International Journal for Pharmaceutical Research Scholars (IJPRS)
ISSN No: 2277-7873
RESEARCH ARTICLE
V-2, I-1, 2013

Formulation and Evaluation of Carvedilol Transdermal Patches by Using Hydrophilic & Hydrophobic Polymers

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Manuscript No: IJPRS/V2/I1/00010, Received On: 16/01/2013, Accepted On: 22/01/2013

ABSTRACT

Carvedilol is an antihypertensive drug use for management of Hypertension. It has the half-life of 6 hr and oral bioavailability of 25% due to first pass metabolism. The total daily dose of Carvedilol is 25 mg, hence it required frequent dosing. Transdermal patches of Carvedilol were prepared for sustained release and improve bioavailability of drug and patient compliance. Different formulations were prepared by varying the amount of HPMC-K4M and Eudragit RS-100 by solvent casting method. The prepared formulations were evaluated for various parameters like thickness, tensile strength, folding endurance, % elongation, % moisture content, % moisture uptake, % drug content, *In-vitro* drug release, *In-vitro* permeation and skin irritation study. A 3^2 full factorial design was applied to check the effect of varying the amount of Eudragit-RS 100 (X_1) and amount of HPMC-K4M (X_2) on the responses i.e. tensile strength and percentage drug released in 20 hr (Q_{20}) as dependent variables. Regression analysis and analysis of variance were performed for dependent variables. *In-vitro* release data were fitted to various models to ascertain kinetic of drug release. The best selected formulation is subjected to *in-Vitro* skin permeation and skin irritation study. Batch F_7 was considered optimum batch which contained 400 mg of Eudragit RS-100 and 600 mg of HPMC-K4M, showed release 95.73% up to 24 hr and was more similar to Zero order release kinetics (r^2=0.982). Batch F_7 showed flux of 125.8 µg/2cm^2/h, hence the patch area of 1.33 cm^2 would be expected to deliver targeted flux of 83.72µg/cm^2/h.

KEYWORDS

Carvedilol, Transdermal patch, Eudragit RL 100, Eudragit RS 100.

INTRODUCTION

Transdermal drug delivery system (TDDS) has been an increased interest in the drug administration via the skin for both local therapeutic effect on diseased skin as well as for systemic delivery of drugs. The skin as a site of drug delivery has a number of advantage over many other routes of drug administration, including the ability to avoid problems of gastric irritation, gastric emptying rate, avoid hepatic first-pass metabolism thereby increasing the bioavailability of drug, reduce the risk of systemic side effect by minimizing plasma concentrations compared to oral therapy, provide a sustained release of drug at the site of application, rapid termination of therapy by removal of the device or formulation, the reduction of fluctuations in plasma levels of drugs, and avoid pain associated with injections.[1-5]

Hypertension is one of the most serious concerns of modern medical practice. Carvedilol is multiple-action cardiovascular drug for the treatment of hypertension. The reduction in blood pressure produced by carvedilol results

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primarily from beta-adrenoceptor blockade and vasodilatation, Carvedilol is well absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism in the liver; its absolute bioavailability is about 25%. It has a half-life about 6 hour. Carvedilol was chosen 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 a high degree of first-pass metabolism.[6-10]

The aims of the present study were to develop different matrix patches with various ratios of hydrophilic and hydrophobic polymer combinations such as HPMC k4M and Eudragit RS-100 containing Carvedilol and perform physicochemical characterization and *in-vitro* permeation studies through rat skin. The purpose was to provide the delivery of the drug at a controlled rate across intact skin to improve bioavailability and hypertension control for longer period from transdermal patches.

