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Original Article

FORMULATIONOF MATRIX TYPE TRANSDERMAL PATCHES OF DILTIAZEM HYDROCHLORIDE: IN VITRO AND EX VIVO CHARACTERIZATION

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ABSTRACT

D*iltiazem is a calcium channel blocker, used in the treatment of hypertension, angina pectoris and some types of arrhythmia. The bioavailability of Diltiazem is 40-67% due to extensive first-pass metabolism in the liver. The transdermal administration of Diltiazem is a possible solution to overcome this problem. The aim of this investigation was to develop and evaluate matrix-type transdermal drug delivery systems of Diltiazem. The matrix-type transdermal patches of Diltiazem were prepared by solvent evaporation technique using HPMC K15, HPMC K100, ERL 100 and ERS 100 in the ratios of 1:1, 1:2 and 1:3. The FTIR studies showed drug-polymer compatibility. The prepared patches were characterized for various physicochemical parameters like weight, thickness, folding endurance, drug content, per cent moisture content per cent moisture absorption, in vitro drug release and ex vivo permeation. The maximum % drug release in 24 hrs for M2 formulation was 93.3±3.03 and showed maximum skin permeation 3691.8±19.25 µg/cm2 in the respective series but the obtained flux meets the required flux. The drug permeation kinetics followed a zero-order profile with a diffusion mechanism. The mechanical properties, tensile strength, and elastic modulus reveal that the formulations were found to be strong but not brittle. The results indicate that Diltiazem hydrochloride matrix type transdermal therapeutic systems could be prepared with the required flux having suitable mechanical properties.*

Keywords: *Diltiazem hydrochloride, transdermal, solvent casting, diffusion, drug release*

INTRODUCTION

Transdermal drug delivery system (TDDS) has increased interest in clinical practice through the skin for both local therapeutic effects on diseased skin (topical delivery) and systemic drug delivery. The ability to avoid issues with gastric irritation, pH and emptying rate effects, avoid hepatic first-pass metabolism thereby increasing the bioavailability of the drug, reduce the risk of systemic side effects by reducing plasma concentrations compared to oral therapy, and provide a sustained release of drug at the site of application are only a few of the significant advantages that the skin as a site of drug at the site of application are only a few of the significant advantages that the skin as a site of drug delivery has over many other routes of drug administration. Transdermal administration can also minimise pulsed entrance into the systemic circulation, which can frequently result in unwanted side effects[1].

Diltiazem hydrochloride is a calcium channel blocker that is used to treat arrhythmia, angina pectoris, and high blood pressure. It has a mean plasma half-life of 3.5 hours. According to the literature review, it undergoes variable and significant first-pass metabolism before entering systemic circulation[2, 3], and this differs by species [4, 5]. Although the liver is thought to be the primary organ for Diltiazem biotransformation, extrahepatic organs such as the intestine and lungs also contribute to first-pass absorption and systemic elimination[6, 7]. Transdermal delivery of drugs, which undergo first-pass metabolism, is well known to improve bioavailability and minimise dose frequency when compared to the oral route. The current study aimed to investigate the permeability of diltiazem hydrochloride from polymeric films via mouse skin into in vitro fluid, and the results

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could provide additional insight into how to avoid the drug's hepatic first-pass effect.

The aim of the present study was to develop different transdermal polymeric films with HPMCK15, HPMC K100, Eudragit RL 100, and Eudragit RS containing the drug diltiazem hydrochloride and to evaluate invitro release of the drug at a controlled rate to provide a therapeutically effective drug level for a longer period of time from the Transdermal patches. This study was further amalgamated with investigation of different physical properties of these patches.

Moreover, here an attempt was made to establish the best possible formulation with maximum sustained drug-releasing capability as well as stability in terms of its physical characteristics from the experimental polymeric films.

MATERIALS AND METHODS

2.1 Materials

Diltiazem hydrochloride was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad and polymers HPMCK15, HPMC K100,Eudragit RL 100, Eudragit RS 100from Degussa, Germany, solvents such as Dichloromethane AR, Methanol AR from Merck Ltd, Mumbai, Dialysis Membrane from Himedia Laboratories, Propylene glycol, Calcium chloride, Aluminium chloride, Potassium dihydrogen ortho phosphate, Sodium hydroxide from Finar chemicals limited, Ahmedabad were purchased.Distlled water was used throughout the experiment.

