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Research Article

PREPARATION OF CARVEDILOL TRANSDERMAL PATCH AND THE EFFECT OF PROPYLENE GLYCOL ON PERMEATION

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ABSTRACT

Transdermal drug delivery systems of carvedilol have been formulated by using solvent casting method. Matrix patches were prepared by using hydroxyl propyl methyl cellulose (HPMC) and eudragit RS100 polymers by incorporating dibutyl phthalate and propylene glycol as plasticizer and permeation enhancer, respectively. All the patches were uniform with respect to physicochemical and scanning electron microscopy (SEM) evaluation. The *in-vitro* permeation studies indicated that matrix patches containing hydroxyl propyl methyl cellulose and eudragit RS100 in the ratio of 1:4 shown better release. Propylene glycol was incorporated at different concentration to enhance the permeation of drug. The formulation containing 30% w/w propylene glycol has exhibited better enhancement for the permeation of carvedilol. Skin irritation study revealed that the free of irritation. The selected patch was found to be stable at 37^{o}C and 45^{o}C with respect to their physical parameters and drug content.

Keywords: Transdermal patch, Eudragit RS 100

INTRODUCTION

There has been increased interest and challenges in the delivery of an active ingredient through the skin. Transdermal drug delivery systems are a class of novel drug delivery systems, which are gaining worldwide accolade, as evidenced by the numerous scientific documents being published. Transdermal drug delivery offers many advantages such as reduced side effects, less frequent administration to produce the desired constant plasma concentration associated with improved patient compliance, elimination of the first-pass effect, sustained drug delivery and interruption of treatment when necessary.[1, 2]

Carvedilol, a cardiovascular drug that is currently used for the treatment of hypertension in many countries. The reduction in blood pressure produced by carvedilol results primarily from beta-adrenoceptor blockade and vasodilatation, resulting from alpha 1-adrenoceptor blockade. These actions as well as several other carvedilol activities are associated with cardioprotection in animal models that occurs to a degree that is greater than that observed with other drugs. The multiple actions of carvedilol may also provide that underlying rational for the use of the drug in the treatment of coronary artery disease and congestive heart failure.[3]

Carvedilol is well absorbed from the gastrointestinal tract but is subjected to significant first-pass metabolism in the liver. Oral bioavailability of the drug has been reported about 25%. It has a short biological half-life (2.2±0.3h); longer half-lives of about 6h have been measured at low concentration. [4, 5]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 mass, high lipid solubility, effective in low plasma concentration as well as high degree of first-pass metabolism. It also means multiple daily administrations with subsequent lack of patient compliance. Reservoir type transdermal patch of carvedilol has been already reported based on the use of HPMC and eudragit RS100 as drug reservoir and rate controlling membrane respectively and surfactant (Tween 80 or Span 80) as permeation enhancer.[6] The reported transdermal formulation of carvedilol did not involve any attempt to use of propylene glycol as permeation enhancer in the formulation of carvedilol matrix patch.

In the present study, it was envisaged to select the suitable polymer composition of HPMC and eudragit RS100 for the transdermal delivery of carvedilol and the effect of propylene glycol was evaluated.

EXPERIMENTAL

MATERIALS AND METHODS

Carvedilol was gift from Sun Pharmaceutical Industries Ltd. (India). Eudragit RS100 was supplied by Dabur Research Foundation (India). HPMC and

propylene glycol were purchased from Loba Chemie Ltd. (India). All the other chemicals were of analytical grade.