MATERIALS AND METHODS

Materials

Carvedilol was received as a gift sample from Zydus research centre, Ahmedabad, Gujarat. HPMC K4M was purchased from Colorcon, Goa. Eudragit RS-100, Polyethylene glycol 400 and Polyvinyl Alcohol (PVA) obtained from Seva fine Chemical Ltd, Mumbai. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Methods

Development of Polymeric Matrix Device

Backing membrane was prepared by casting 5% aqueous solution of PVA followed by drying at 60°C for 6 Hrs. Drug loaded matrix type transdermal patches of Carvedilol were prepared by using solvent casting method. Petridish with total area of 63.585 cm^2 were used. Polymers were accurately weighed keeping total polymer weight 1.00 g and dissolved in 30 ml of methanol: chloroform (3:2) solution and kept aside to form clear solution. Drug was dissolved in the above solution and mixed until clear solution was obtained. Add 30% w/w polyethylene glycol (PEG 400) and add permeation enhancer DMSO then stir this solution. The resulted uniform solution was casted on the backing membrane as a plain surface and dried at room temperature for 24 hrs. An inverted funnel was placed over the Petridish to prevent fast evaporation of the solvent. The films were cut into small patches (2 cm^2) containing 3.25 mg of carvedilol. After 24 hrs the dried patches were taken out and stored in a desiccators for further studies.[12, 13, 14]

Preliminary Screening

Preliminary study was carried out to check effect of various polymer combinations on transdermal patch formulation. Composition of preliminary trial batches B1 to B5 is shown in Table 1.

Optimization of Variables Using Full Factorial Design

A 3^2 randomized full factorial design was used in the present study. In this design 2 independent factors were evaluated, each at 3 levels and experimental trials were performed for all 9 possible combinations. The concentration of Eudragit RS-100 (X_1) and Concentration of HPMC K4M (X_2) were chosen as independent variables in 3^2 full factorial designs, while Tensile strength, % Cumulative drug release at 20 hrs (Q_{20}) and Diffusion coefficient (n) were taken as dependent variables. Multiple linear regression analysis, ANOVA, and graphical representation of the influence of factor by contour plots and 3D surface plot was performed using Sigma Plot 12. The formulation layout for the factorial design batches (F1 to F9) are shown in Tables: 2

Evaluation Parameters of Transdermal Patch

Weight Uniformity

A specified area of dried patch will be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values will be calculated from the individual weights.[15]

Table 1: Preliminary trial batches

Batch code	Polymer(mg)					Solvent (3: 2)
	HPMC K4M	EC	PVP K 30	EudragitRL 100	Eudragit RS 100	
B1	1000	-	-	-	-	Methanol: Chloroform
B2	-	500	500	-	-	Methanol: Chloroform
B3	500	500	-	-	-	Methanol: Chloroform
B4	500	-	-	500	-	Methanol: Chloroform
B5	500	-	-	-	500	Methanol: Chloroform

PVP K30= Polyvinyl Pyrrolidone K30, HPMC= Hydroxy Propyl Methyl Cellulose, EC= Ethyl Cellulose, PG= Propylene glycol, PEG 400= Poly ethylene glycol 400

Table 2: Design layout for 3^2 Full Factorial Batches

Batch	Coded value		Actual Value (mg)	
Code	X_1 (Eudragit RS 100)	X_2 (HPMC K4M)	X_1 (Eudragit RS 100)	X_2 (HPMC K4M)
F1	-1	-1	200	600
F2	-1	0	200	700
F3	-1	1	200	800
F4	0	-1	300	600
F5	0	0	300	700
F6	0	1	300	800
F7	1	-1	400	600
F8	1	0	400	700
F9	1	1	400	800

Folding Endurance

A patch of specific area (2 cm^2) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film was folded at the same place without breaking gave the value of the folding endurance. [15]

Tensile Strength

The tensile strength of the patch was evaluated by using the tensilometer. It consists of two load cell grip. The lower one was fixed and upper one was movable. Film strips were fixed between these cell grips and force was gradually applied till the film broke. The tensile strength was taken directly from the dial reading in kg.[14]

Percentage Elongation Break Test

The percentage elongation break was determined by noting the length just before the break point, the percentage elongation was determined from the below mentioned formula.

$$\text{Elongation percentage} = [(L_1-L_2)/L_2] \times 100$$

Where, L_1 is the final length of each strip and L_2 is the initial length of each strip. [14]

Thickness

Patch thickness was measured using digital micrometer screw gauge at three different places and the mean value was calculated. [14]

Drug Content

A specified area of patch ($2cm^2$) was dissolved in 100ml methanol in volumetric flask and shaken continuously for 12 hrs. Then the whole solution was ultra sonicated for 15 min. After filtration, 1 ml was withdrawn from the solution and diluted to 10ml with methanol. The absorbance of the solution was taken at 242 nm and concentration was calculated and determined the drug content.[14]

