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### Formulation of transdermal patch of Carvedilol by using novel polymers

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#### ABSTRACT

The present investigation was aimed to formulate and optimize the transdermal patch of carvedilol by using the combination of HPMC K100M, HPMC E5, PVA, Eudragit RL100, oleic acid and propylene glycol. Formulation optimization of transdermal patch was done by using  $3^2$  factorial design and by response surface methodology. The formulations were evaluated for thickness, tensile strength, folding endurance, drug content, MVT in 24 hr, moisture content. The values for these were practically acceptable. The *in vitro* permeation studies showed higher permeation of carvedilol with permeation rate ranges from 0.964 to 1.616 mg/cm<sup>2</sup>/hr. The kinetic treatment of permeation data reveals zero-order drug release. Stability studies of the optimized batch at  $25 \pm 2$  °C, 4 °C and  $45 \pm 2$  °C showed no significant alteration in drug content.

**Keywords:** Transdermal patch, HPMC K100M, HPMC E5, PVA, Eudragit RL100.

#### INTRODUCTION

Currently transdermal drug delivery is one of the most promising methods for drug application. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation via skin. The transdermal route offers several advantages over conventional dosage forms such as tablets and injections, including avoidance of first-pass metabolism by the liver. Transdermal drug delivery systems are devices containing drug of defined surface area that delivers a pre-determined amount of drug to the surface of intact skin at a pre-defined rate. This system overcomes the disadvantages associated with oral products like first pass hepatic metabolism, reduced bioavailability dose dumping and dosing inflexibility. Systemic hypertension represents a significant risk factor for the development of atherosclerotic coronary artery disease and myocardial infarction and congestive heart failure. A major barrier to the management of hypertension is the extent to which patient comply with the treatment regime.

Transdermally delivered antihypertensives provides the patient a unique and convenient dosing schedule while providing nearly constant serum levels of medication over a prolonged period.

Carvedilol is the most widely prescribed drug in the long term treatment of hypertension. Carvedilol (non-cardioselective $\beta$ -blocker) is an antihypertensive used in the management of hypertension, angina pectoris and heart failure. But its oral bioavailability is about 25-35% only due to its significant first pass metabolism by cytochrome P450. Carvedilol has a short plasma half-life of 6 hours. Long term therapy of hypertension by carvedilol oral administration may result in poor patient compliance because of low bioavailability and short plasma half-life, leading to increase frequency of administration. The drug carvedilol (CDL) has gastrointestinal side effects such as diarrhea, gastrointestinal pain and gastric irritation.

Carvedilol was chosen as the model candidate for this study since it possesses near ideal characteristics that a drug must have in formulating a transdermal drug delivery system: low molecular weight, a favourable logarithmic partition coefficient, smaller dose range, short plasma half-life, poor oral bioavailability and high degree of first-pass metabolism. It also means multiple daily administrations with subsequent lack of patient compliance. The aim of the present investigation was to develop and evaluate transdermal patches of carvedilol to provide drug at a controlled-release rate with a goal of reducing the frequency of oral administration for effective treatment of hypertension and left ventricular dysfunction.

## MATERIALS AND METHODS

Carvedilol was received as a gift sample from Sun Pharmaceuticals, India. HPMC E5, HPMC K100M were received from Colorcon Asia Pvt. Ltd, India. All other chemicals were of analytical grade and were used as procured.

### Preparation of transdermal patch of carvedilol

A 3<sup>2</sup> factorial design was used for the formulation of transdermal patch of carvedilol. Transdermal patches were prepared by solvent evaporation technique and by incorporating permeation enhancers (oleic acid and PEG-400) in a glass mold with one side open and aluminum foil as a substrate. The backing membrane (63.64 cm<sup>2</sup> area) was cast by pouring a 5% solution of polyvinyl alcohol and drying at 65 °C. The drug reservoir was prepared by dissolving HPMC K100M and HPMC E5 in different proportions in distilled water. Dibutyl phthalate 25 % w/w of polymer composition was used as a plasticizer. Carvedilol (in 10 ml methanol) was added into the above solution with stirring. The obtained homogeneous solution was cast on a backing membrane and dried at 65 °C for 4-5 hours. The rate controlling membrane was cast on the reservoir using 5 % Eudragit RL 100 in dichloromethane and 25 % propylene glycol. The dried cast films were then detached from the aluminum foil and films were cut to generate transdermal patch of 2.0 cm diameter and the formulated patches were stored in dessicator.

### Evaluation of transdermal patches of carvedilol

The formulated batches of carvedilol transdermal patch were evaluated for their physicochemical properties such as thickness, tensile strength, folding endurance, drug content, moisture vapour transmission and moisture content.