Drug partition coefficient

Partition coefficient study was performed using n-octanol as the oil phase and phosphate buffer (pH 7.4) as the aqueous phase. The two phases were mixed in equal quantities and were saturated with each other on a mechanical shaker at 37°C for 24h. The saturated phases were separated by separating funnel. Standard plots of the drug were prepared from both phosphate buffer pH 7.4 and n-octanol. Equal volume (10mL) of the two phases were placed in triplicate in conical flasks and, to each, 100mg of drug was added. The flasks were shaken occasionally for 24h to achieve complete partitioning. The two phases were separated by centrifugation at 1500rpm for 5min and were then analyzed for respective drug content.[7]

Method of preparation of transdermal patch

Transdermal patches containing carvedilol were prepared by solvent casting method using aluminum foil as the backing membrane. Transdermal patches were prepared according to the formula shown in Table 1. Eudragit RS100 and HPMC were weighed in requisite ratios and they were then dissolved in methanol as solvent using magnetic stirrer. Carvedilol (20mg) was added into homogenous dispersion under slow stirring with a magnetic stirrer. Dibutyl phthalate 30%w/w of polymer composition was used as plasticizer, added to the above dispersion under continuous stirring. The uniform dispersion was casted on aluminum backing membrane. The rate of evaporation of solvent was controlled by inverting cut funnel over the patches. After 24h, the dried films were taken out and stored in desiccator. Different concentration of propylene glycol as permeation was incorporated in the formulation F_{10}, F_{11}, F_{12}, and F_{13}.

Physicochemical evaluation

The films were evaluated for the following physicochemical properties:

Thickness[8]: The thickness of patches was measured at five different places using a micrometer (Mitutoyo Co; Japan) and mean values were calculated.

Weight variation study[9]: The patches were subjected to weight variation by individually weighing five different randomly selected patches. Such determination was carried out for each formulation.

Folding endurance[10]: This was determined by repeatedly folding the film at the same place until it broke. The number of times the films could be folded at the same place without breaking/cracking gave the value of folding endurance.

Drug content uniformity: Transdermal patches with an area of 2cm² was cut into small pieces and transferred into 100ml phosphate buffer (pH 7.4) and shaken for 6h to extract the drug. A blank was prepared using a drug-free patch treated similarly. The solutions were filtered through a 0.45µm membrane, diluted suitably and absorbance was measured at 241nm in a UV-Vis Spectrophotometer (Shimadzu, Japan).

Moisture content[10]: The prepared films were marked, then weighed individually and kept in desiccator containing activated silica at room temperature for 24h. The films were weighed again, until constant weight is achieved. The % moisture content was calculated as a difference between initial and final weight with respect to final weight.

$$\%\ \text{Moisture content (MC)} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \quad ---(2)$$

Percentage moisture absorption: The films were weighed accurately and placed in the desiccator containing 100mL of saturated solution of aluminum chloride, which maintains 79.50%RH. After, three days, the films were taken out and weighed. The percentage moisture absorption was calculated using the formula[11]

$$\text{Percentage moisture absorption} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \quad ---(3)$$

Percentage moisture loss: The films were weighed accurately and kept in a desiccator containing anhydrous calcium chloride. After three days, the films were taken out and weighed. The moisture loss was calculated using the formula[11]

$$\text{Percentage moisture loss} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \quad ---(4)$$

Water vapour transmission rate: Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1gm anhydrous calcium chloride was placed in the cells and the respective polymer films were fixed over the brim. The cells were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride to maintain a humidity of 84%. The cells were taken out and weighed after 6, 12, 24, 36, 48 and 72 hrs of storage.

The amount of water vapour transmitted was found using the formula. [12]

$$\text{Water vapour transmission rate} = \frac{\text{Final weight - Initial weight}}{\text{Time}} \times \text{Area} \quad ---(5)$$

Water vapor transmission rate is usually expressed as the number of grams of moisture gained/h/cm^2.

In-vitro permeation across mice abdominal skin

Preparation of mice skin[11]**:** The Swiss albino mice with a weight range of 20-25gm were decapitated. The abdominal skin of excised hairless mice skin was separated along the epidermal junction and it was kept in water bath, which was maintained at 60^{o}C for 50s. The heat-treated skin was cleared of its subcutaneous fatty substances and immediately kept in normal saline solution for flattering and smoothing.