Percentage Moisture Content

The prepared patches were weighed individually and kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the patches were reweighed and determine the percentage moisture content from the below mentioned formula.[15]

Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100

Percentage Moisture Uptake

The weighed patches were kept in desiccators at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the patches were reweighed and determine the percentage moisture uptake from the below mentioned formula.[15]

Percentage moisture uptake = [Final weight- Initial weight/ initial weight] ×100

Water Vapour Transmission (WVT) Studies

Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1 g of anhydrous calcium chloride was placed; the film was fixed over the brim. The cells were accurately weighed and kept in a closed desiccators containing a saturated solution of potassium chloride to maintain a RH of 84%. The cells were taken out and weighed after 24 hrs. The amount of water vapour transmitted was found using following formula.[15]

$$WVT = \frac{\text{Final Weight - Initial Weight}}{\text{Area}}$$

Water vapour transmission is expressed as the number of grams of moisture gained per square centimetre in 24 hrs($g/cm^2/24h$).

In-vitro Drug Release Study

In-vitro drug release studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 25 ml. The cellophane membrane was used for the determination of drug release from the prepared transdermal matrix type patches. The semi-permeable cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The prepared transdermal patch was placed on the cellophane membrane. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4 containing 30% PEG. The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads and the temperature was maintained at 32 ±0.5°C, because the normal skin temperature of human is 32°C. The samples were withdrawn at predetermined time up to 24 hrs and analyzed for drug content at wavelength of 242 nm using a Shimadzu UV-1700 double-beam spectrophotometer (Shimadzu, Kyoto, Japan). The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. Cumulative percentage drug release was calculated using an equation obtained from a calibration curve.[14,16]

In-vitro Skin Permeation Studies

An *in-vitro* permeation studies were carried out on selected batch using franz diffusion cell. Full thickness abdominal skin of male Wistar rats of weight about 200 to 250 gm was used. Hair from the abdominal region were removed carefully and the dermal side of the skin will thoroughly clean with distilled water to remove any adhering tissues or blood vessels, equilibrate for an hour in dissolution medium or phosphate buffer pH 7.4 containing 30% PEG before starting the experiment and was placed on a magnetic stirrer. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated

rat skin piece was mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample of definite volume was removed from the receptor compartment at regular intervals, and an equal volume of fresh medium was replaced. Samples were filtered through watman filter and were analysed spectrophotometrically. Flux was determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm^{-2}) vs. time in hrs & permeability coefficients was deduced by dividing the flux by the initial drug load (mg cm^{-2}).[14,16]

Kinetic Modeling of Dissolution Data

The dissolution profile was fitted to various models such as zero order, first order, Higuchi, Korsemeyer and Peppas, to ascertain the kinetic of drug release. The method described by Korsemeyer and Peppas was used to describe mechanism of drug release. [18.19, 20]

Skin Irritation Study of Final Optimized Formula

30 healthy male Wistar rats were divided into 5 groups. On the day prior to the experiment, the hairs on the back of the rat were removed using an electrical clipper. Rat were divided into five groups (*n* = 6 per group) and were treated once daily over a period of up to 7 days as followed groups. (i)Group 1, Normal (no treatment) (ii) Group 2,control (application of commercially available adhesive tape) (iii)Group 3, 0.8% v/v aqueous formalin solution (standard irritant) (iv) Group 4, Blank transdermal patch (without drug) and (v) Group 5, Transdermal patch with drug. On the 8th day, the application sites will be evaluated visually for erythema and oedema. Erythema scale: 0, none; 1, slight; 2, well defined; 3, moderate; 4, scar formation. Edema scale: 0, none; 1, slight; 2, well defined; 3, moderate; 4, severe.[17]

Short-Term Stress Stability Studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors. To assess the drug and formulation stability, stability studies were done as per ICH guidelines. The optimized formulation was wrapped in aluminium foil and stored at 60 ± 0.5ºC and 75%RH for period of two weeks. After the period of two weeks, patch was tested for drug content and *In-vitro* release profile. The similarity factor (f_2) was used as a basis to compare dissolution profiles. The dissolution profiles are considered to be similar when f_2 is between 50 and 100. The dissolution profile of products were compared using a f_2 which is calculated from following formula,

$$f_2 = 50 \times \log\left(\left[1 + \frac{1}{n}\sum_{t=1}^{n} w_t (R_t - T_t)^2\right]^{-0.5} \times 100\right)$$

Where, n is dissolution time & R_t (dissolution profile of before stability study & T_t dissolution profile after one month for stability study).