2.2 Preformulation studies

Before formulating the drug substance into a Transdermal patch (dosage form), preformulation studies were carried out to establish the physicochemical characteristics of adrug and its compatibility with different excipients. Compatibility study of drug with the excipients was determined by Fourier transform infrared (FTIR) spectroscopy (Shimadzu FTIR -5300). The samples were scanned from 400 cm-1 to 4000 cm-1).

2.3 Calibration curve of Diltiazem hydrochloride

Wavelength maximum of Diltiazem hydrochloride was found to be 240 nm using ultraviolet (UV)-visible spectroscopy Shimadzu UV -1800). Standard solution (10 µg/ml) was prepared from stock solution (1 mg/ml) with phosphate buffer (pH 7.4). Aliquotes of standard drug solution ranging from 1 to 8 ml were transferred into 10 ml volumetric flask and were diluted up to the mark with phosphate buffer pH 7.4. Thus, the final concentration ranges from1-8 µg/ml. The absorbance of each solution was measured at 240 nm against phosphate buffer (pH 7.4). A plot of concentrations of the drug versus absorbance was plotted. The linear regression analysis was applied.

2.4 Fabrication of transdermal patches

Matrix type Transdermal patches containing Diltiazem hydrochloride were prepared by solvent evaporation technique[8], using differentratios of polymers HPMCK15 (M1 to M3), HPMC K 100(M4 to M6), Eudragit L100(M7 to M9) and Eudragit S100 (M10 to M12). Dibutyl phthalate (15 %) was incorporated as plasticizer in all formulations. Table 1 shows the formulae and composition for the different types of formulated patches. The polymers were weighed inrequisiteratios by keeping the total polymer weight 1.0gm and allowed for swelling for about 6hrs in the solvent mixture consisting of 1:1 ratio of dichloromethane, methanol. Then the drug solution was added to the polymeric solution, casted on to an umbra petri plate of surface area about 72.35sq.cm and allowed for air drying overnight followed by vacuum drying for 8-10hr. The entire sheet was cut into small patches with an area of 5.30sq.cm i.e. with a diameter of 2.6cm. Each patch (5.30 cm2) contains 60 mg of Diltiazem hydrochloride. About 8 patches were obtained from each sheet.

Table 1: Composition of Diltiazem hydrochloride transdermal patches (M1 to M12)

Formulation code	Ingredients				
	Drug (gm)	HPMC K15 (gm)	HPMC K100 (gm)	ER L100 (gm)	ER S100 (gm)
M1	0.8	0.8	-	-	-
M2	0.8	1.6	-	-	-
M3	0.8	2.4	-	-	-
M4	0.8	-	0.8	-	-
M5	0.8	-	1.6	-	-
M6	0.8	-	2.4	-	-
M7	0.8	-		0.8	-
M8	0.8	-		1.6	-
M9	0.8	-		2.4	-
M10	0.8	-		-	0.8
M11	0.8	-		-	1.6
M12	0.8	-		-	2.4

*15% Dibutylpthalate was used as plasticizer.

2.5 Evaluation of transdermal patches

Physical appearance

All the prepared patches were visually inspected for color, clarity, flexibility, and smoothness.

2.5.1 Thickness[9]

The thickness of the drug loaded patches was measured by using a screw gage micrometer at three different points on the patches. Average values and standard deviation values of the three readings were calculated for each drug loaded patch.

2.5.2 Weight variation[10]

The patches were subjected to weight variation by individually weighing ten selected patches randomly and the average was calculated.

2.5.3 Folding endurance[11]

Folding endurance of the patch was determined manually by repeatedly folding a small strip at the same place till it tends to break. The number of times the strip could be folded at the same place without breaking gives the folding endurance number.