Permeation studies: Permeation studies were carried out using vertically assembled Keshary-Chein diffusion cells having diffusional surface area of 5.31cm^2. The full thickness skin samples with surface area of 5.31cm^2 was mounted on Keshary-Chein diffusion cell, with the stratum corneum side in intimate contact with the carvedilol releasing surface of the film and the dermal side facing the receptor solution. The receptor compartment of the cell was filled with 60mL of saline phosphate buffer (pH 7.4) and the temperature was maintained at 37±1^{o}C. The samples were withdrawn from receptor side at predetermined intervals (1, 2, 4, 6, 8, 10 and 12h) and replaced with same volume of fresh pre-warmed saline phosphate buffer (pH 7.4) to maintain the sink condition. The samples were then analyzed by UV-Vis spectrophotometer at 241nm.

Skin irritation test[13]**:** A primary skin irritation test was performed since skin is a vital organ through which drug is transported. The test was carried out on healthy rabbits weighing 1.3 to 1.5 kg. Drug free polymeric film of diameter 4.1cm were used as control. The dorsal surface of rabbits was cleared well and the hair was removed by using a depilatory preparation. The skin was cleared with rectified spirit. The patches were applied to the shaved skin of rabbits and secured using adhesive tape USP (Leucoplast™). On one side of the back control patch (without any drug, group I) and on the other side an experimental patch (group II) were secured. A 0.8%v/v aqueous solution of formaldehyde was applied as a standard irritant (group III) and its effect was compared with test. The animals were observed for any size of erythema or oedema for a period of 7days. All the experimental protocols involving laboratory animals were approved by the IAEC.

Stability studies[14]**:** All the film was exposed to two selected temperature of 37^{o}C and 45^{o}C in two different hot air ovens. Transdermal films with an area of 15.63cm^2 were kept in the oven for a period of four weeks. The film sample with an area of 1cm^2 was cut from each formulation, and it was analyzed for the physical parameter and drug content at the end of every week. The average of triplicate reading was taken.

Scanning electron microscopy (SEM): Sample, for the SEM was prepared by sprinkling the film on one side of a double adhesive stub. The stub was then coated with gold under vacuum (Fine coat, in sputter, EC-1100). The transdermal films were then observed under scanning electron microscope (JEOL, JSM-6360 Scanning Electron Microscope, Japan) at 15kV. The samples include blank film (without drug), film before permeation study and after permeation study.

RESULTS AND DISCUSSION

n-octanol and phosphate buffer (pH 7.4) are considered to be the standard system for determining the drug partition coefficient between skin and *in-vitro* fluid. The logarithmic rule of the partition coefficient (logP) was found to be 0.80±0.02. The results revealed that the drug possesses sufficient lipophilicity, which meets the requirement of formulating it into a transdermal patch.

In the present study, transdermal patches of carvedilol were formulated using different ratios of hydrophilic polymer (HPMC) and lipophilic polymer (Eudragit RS100) as polymer matrix and evaluated them to select the suitable formulation. The effects of propylene glycol as permeation enhancer in the permeation of carvedilol from the optimized transdermal patch were investigated.

Table 1: Detailed formulas of transdermal patch containing carvedilol

Formulation Code	Ingredient				
	Carvedilol (mg)	Eudragit RS100 (mg)	HPMC (mg)	Dibutyl phthalate (%w/w)	Propylene glycol (%w/w)
F_1	20	250	150	30	-
F_2	20	300	100	30	-
F_3	20	240	160	30	-
F_4	20	320	80	30	-
F_5	20	228	172	30	-
F_6	20	333	67	30	-
F_7	20	400	-	30	-
F_8	20	290	110	30	-
F_9	20	267	133	30	-
F_{10}	20	320	80	30	25
F_{11}	20	320	80	30	30
F_{12}	20	320	80	30	35
F_{13}	20	320	80	30	40