Table: 1 Composition of transdermal patch of carvedilol

Batch	Backing layer (% w/v)	Drug reservoir (60 % w/v)		Rate controlling membrane (% w/v)	Permeation enhancer ratio (10 %v/v)	
		Ratio of polymer			Oleic acid	Propylene glycol
	PVA	HPMC K100M	HPMC E5	Eudragit RL100		
F1	5	1	3	4	1	0
F2	5	1	5	4	1	1
F3	5	1	7	4	1	2
F4	5	1	7	4	1	0
F5	5	1	5	4	1	3
F6	5	1	3	4	1	1
F7	5	1	7	4	1	2
F8	5	1	3	4	1	1
F9	5	1	5	4	1	3

### In-vitro permeation study of transdermal patch

A Franz diffusion cell was used in this experiment. The Franz diffusion cell was fabricated from borosilicate glass and consisted of two compartments i.e. receptor and donor. The cell had lower jacketed halve through which water maintained at  $37 \pm 5^\circ\text{C}$  was circulated and this lower halve had an effective receptor volume of 12 ml and skin surface area of  $3.14 \text{ cm}^2$ . The two halves of the cell were secured in place with the help of strong metallic clips. The receptor solution was stirred by a teflon bead of 12 mm length on a magnetic stirrer.

The in-vitro permeation study of fabricated transdermal patches of carvedilol was carried out by using excised rat abdominal skin and Franz diffusion cell. The skin was sandwiched between donor and receptor compartments of the diffusion cell, so that the epidermis faces the donor compartment. A 2.0 cm diameter patch was placed in intimate contact with the stratum corneum side of the skin; the top side was covered with aluminum foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 12ml of normal saline. The cell contents were stirred with a magnetic stirrer and a temperature of  $37 \pm 5^\circ\text{C}$  was maintained throughout the experiment. Samples of 1ml were withdrawn through the sampling port at different time intervals for a period of 24 hr, simultaneously replacing equal volume by phosphate buffer pH 7.4 after each withdrawal. The samples were analyzed spectrophotometrically at 241.0 nm.

### Short-term stability study of carvedilol transdermal patch

Stability study of the transdermal patches was performed at room temperature ( $25 \pm 2^\circ\text{C}$ ), at refrigeration temperature ( $4^\circ\text{C}$ ) and at elevated temperature ( $45 \pm 2^\circ\text{C}$ ) for one month. The patch was subjected for drug content analysis after 0, 5, 10, 15, 20, 25 and 30<sup>th</sup> day to illustrate the effect of aging on the drug content of the transdermal patch.

## RESULTS AND DISCUSSION

The thickness of the patch varied from  $87.3 \pm 1.00$  to  $96.2 \pm 0.92 \mu\text{m}$  ( $n=3$ ). The casting of the rate controlling membrane of Eudragit RL100 increased the thickness. The tensile strength of the patches was found to vary with the ratio of polymer composition. It was found to vary between  $1.125 \pm 0.11 \text{ kg/mm}^2$  to  $3.920 \pm 0.03 \text{ kg/mm}^2$ . The transdermal patches containing higher ratio of polymer showed higher tensile strength. The Tensile strength of transdermal patches may be also

due to availability of oleic acid and propylene glycol in the matrix. The folding endurance measures the ability of patch to withstand rupture. The values for folding endurance was in the range of  $211 \pm 0.25$  to  $255 \pm 1.37$ . The patch F8 representing the least value while patch F5 highest value: the reason for this could be the availability of higher amount of HPMC E5 and propylene glycol in F5 as compare to F8. The drug content was between  $27 \pm 0.82$  to  $35 \pm 0.27$  mg per patch. The MVT of patches varies from  $0.153 \pm 0.06$  to  $0.193 \pm 0.01$  and percent moisture content from 1.96 to 3.00 %. These results suggest that casting of matrix reservoir with Eudragit RL100 decreased the values of moisture vapour transmission and subsequently percent moisture content.

The *in-vitro* drug permeation studies of factorial formulations of transdermal patches were performed on freshly excised rat abdominal skin. The results of these studies showed marked variations in permeation profiles of carvedilol. The reason for this could be a different permeation enhancement effects exerted by different ratio of permeation enhancer (oleic acid: propylene glycol). The formulation F6 showed highest and linear permeation of carvedilol at the end of 12 hours. This indicated that oleic acid and propylene glycol in the ratio of 1:1 has significant effect on permeation of carvedilol. This conclusion was supported by the higher permeation rate values of formulation F6 ( $2.005 \text{ mg/cm}^2/\text{h}$ ).

