Formulation Characterization and Evaluation of Matrix type Transdermal Patches of Carvedilol

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Abstract: The present study was carried out to formulate, characterize and evaluate a matrix-type transdermal formulation containing Carvedilol with different ratios of polymer (Eudragit RL100, HPMC and Ethyl Cellulose) combinations plasticized with dibutylpthalate by the solvent evaporation technique. The interference of the polymers were ruled out by infrared spectroscopy. *In-vitro* release study was performed using Franz diffusion cell with cellophane membrane as barrier. The prepared patches were tested for their physicochemical characteristics such as thickness, drug content uniformity, Percentage moisture uptake and folding endurance. *In-vitro* release studies of Carvedilol-loaded patches in phosphate buffer saline of pH 7.4 exhibited drug release in the range of 52% to 81% in 24h for the formulations F1-F6. The *in-vitro* drug permeability studies of optimized formulation F1 was found to be 48.67 µg/cm2/hr. Data of *in vitro* release from patches were fit in to different equations and kinetic models to explain release kinetics. The release of Carvedilol from the optimized formulation F1 follows zero order kinetics and the mechanism of drug release was concluded as diffusion controlled. The developed transdermal patches increase the efficacy of Carvedilol for the therapy of hypertension.

***Keywords*:** Carvedilol; Transdermal; Eudragit RL 100, HPMC E15, EC; In-vitro permeation.

1. INTRODUCTION

Transdermal drug delivery systems (TDDS) are adhesive drug containing devices of defined surface area that delivers predetermined amount of drug to the intact skin at a preprogrammed rate[1]. The transdermal delivery has gained importance in recent years[2]. The transdermal drug delivery system has potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood levels for longer period of time resulting in a reduction of dosing frequency, improved bioavailability, decreased gastrointestinal irritation that occur due to local contact with gastric mucosa, and improved patient compliance[3].

2. PLAN OF WORK

A) Preparation of transdermal patches.
B) Physico-chemical evaluation

1. Physical appearance 2. Folding endurance 3. Thickness of the film 4. Weight uniformity
5. Drug content 6. Percentage moisture uptake 7.Percentage moisture content 8. *In-vitro* diffusion study

2.1 Preparation of Transdermal patches

Transdermal patches containing Carvedilol were prepared by solvent evaporation method using varying ratios of different grades of polymers. The polymers Eudragit RL100, HPMC E15 and Ethyl cellulose (total weight = 1000 mg) were weighed in requisite ratios and dissolved in 15 ml of methanol to form a 15% w/v solution. To the above solution 110mg of Carvedilol is then added and stirred by using a magnetic stirrer until drug dissolves. Then 20% of plasticizer, DBP was added to the above solution. The solution was poured in a glass petri dish of 65cm^2 area and dried at room temperature for 24 hours. The organic solvent evaporates to leave stable patches.

Table No.1: Formulation design of Carvedilol transdermal patches

Formulation	Drug (mg)	HPMC E15 (mg)	EC (mg)	Eudragit RL100 (mg)	Dibutylpthalate (%)	Methanol (ml)
F1	110	1000	-	-	20	15
F2	110	-	1000	-	20	15
F3	110	-	-	1000	20	15
F4	110	800	200	-	20	15
F5	110	600	400	-	20	15
F6	110	400	200	-	20	15

2.2 Evaluation of transdermal formulation

Physical appearance

All the transdermal systems were visually inspected for colour, clarity, flexibility and smoothness.

Folding Endurance

Folding endurance of the film was determined manually by folding a small strip of the film (4×3 cms) at the same place till it breaks. The maximum number of folding operation done at the same place of the film without breaking, gives the

value of folding endurance, where the cracking point of the films were considered as the end point.

Thickness of the films

The thickness of the patches was measured at three different places by using a Digital Screw Gauge micrometer (Mitutoyo, Japan) and mean thickness was calculated.

Weight uniformity

The dried patches were weighed on electronic balance (Sartorius UK). The average
of 3 observations was calculated.

Drug content

Transdermal systems of specified area (5.088 cm^2) was cut into small pieces and taken into 50 ml volumetric flask, 25ml of phosphate buffer saline pH 7.4 was added and gently heated to 450˚C for 15 min and kept for 24 hrs with occasional shaking. Then the volume was made up to 50ml again with phosphate buffer saline pH 7.4 and further dilutions were made from this solution. Similarly, a blank was carried out using a drug free patch. The solutions were filtered and absorbances were read at 242 nm by UV spectrophotometer.

Percentage moisture uptake

The weighed films were kept in a desiccator at room temperature for 24 hours[15]. They were then taken out and exposed to 84% relative humidity using a saturated solution of potassium chloride in a desiccator until a constant weight was achieved[63]. Then the films were weighed and percentage moisture uptake was calculated by using the following formula.

Percentage moisture uptake = [Final wt.−Initial wt./Initial wt.]×100 .