Table 2: Physical parameter and drug content of the transdermal patch

Batch Code	*Thickness (mm)	*Weight (mg)	**Folding endurance	**Drug content	**[1]%MC (w/w)	**[2]%MA	**[3]%ML	**[4]WVTR ($gm/cm^2/h)\times10^{-4}$
F1	0.46±0.04	530.6±0.36	5	98.96±0.16	4.76±0.07	9.17±1.31	4.78±0.24	2.34±0.06
F_2	0.43±0.05	561.0±0.32	5	96.67±0.38	4.99±0.03	9.11±1.37	4.23±0.52	2.25±0.07
F_3	0.37±0.03	544.8±0.42	6	97.30±0.26	5.00±0.12	12.12±1.40	6.10±0.63	3.97±0.02
F_4	0.45±0.04	532.6±0.41	4	98.90±0.30	3.75±0.02	8.24±0.75	3.97±1.02	2.07±0.01
F_5	0.46±0.02	530.6±0.38	6	97.82±0.42	3.99±0.04	15.75±2.13	6.17±1.51	4.73±0.01
F_6	0.42±0.05	520.2±0.41	3	98.80±0.32	4.60±0.10	6.25±0.18	2.35±1.03	1.59±0.02
F_7	0.42±0.06	540.3±0.44	2	98.42±0.22	5.23±0.08	4.11±1.96	1.67±0.63	0.97±0.03
F_8	0.48±0.02	534.4±0.36	5	97.40±0.24	3.65±0.04	6.07±2.07	1.98±0.32	1.07±0.02
F_9	0.45±0.05	540.3±0.44	3	98.82±0.28	3.87±0.06	10.73±1.73	5.11±1.02	2.75±0.05

*Average of five observation; ** Average of six observation; [1]Percentage moisture content; [2]Percentage moisture absorption; [3]Percentage moisture loss; [4]water vapor transmission rate.

The physicochemical properties of carvedilol trandermal patches were presented in the Table 2. They were found to be uniform in their weight and thickness with low SD values. The folding endurance measures the ability of patch to withstand rupture. The folding endurance was found to be increased with increasing HPMC concentration. The WVTR for all the patches was determined and they followed the order: $F_5>F_3>F_1>F_9>F_2>F_4>F_6>F_8>F_7$. The WVTR was found to be increased with increasing in HPMC concentration; which might be attributed to the hydrophilic nature of the HPMC. It was found that the %MA and %ML was increased with increasing in HPMC concentration. The results revealed that the drug content was almost uniform in all the patches with low SD values.

Table 3: Steady state flux, diffusion coefficient, permeability coefficient, enhancement ratio of transdermal formulation

Form. Code	Steady state flux ($\mu g/cm^2.h$)±SD	Diffusion coefficient (cm^2/h) ±SD	Permeability coefficient (cm/h) ±SD	Enhancement ratio ±SD
F_1	63.17±1.12	8.95±0.10	44.89±0.18	-
F_2	53.24±2.13	7.50±0.13	33.57±0.12	-
F_3	67.57±0.13	11.11±0.05	40.44±0.06	-
F_4	33.68±0.07	7.05±0.01	21.97±0.02	1
F_5	75.07±1.21	16.66±1.02	41.81±0.14	-
F_6	20.37±0.32	6.97±0.30	12.22±0.21	-
F_7	16.20±1.06	4.54±0.32	9.57±0.20	-
F_8	55.44±0.78	8.82±0.12	24.34±0.23	-
F_9	58.64±0.21	8.95±0.32	25.78±0.22	-
F_{10}	40.34±1.02	8.95±0.10	22.68±0.03	1.03±0.04
F_{11}	46.71±0.36	10.95±0.02	29.68±0.02	1.35±0.27
F_{12}	48.46±0.22	12.76±0.12	28.71±0.04	1.30±0.03
F_{13}	49.60±0.10	8.82±0.25	28.27±0.07	1.28±0.02

Table 4: Kinetics of *in-vitro* carvedilol permeation across mouse skin from transdermal patch