The results of stability study showed no significant alteration in drug content of optimized fabricated transdermal patches of carvedilol.

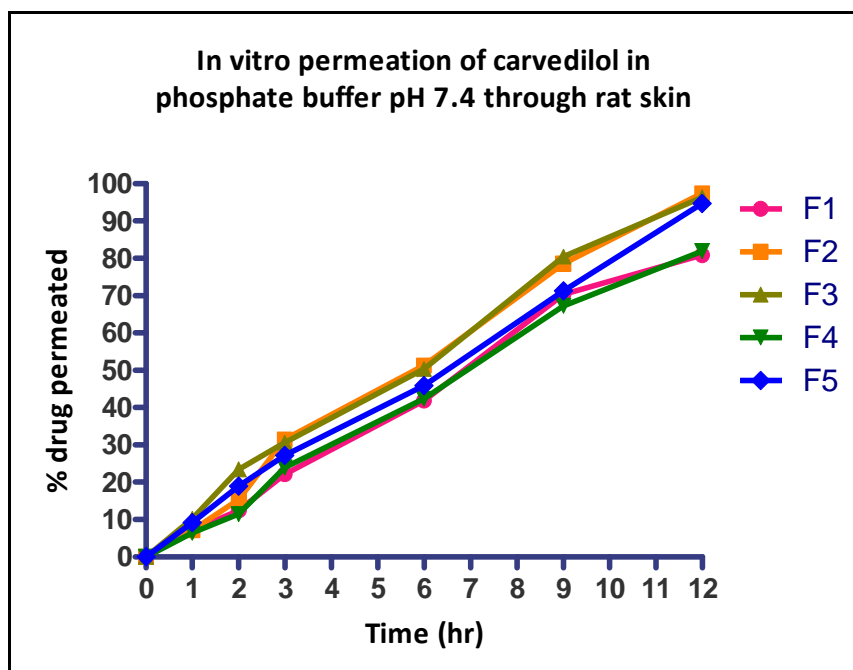


Fig. 1: Permeation profile of carvedilol from transdermal patch (F1-F5)

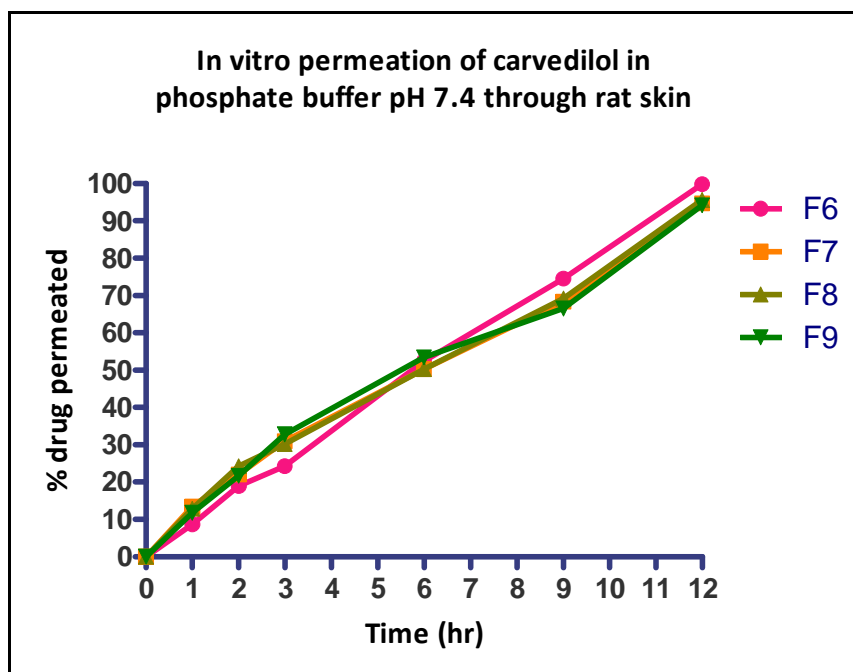


Fig. 2: Permeation profile of carvedilol from transdermal patch (F6-F9)

### CONCLUSION

The carvedilol transdermal patch was prepared by utilizing  $3^2$  full factorial experimental design by using HPMC K100M and HPMC E5 with mixed system of penetration enhancer containing oleic acid and propylene glycol. The results of in-vitro skin permeation studies performed using freshly excised abdominal skin of rat showed highest permeation rate of carvedilol. The higher permeation responses of the formulations may be attributed to permeation enhancing effect of oleic acid in presence of propylene glycol.

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