RESULTS AND DISCUSSION

Preliminary Study

All the preliminary trial batches of transdermal patch showed thickness variation range from 0.40 to 0.43 mm as shown in Table 3. All the batches of transdermal patch showed tensile strength and % elongation in uniform range from 1.8 to 2.6 kg/cm^2 and 12.54 to 23.22 respectively. According to *in-vitro* drug release study of Batch B1 to B3 shown fast release and leads to saturation level after certain period of time as compared to B4 & B5. It may be because formulation B1, B2 and B3 contains hydrophilic polymers like HPMC K4M and PVP K30 which have more solubility whereas B4 & B5 contains HPMC K4M, Eudragit RL 100 & Eudragit RS 100 polymer. Eudragit RL 100 is relatively more permeable to water than the Eudragit RS 100. An optimum combination of the HPMC K4M and Eudragit RS 100 could be able to achieve desired release profile. So batches B1, B2, B3 and B4 are eliminated and concentration of HPMC K4M & Eudragit RS 100 are assigned as independent variable in 3^2 factorial designs in order to understand their effect & to optimize concentration of both for desired release profile.

Table 3: Results for preliminary trial batches

Batch code	**Thickness (mm)**	**Tensile strength (kg/cm^2)**	**% Elongation**	**Folding endurance**	**WVT ($g/cm^2/24h$)**	**% CPR (12 hr)**
B1	0.43±0.015	2.2±0.8	23.22±1.58	105±7	5.81±0.07	95.67
B2	0.40±0.009	1.8±0.6	12.54±0.96	43±4	4.11±0.11	76.55
B3	0.41±0.019	1.9±0.7	13.64±1.06	52±6	4.87±0.08	80.86
B4	0.43±0.021	2.5±0.9	19.5±1.15	78±8	3.22±0.05	60.64
B5	0.43±0.016	2.6±0.4	17.87±1.23	77±9	2.44±0.06	49.74

*Data expressed (±SD); n = 3

Table 4: Evaluations of Thickness, Tensile Strength, % Elongation and Folding endurance of 3^2 full factorial design batches

Batch code	**Thickness (mm)**	**Tensile strength (kg/cm2)**	**% Elongation**	**Folding endurance**	**Moisture content (%)**	**Moisture uptake (%)**	**WVT(g/cm2/24h)**	**Drug content**
F1	0.34±0.019	2.2±0.6	16.52±0.68	75±4	1.94±0.08	2.34±0.19	2.41±0.09	98.5±0.2
F2	0.38±0.015	2.3±0.8	16.87±1.12	79±6	1.88±0.09	2.41±0.09	3.81±0.08	98.9±0.4
F3	0.41±0.013	2.4±0.5	17.85±0.84	75±6	2.09±0.09	2.48±0.12	4.22±0.06	97.8±0.5
F4	0.37±0.025	2.4±0.7	17.13±0.68	78±5	1.97±0.12	2.33±0.12	2.79±0.09	99.1±0.1
F5	0.42±0.017	2.6±0.8	17.96±0.79	80±4	1.88±0.09	2.60±0.22	3.70±0.07	97.6±0.6
F6	0.47±0.009	2.7±0.6	18.61±0.94	78±7	2.08±0.08	2.50±0.20	4.16±0.08	98.3±0.4
F7	0.42±0.020	2.6±0.7	18.08±0.73	81±5	1.85±0.12	2.41±0.22	3.27±0.07	98.5±0.3
F8	0.46±0.014	2.7±0.5	18.74±0.46	80±6	1.90±0.14	2.53±0.13	3.61±0.06	97.4±0.5
F9	0.50±0.021	2.8±0.7	19.2±0.58	82±8	2.12±0.11	2.65±0.10	3.90±0.05	97.3±0.4

*Data expressed (±SD); n = 3

Folding Endurance, Tensile Strength, % Elongation and Thickness

The results of folding endurance, tensile strength, % elongation and thickness of factorial design batches are shown in Table 4. The folding endurance values of all the factorial design patches were found satisfactory which indicates that the patches prepared using PEG 400 in a concentration of 30% w/w of polymer were having optimum flexibility and were not brittle. The tensile strength of the patches prepared with HPMC K4M and Eudragit RS 100 were found in between 2.2 to 2.7 kg/cm^2. The % elongation was found to be in the range of 16.52 % to 19.2 %. The thickness ranges were 0.35 to 0.50 mm. The results showed that the patches were uniform.