Formulation Code	Zero-order		First-order		Korsmeyer-Peppas	
	ko (mgh^{-1})	R^2	k_1 (h^{-1})	R^2	n	R^2
F_1	0.021	0.995	55.064	0.952	0.980	0.992
F_2	0.394	0.989	77.800	0.960	1.082	0.995
F_3	0.392	0.988	44.648	0.919	1.118	0.993
F_4	0.634	0.991	135.429	0.950	1.206	0.999
F_5	0.214	0.971	57.337	0.908	1.042	0.996
F_6	0.431	0.989	256.910	0.981	1.112	0.997
F_7	0.551	0.974	488.560	0.969	1.206	0.998
F_8	0.930	0.984	130.135	0.968	1.080	0.995
F_9	0.426	0.967	112.722	0.945	1.098	0.994
F_{10}	0.418	0.980	110.311	0.955	0.998	0.003
F_{11}	0.165	0.990	91.207	0.948	1.044	0.996
F_{12}	0.407	0.992	89.327	0.968	1.106	0.998
F_{13}	0.470	0.987	85.502	0.960	1.038	0.997

Drug permeation profile from different formulations are shown in Figure 1 .*In-vitro* release of carvedilol across mouse skin from F_7 and F_6 formulation showed only 10.81% and 19.51% at the end of 12h, respectively. The flux was calculated from the slope of linear graph, and it was found to be 16.20 and 20.37$\mu g/cm^2.h$, diffusion coefficient was 4.54×10^{-6} and 6.97×10^{-6} cm^2/h. respectively. It was evident from the above result that there was a lower flux and lower diffusion rate through the mouse skin. However, at the end of 12h, *in-vitro* release of carvedilol across mouse skin from formulation F_2, F_8, F_9, F_1, F_3, and F_5 were 47.09%, 48.57%, 51.75%, 65.40%, 73.53% and 80.48%, respectively. The flux for the formulation of F_2, F_8, F_9, F_1, F_3 and F_5 was 53.24, 55.44, 58.46, 63.17, 67.57 and 75.07$\mu g/cm^2.h$, diffusion coefficient was

7.50×10^{-6}, 8.82×10^{-6}, 8.95×10^{-6}, 8.95×10^{-6}, 11.11×10^{-6} and 16.66×10^{-6}. It was revealed from the above results that with decreasing in the concentration of eudragit RS100, the carvedilol released also increased. It might be due to lower proportion of quaternary ammonium in eudragit RS100 for prolonged release of carvedilol.[15]