Percentage moisture content

The prepared films were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 hours. The films were weighed repeatedly until they showed a constant weight. The percentage moisture content was calculated using the following formula:

Percentage moisture content = [Initial wt.−Final wt./Final wt.]×100.

***In-vitro* Permeation Study**

In vitro permeation studies were carried out from each formulation by using modified Franz diffusion cell. The surface area of the release membrane was 3.14 cm^2. The volume of a receptor medium was 50 ml and composed of phosphate buffer saline (pH 7.4) and stirred by a magnetic bead at 150 rpm. Temperature of the receptor fluid was maintained at 37±0.5^{0}C.

The samples (2ml) were withdrawn at regular intervals (1, 2, 3, 4, 5, 6, 7, 8, 24 hours), filtered and analyzed for drug content from receiver compartment and replaced by same volumes of freshly prepared phosphate buffer saline(pH 7.4).The samples were analyzed by spectrophotometrically at 242nm

3. RESULTS AND DISCUSSION

Table: 2. Data showing physical parameters of Carvedilol transdermal patches

S.NO	Formulation	Folding endurance	Thicknesss (mm)	Weight variation (gm)	% Moisture uptake	% Moisture content	Tensile Strength (kg/mm^2)	Drug content (%)
1	F1	217±13.1	0.110±0.029	1.003	1.05	14.28	0.575±0.01	96.77±0.05
2	F2	170±15.2	0.103±0.023	1.012	0.75	5.45	0.385±0.01	91.45±0.05
3	F3	210±7.50	0.083±0.011	1.063	0.88	3.44	0.424±0.01	89.48±0.6
4	F4	178±6.39	0.100±0.017	1.037	1.71	5.55	0.474±0.00	92.27±0.4
5	F5	179±8.08	0.097±0.028	1.092	1.36	11.11	0.324±0.01	90.72±1.2
6	F6	120±4.72	0.092±0.015	1.097	1.23	7.01	0.384±0.01	96.34±1.0

S.D,±n =3.

***In-vitro* diffusion studies of Carvedilol Transdermal patches**

The *in-vitro* release of Carvedilol across cellophane membrane from formulation F1, F2, F3, F4, F5, F6, were 81%, 52%, 68.3%, 74.9%, 79.53% and 72.9%, respectively. The flux for the formulations was 48.67, 30.27, 42.34, 46.10, 48.71, 44.93 µg/cm2/h and diffusion coefficient was 7.7×10^{-3}, 4.8×10^{-3}, 6.7×10^{-3}, 7.3×10^{-3}, 7.7×10^{-3}, 7.1×10^{-3}.

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 F1, containing HPMCE15 showed 81 % Carvedilol release at the end of 24h study. The physicochemical properties of the formulation F1 depicted suitable formulation for the transdermal delivery. Therefore, F1 formulation was selected as a optimized formulation.

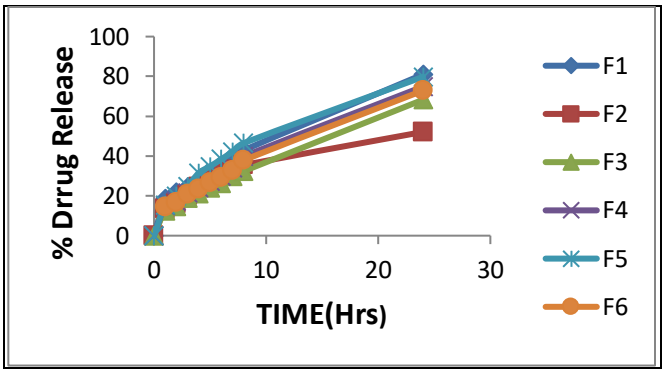

Figure 1: Comparative *in-vitro* diffusion profile of Carvedilol transdermal patches for formulations F1-F6

Permeation data analysis

The permeability parameters of different formulations are given in the following table.

Table 2: Permeability parameters of different formulations of Carvedilol patches

S.NO.	Formulation	Jss± SD (µg/cm2/hr)	Kp± SD *10^{-2} (cm/hr)	Enhancement Ratio (Er)
1	F1	48.67	0.77	1.183609
2	F2	30.27	0.48	0.736138
3	F3	42.34	0.67	1.029669
4	F4	46.10	0.73	1.121109
5	F5	48.71	0.77	1.184582
6	F6	44.93	0.71	1.092656

Drug release kinetics

The release of Carvedilol from the optimized formulation F1 follows zero order kinetics and the mechanism of drug release was concluded as diffusion controlled.

4. CONCLUSION

On the basis of the in vitro characterization it was concluded that Carvedilol could be administered transdermally through matrix type TDDS developed in our laboratory. Transdermal patches consisting of the rate-controlling polymers Eudragit RL100, HPMCE15, EC demonstrated sustained and controlled release of the drug during in vitro permeation

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