Moisture Content, Moisture Uptake, Water Vapour Transmission (WVT) Studies and Drug Content Studies

The moisture content in the patches ranged from 1.85 to 2.12 %. The moisture content in the formulations was found to be increased by increase in the concentration HPMC. The moisture uptake in the patches ranged from 2.33 to 2.65 %. The lower moisture content in the formulations helps them to remain stable and become a completely dried and brittle patch. Again, low moisture uptake protects the material from microbial contamination and bulkiness and the drug content ranged from 97.4 to 99.1%.

***In-Vitro* Drug Release Study**

The drug release characteristics of the formulation were studied by using semi permeable membrane. The formulation F1–F3 has shown release of about 98.55%, 94.74% and 91.22% at 24 hrs, respectively. This is may be due to hydrophilic polymer of HPMC K4M. The formulation F4–F6 has shown release of about 97.72%, 91.74% and 88.22%, at 24 hr, respectively and the formulation F7–F9 has shown release of about 95.93%, 88.5% and 85.22%, at 24 hrs, respectively From the graph it can be concluded that the drug release appeared to decrease more with an increasing amount of the Eudragit RS 100 as compared to HPMC K4M. Eudragit RS 100 shows slow release of drug from patch due to its hydrophobic nature. The kinetic parameters of drug permeation for different formulations are presented in Table 4. The zero-order plots of F1 to F9 were found to be fairly linear, as indicated by their high regression values between 0.972 and 0.982. Therefore it was ascertained that the drug permeation from these formulations could follow zero-order kinetics. Hence, to confirm the exact mechanism of drug permeation from these patches, the data were fitted to the Korsmeyer-Peppas model. In the present study, the coefficient of determination (R^2 =0.992 to 0.995) was found to be much closer to 1 and the release exponent 'n' value vary between 0.426 to 0.771, which explained that drug released from the film occurs by Non- fickian type of diffusion. Overall results of kinetic modeling suggest that diffusion is dominant mechanism for drug release following Non-Fickian type of diffusion.

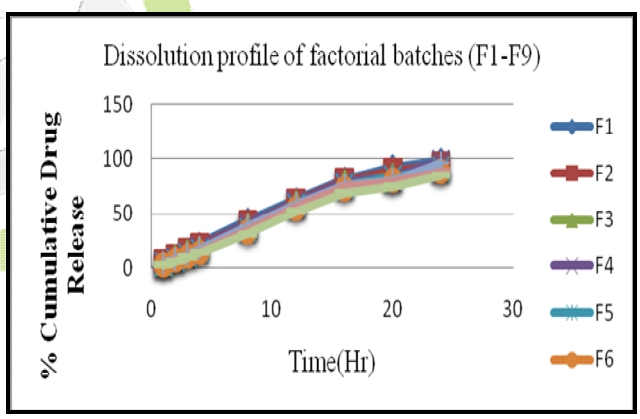

Figure 1: *In-vitro* drug release profile for batch F1 to F9.

3^2 Full Factorial Design Model Evaluation

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses: $Y=b0 +b_1X_1 +b_2X_2 +b_{12}X_1X_2 +b_1^1X_1^2 +b_2^2X_2^2$, where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs and any *b*i is the estimated coefficients for the related factor Xi. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction term "X_1X_2" shows

how the response changes when the two factors change simultaneously. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The fitted equations (full model) relating the responses that is, Tensile strength (TS), % drug release at 20 hrs (Q_{20}) and Diffusion coefficient (n) to the transformed factor. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative). The results of ANOVA suggested that F values calculated for TS, Q20 and n are 44.282, 27.189 and 78.990 respectively (Table 5). Tabulated F value was found to be 9.013 at $\alpha = 0.05$. Calculated F values are greater than tabulated for TS and Q20 and "n" .Therefore all selected factors have shown significant effects. R^2 value for tensile strength, Q20 and diffusion coefficient "n" is 0.987, 0.978 and 0.992 respectively, indicating good correlation between dependent and independent variables.