2.5.4 Drug content uniformity[12]

Pieces of 2 × 2 size were cut from each type of formulation and put in 100 ml of phosphate buffered saline pH 7.4 solution. The contents were magnetically stirred for 24 h. The solution was then filtered through Whatman filter paper (0.45 μ) and diluted suitably with phosphate buffer saline pH 7.4. The solution was then analyzed for its absorbance at 240 nm using placebo patch as blank. From the absorbance values, the drug content was determined.

2.5.5 Percentage moisture content[13]

The prepared films were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 h. After24 h, the films were reweighed and determined the percentage moisture content from the below mentioned formula:

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{X } 100$$

2.5.6 Percentage moisture uptake

The patches were weighed accurately and placed in the dessicator containing 100ml of saturated solution of Aluminium chloride, which maintains 84 % RH. After 3 days, the patches were taken out and weighed. The percentage moisture absorption was calculated using the following formula

$$\% \text{ Moisture absortption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \text{X } 100$$

2.5.7 In-vitro release studies[14]

Franz diffusion cell was employed for the in vitro characterization of transdermal formulations. This is a reliable method for the prediction of drug transport across the skin from topical formulations. The receptor compartment of the diffusion cell was filled with 30.0 ml of phosphate buffered saline (pH 7.4), and in vitro drug release studies were carried out using synthetic cellophane membrane. The prepared formulations were applied on to the membrane in the donor compartment and were uniformly spread onto the cellophane membrane. The assembly was constantly maintained at 32 ± 0.5 °C, because thenormal skin temperature of human is 32°C. Samples (1.0 ml aliquots) were then withdrawn at suitable time intervals(0, 0.5, 1, 1.5, 2, 2.5, 3, 6, 12, and 24 h) and replenished with an amount of medium to maintain the receptor phase volume to 30 ml. The samples were analyzed spectrophotometrically at 240 nm.

2.5.8 Ex-vivo Permeation Studies[15, 16]

An in vitro permeation study was carried out by using Franz diffusion cell. Full thickness abdominal skin of male Wistar rat weighing 200 to 250g was used. Hair from the abdominal region was removed carefully by using an electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrate for an hour in phosphate buffer pH 7.4 before starting the experiment, and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. 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 volume of 5mL was removed from the receptor compartment at regular intervals, and an equal volume of fresh medium was replaced. Samples were filtered through whatman filter and were analyzed using Shimadzu UV 1800 double-beam spectrophotometer. Flux was determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg*cm2) versus time in hours and permeability coefficient was deduced by dividing the flux by the initial drug load (mg*cm2).

2.5.9 Kinetic modeling of dissolution data[17]

Drug release kinetics were analyzed by various mathematical models such as a zero-order and first-order kinetic models; Higuchi and Korsmeyer–Peppas models to ascertain thekinetics of drug release.

Zero order kinetics

$Q1 = Q0 + K0t$

Where Q is the amount of the drug dissolved in time t, Qis the initial amount of drug in the solution (most times,Q50) and K is the zero order release constant.

First order kinetics

$\ln Qt = \ln Q0 - K1t$

Where Qt is the amount of drug released in time t, Q0 isthe initial amount of drug in the solution and K is the firstorder release constant.

Higuchi model

$Qt = KH\ t1/2$

Where Qt is the amount of drug released in time t, KH is release rate constants.

Korsmeyer–Peppas model

$Qt/Q\infty = atn$

Where n is the release exponent and the function of t is $Qt/Q\infty$ (fractional release of the drug).

RESULTS AND DISCUSSION

Release of the drug from transdermal patches is controlled by the chemical properties of drug and delivery form, as well as the physiological and physicochemical properties of the biological membrane.

3.1 Preformulation studies

Preformulation studies were primarily done to investigate the physicochemical properties of drug and to establish its compatibility with other excipients.

Preformulation studies, that is, FTIR studies revealedthe compatibility of excipients and polymers with Diltiazem hydrochloride. Calibration curve of Diltiazem Hydrochloride was constructed and found to be linear.

