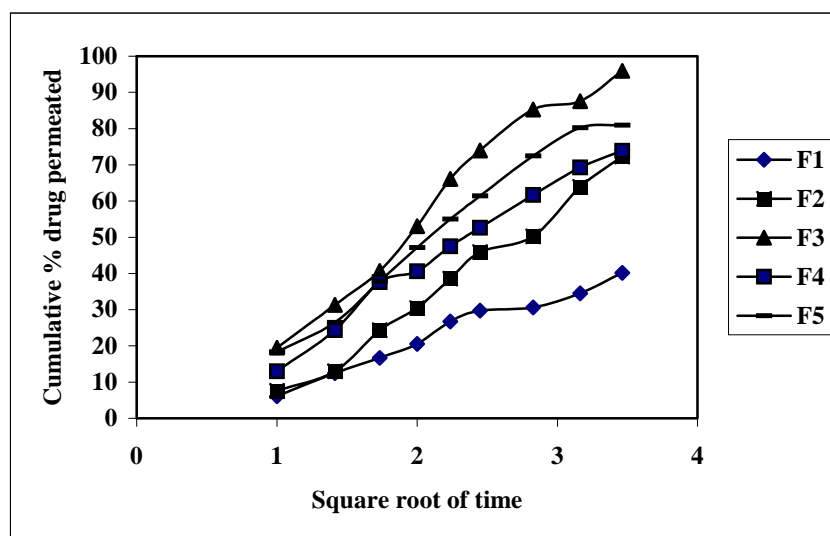


Figure 2. Higuchi's Plot of permeation of salbutamol sulphate

## CONCLUSION

Eudragit RL100-PVP transdermal films with propylene glycol as plasticizer were found to be promising for controlled release of salbutamol sulphate. Incorporation of PEG-400 and tween 60 into the films enhanced the permeation rate. The prepared films exhibited zero order kinetics and the permeation profile was matrix diffusion type.

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