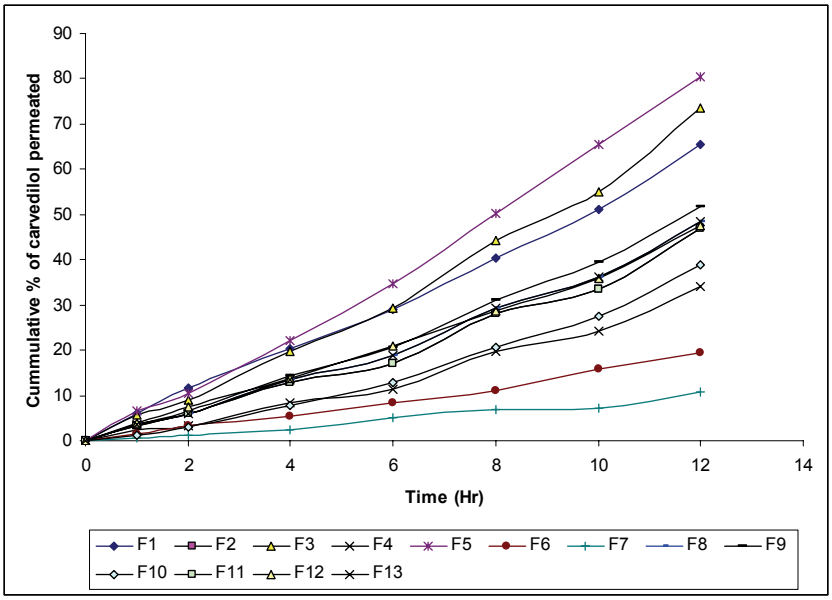
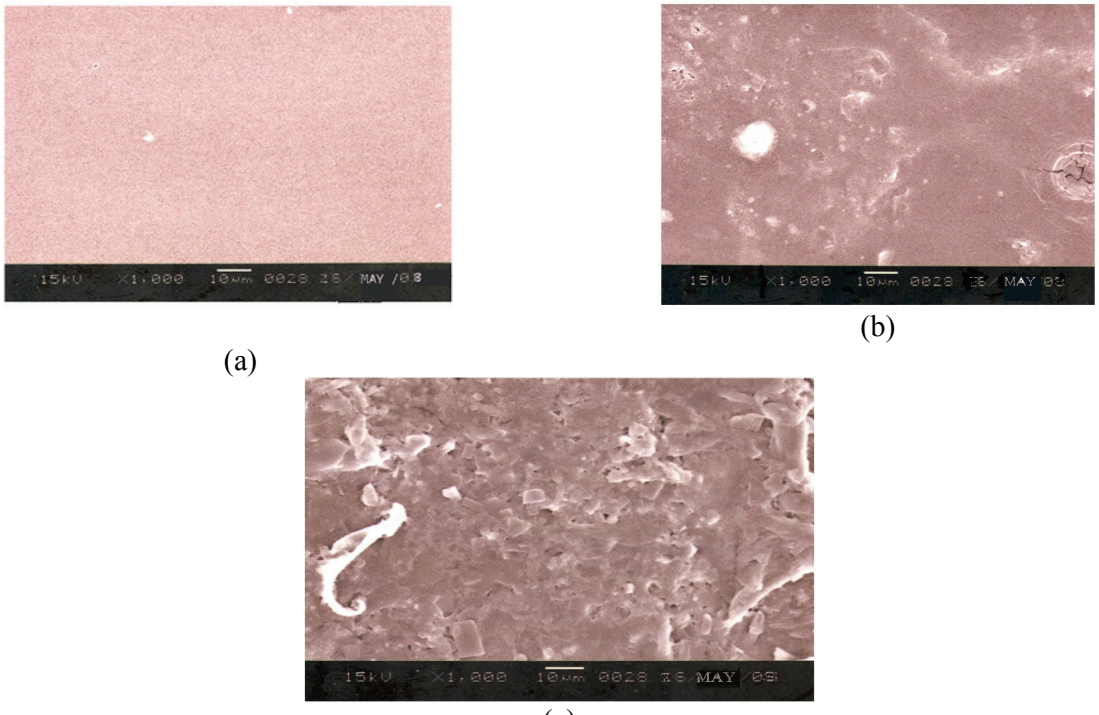


Fig. 1: ***In-vitro*** **permeation profile of carvedilol through excised hairless mouse skin (mean± sd, n=3)**



(a) (b) (c)

Fig. 2: **SEM photograph of (a) blank film; (b) carvedilol loaded film before permeation; (c) carvedilol loaded film after permeation.**