Table 5: Kinetic Treatment of Dissolution Data.

Batch Code	Zero order	First order	Higuchi	Korsmeyer-Peppas	
	r^2	r^2	r^2	r^2	N
F1	0.977	0.833	0.991	0.995	0.771
F2	0.974	0.834	0.988	0.995	0.740
F3	0.972	0.831	0.986	0.994	0.687
F4	0.980	0.837	0.988	0.994	0.661
F5	0.978	0.827	0.984	0.994	0.538
F6	0.978	0.820	0.982	0.992	0.474
F7	0.982	0.843	0.986	0.993	0.629
F8	0.974	0.824	0.983	0.993	0.525
F9	0.980	0.826	0.983	0.993	0.426

The reduced models were developed for response variables by omitting the insignificant terms with $P > 0.05$. The terms with $P < 0.05$ were considered statistically significance and retained in the reduced model. The coefficients for full and reduced models for response variables are shown in Table 7.

Full and Reduced Model for Tensile Strength

For Tensile strength, as seen from Figure 2 3D surface plots respectively revealed that a corresponding increase in the Tensile strength of patch was observed with increase in concentrations of Eudragit RS 100 and HPMC K4M. From the graph and the regression coefficient values of both factors it can concluded that increase in tensile strength is more with an increasing amount of the Eudragit RS 100 as compared to HPMC K4M. For Tensile strength, the significance levels of the coefficients b_{12}, b_1^2 and b_2^2 were found to be P= 0.889, 0.09 and 0.574 respectively, so they were omitted from the full model to generate a reduced model. The coefficients b_1 and b_2 were found to be significant at $P < 0.05$; hence they were retained in the reduced model. The reduced model for Tensile strength, $TS = 2.578 + (0.200 * X_1) + (0.117 * X_2)$.

Full and Reduced Model for % drug release at 20 hrs (Q_{20})

For % drug release at 20 hrs (Q_{20}), as seen from Figure 3, 3D surface plots respectively revealed that a corresponding decrease in the % drug release of patch was observed with increase in concentrations of Eudragit RS 100 and HPMCK4M. From the graph and the regression coefficient values of both factors it can be concluded that the drug release appeared to decrease more with an increasing amount of the Eudragit RS 100 as compared to HPMC K4M. The more decrease in the drug release by Eudragit RS 100 as compared to HPMC K4M could be explained by difference in the permeability characteristics. HPMC K4M is freely permeable to water whereas Eudragit RS 100 is slightly permeable to water.

Table 6: Results of the ANOVA for dependent variables

Source of variation	DF	SS	MS	F	P
TS					
Regression	5	0.331	0.0662	44.282	0.005
Residual	3	0.00442	0.00147		
Total	8	0.336	0.041		
Q_{20}					
Regression	5	235.418	47.084	27.189	0.011
Residual	3	5.195	1.732		
Total	8	240.613	30.077		
"n"					
Regression	5	0.115	0.0231	78.990	0.002
Residual	3	0.000877	0.000292		
Total	8	0.116	0.0145		

TS were measured in kg/cm^2; Q_{20} was the % drug release at 20 hour; DF is degree of freedom, SS is sum of square, MS is mean square and F is Fischer's ratio.

Table: 7 Summary of regression output of significant factors for measured

Responses		Coefficient of regression parameters						
		b_0	b_1	b_2	b_{12}	b_1^2	b_2^2	R^2
TS	FM	2.578	0.200	0.117	0.00250	-0.0663	-0.0175	0.987
	RM	2.578	0.200	0.117	---	---	---	---
Q_{20}	FM	83.556	-5.536	-2.902	0.518	0.970	-1.574	0.978
	RM	83.556	-5.536	-2.902	---	---	---	---
N	FM	0.546	-0.0981	-0.0790	-0.0295	0.0671	0.0168	0.992
	RM	0.546	-0.0981	-0.0790	-0.0295	0.0671	---	---

For % drug release at 20 hrs (Q_{20}), the significance levels of the coefficients b_{12}, b_1^2 and b_2^2 were found to be P= 0.467, 0.376 and 0.197, respectively, so they were omitted from the full model to generate a reduced model. The coefficients b_1 and b_2 were found to be significant at $P < 0.05$; hence they were retained in the reduced model.

The reduced model for % drug release at 20 hrs (Q_{20}).

$$Q_{20} = 83.556 - (5.536 * X_1) - (2.902 * X_2)$$

Full model and Reduced Model for Diffusion coefficient (n)

For Diffusion coefficient (n), as seen from Figure 4, the 3D surface plots respectively revealed that a corresponding decrease in Diffusion coefficient (n) of patch was observed with increase in concentrations of Eudragit RS 100 and HPMCK4M. From the graph and the regression coefficient values of both factors it can be concluded that the Diffusion coefficient (n) appeared to decrease more with an increasing amount of the Eudragit RS 100 as

compared to HPMC K4M. The more decrease in the Diffusion coefficient (n) by Eudragit RS 100 as compared to HPMC K4M could be explained by difference in the Diffusion characteristics. The significance levels of the coefficients b_2^2 were found to be P= 0.267, so they was omitted from the full model to generate a reduced model. The coefficients b_1 and b_2 b_{12} and b_1^2 were found to be significant at $P < 0.05$; hence they were retained in the reduced model. The reduced model for Diffusion coefficient (n)

Diffusion coefficient (n) = $0.546 - (0.0981 * X_1) - (0.0790 * X_2) - (0.0295 * X_1 X_2) + (0.0671 * X_1^2)$

In-vitro Skin Permeation Study

In skin permeation study the formulation F7 exhibited 88.88% of drug permeated in 24 hr. Plotting the cumulative amounts of drug permeated per 2 cm^2 of the patches through the rat abdominal skin against time showed that the permeation profiles of drug might follow zero-order kinetics as it was evident by correlation co-efficients 0.947, According to korsmeyer-Peppas model, a value of slope for F7 was between 0.5 and 0.85 (0.546) which indicates that the release mechanism was non-Fickian diffusion. The results of drug permeation from transdermal patches through the rat abdominal skin confirmed that it was released from the formulation and permeated through the rat skin and, hence, could possibly permeate through the human skin. *In-vitro* skin permeation study is predictive of in vivo performance of a drug. The parameters listed in this table are useful for bio-pharmaceutics and pharmacokinetics of the matrix diffusional system evaluated. *Computation of desired release rate (in-vivo input) for target steady state plasma concentration of drug*

For Carvedilol, CL = 0.52 L/h/kg and targeted steady state plasma concentration (Css) = 2.3 µg/L and therefore the desired drug release can be calculated as follows.

In vivo input = *In vivo* output

= Css * CL *70

= 2.3 µg /L * 0.52 L/h/kg * 70 kg

= 83.72µg/hr

Desired release rate = 83.72µg/hr

Computation of area of patch required for target steady state plasma concentration (Css)

In vivo input = *in vivo* output = 83.72µg/hr

J_{ss}(skin) x A = Css * CL *70= 83.72µg/hr

Area of patch = (83.72 µg/hr)/ J_{ss}(skin)

= 83.72 µg/hr/125.25µg/ 2cm^2/hr

=1.33 cm^2

Irritation Study

The visual evaluation of the skin irritation study shown that the erythema and edema produced in the group-5 are considerably less as compared to the group treated with standard irritant, so it can be concluded that the formulation produced no or very little irritation.

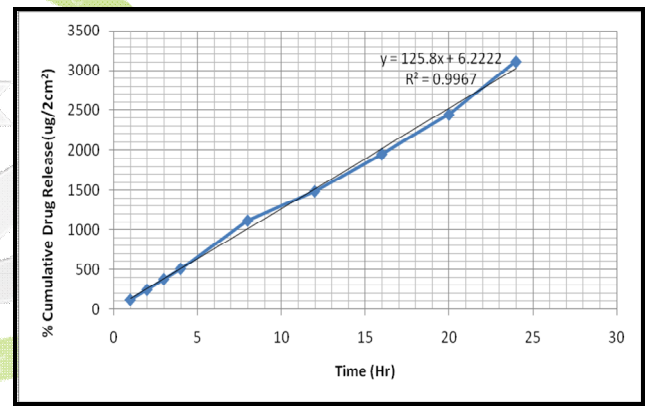

Figure 2: *In-vitro* skin permeation profile of Carvedilol from Factorial batch F4 through rat abdominal skin

Table 8: Parameters of diffusion kinetics of Carvedilol from F4 batch patch through rat abdominal skin.