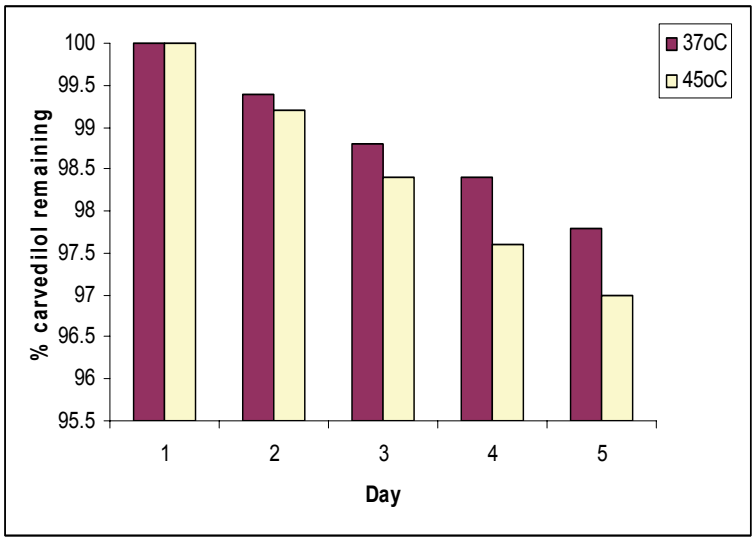


Fig. 3: stability studies of f_{11} formulation at 37°c and 45°c

It was revealed from the above result that with increasing in the concentration of HPMC the carvedilol released also increased. It might be attributed due to the hydrophilic nature of HPMC. In the formulation of F_4, containing eudragit RS100 and HPMC in the ratio of 4:1, showed 34.22% carvedilol release at the end of 12h study. The flux and diffusion coefficient was found 33.68µg/cm^2.h and 7.05×10^{-6} cm^2/h respectively. The physicochemical properties of the formulation F_4 depicted suitable formulation for the transdermal delivery. Therefore, F_4 formulation was selected as a optimized formulation. In the latter studies, the effect of propylene glycol as permeation enhancer on the release of carvedilol from the transdermal formulation was conducted. Various concentration of propylene glycol (25, 30, 35 and 40%w/w) was used for this study. A marked effect of propylene glycol on carvedilol permeation was observed for transdermal formulation containing propylene glycol. The steady state flux values were ranging from 40.34±1.02 to 49.60±0.10 µg/cm^2.h from transdermal formulation containing 25%w/w to 40%w/w of propylene glycol glycol. It may be observed from the results (Table 3) that as propylene glycol concentration increased from 25%w/w to 30%w/w, the enhancement ratio increased markedly. However, further increased in the propylene glycol, there was little increased in the enhancement ratio. Therefore, it was concluded that the formulation F_{11} containing 30%w/w of propylene glycol as permeation enhancer is suitable for the transdermal delivery of carvedilol.

To know the mechanism of drug release, the data were fitted to models representing zero-order, first-order and Korsmeyer-Peppas.[16] It was found that the release of carvedilol from the transdermal patch followed zero-order kinetics. The coefficient of determination (R^2) was found to be much closer to 1 for the Kormeyer-Peppas equation. Slope values (n>1.0) suggest that the drug permeation from transdermal patches followed the supercase II transport mechanism, possibly owing to chain disentanglement and swelling of hydrophilic polymer.

A primary skin irritation test of patch F_{11} on rabbit was studies. No signs of erythema, oedema or ulceration were observed on the skin of albino rabbits after 7days.

The formulation F_{11} was observed for the changes of appearance, flexibility and drug content at regular interval of one week for one month. The film was found to be stable at 37°C and 45°C with respect to their physical parameters and drug content.

Figure 2a, 2b and 2c represents the SEM photographs of blank transdermal patch; carvedilol loaded transdermal patch before permeation and after permeation study, respectively. The SEM of the drug loaded patch clearly indicates that carvedilol is molecularly dissolved in the patch. After permeation experiment the film showed that the presence of pores/channels indicating the drug permeation is diffusion controlled.

CONCLUSION

Thin, flexible and smooth films were obtained with HPMC and eudragit RS100 polymers using dibutyl phthalate as plasticizers. Thickness weight and drug content of all the formulation remained uniformly with low SD values. The WVTR, %ML and %MA was increased with increasing in HPMC concentration. Transdermal patch containing 30%w/w of polyethylene glycol showed good permeation of carvedilol through mouse skin. No skin irritation was

observed for the selected formulation. The selected formulation was found to be stable at 37°C and 45°C. SEM studies confirmed that there was uniform distribution of drug in the selected formulation and release of drug was diffusion controlled. It may concluded that carvedilol transdermal matrix patch containing HPMC and eudragit RS100 in the ratio of 1:4 and propylene glycol (30%w/w) have shown promising results. Studies have shown promising results; hence, there is a scope for further pharmacodynamic and pharmacokinetic evaluation.

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