Sr. No	Parameters	Value
1	Skin flux (J_{ss})	125.8 µg/ 2cm^2/hr
2	Time lag (t_L)	0.5 hr
3	Diffusion coefficient	38.70×10^{-3} cm^2/hr

Short-Term Stress Stability Studies Release Profile for Selection of Optimum Batch Dissolution profiles of F7 batch of factorial design were compared with theoretical dissolution profile. The values of similarity factor (*f*2) for batch F7 are shown similar value (88.187).

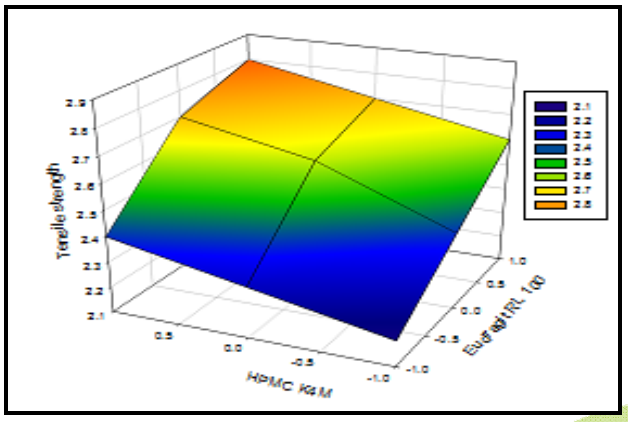

Figure 3: Response surface plot for Tensile Strength

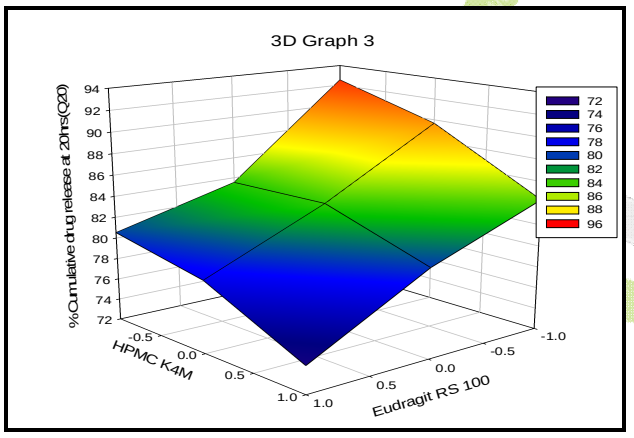

Figure 4: Response surface plot for at 20 hrs

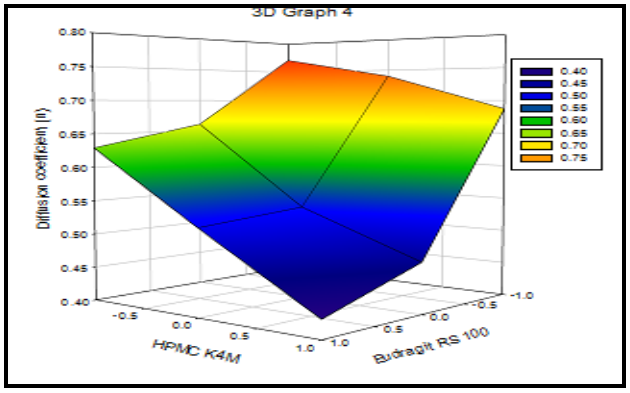

Figure 5: Response surface plot for Diffusion coefficient (n)

CONCLUSION

The prepared transdermal drug delivery system of carvedilol using different grades of HPMC and Eudragit had shown good promising results for all the evaluated parameters. It was concluded that HPMC K4M and Eudragit RS 100 of moderate level useful for preparation of sustained release matrix transdermal patch formulation.

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