3.2 Development of Diltiazem hydrochloride Transdermal Films

Films were formulated with HPMC K15, HPMC K100, ERL 100 and ERS 100. Many experiments were performed by varying the concentrations of polymer. The experiment was initiated by taking 1.50gm of polymer and as the polymer concentration increased the patch could accommodate more amount of Diltiazem. Precipitation of the drug was predominant with 1.50gm of polymer and as the polymer concentration was increased to 2.0gm, the precipitation decreased. No precipitation was observed with 2.5gm of the polymer and the films were flexible. Therefore the polymer amount taken was 2.5gm.

3.3 Evaluation of transdermal patches

The prepared formulations were evaluated for different physicochemical characteristics such as thickness, folding endurance, weight variation and % drug content and the results were shown in Table 2.The weight of the prepared transdermal patches for different type of formulations ranged between 327.3±0.68mg and 424.1±1.13mg, but within a formulation, all the patches showed low standard deviation values. Low SD values in the film ensure uniformity of the patches prepared by solvent casting technique. The thickness of the patches varied from 0.51±1.10mm to 0.59±0.79mm. Low standard deviation values in the film thickness measurements ensured uniformity of the patches which further indicated the reproducibility of the procedure followed for the preparation of the patches. The formulations prepared with HPMC K15was found to have the highest value of folding endurance and formulations made of HPMC K100, Eudragit L100 and Eudragit S100 respectively were found to have the lowest value of folding endurance. The folding endurance values of HPMC K15, HPMC K100, Eudragit L100 and Eudragit S100 containing patches has in the range of 87- 134, 83-129, 65-106 and 66-116 respectively. The folding endurance number was increased with increasing polymer content. These results indicated that the patches would not break and would maintain their integrity with general skin folding when applied. The drug content of all the formulations was in the range of 72.05% ±0.0432 – 93.41%±0.0145 indicated that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability. All formulations were acceptable with regard to Diltiazem hydrochloride content (Table 2).

Table 2: Evaluation of physicochemical characteristics of Diltiazem transdermal patches

Formulation	Polymer	Evaluation Parameters			
		Weight (mg) ± SD	Thickness (mm) ± SD	Folding endurance	Percentage of drug content
M1	HPMC K15	356.2±0.87	0.54±0.75	125±8.94	83.15±0.0035
M2		378.4±0.95	0.56±1.05	115.5±2.65	87.76±0.0072
M3		424.1±1.13	0.58±0.75	91±4.73	93.13±0.0054
M4	HPMC K100	335.5±0.67	0.53±0.82	124.16±5.04	85.19±0.0067
M5		353.2±0.84	0.56±0.89	109.33±2.88	92.26±0.0087
M6		424.2±0.87	0.58±0.75	92±8.94	95.12±0.0043
M7	ER L100	353.3±0.96	0.55±1.17	102.83±4.45	82.54±0.0030
M8		361.1±0.54	0.56±0.89	83.5±5.92	85.19±0.0067
M9		416.3±1.65	0.58±1.52	70.5±5.96	92.10±0.0132
M10	ER S100	327.3±0.68	0.51±1.10	113.67±3.78	83.46±0.0072
M11		358.3±0.65	0.54±0.85	94.83±5.45	87.17±0.0056
M12		413.3±0.59	0.59±0.79	69.83±3.45	90.21±0.0036

3.4 Moisture absorption and moisture content study

The results of moisture content and moisture absorption studies are presented in Table 3. The moisture content and moisture absorption in patches was ranged from 5.79% to 7.98% and 9.6% to 16.65% (for formulation with HPMC K15), 5.02% to 7.03% and 8.18% to 15.56% (for formulation with HPMC K100), 2.98% to 4.93% and 5.85% to 7.56% (for formulation with ERL 100) and 3.42% to 5.12% and 6.91% to 8.93% (for formulation with ERS 100) respectively..Moisture content and moisture uptake studies indicate that the increase in the concentration of hydrophilic polymer i.e. HPMC K15 and HPMC K100 was directly proportional to the increase in moisture content and moisture uptake of the patches. Eudragit RL 100 and Eudragit RS 100 are water insoluble; hence, there is a decrease in the moisture content with an increase in concentration of Eudragits. The moisture content of the prepared transdermal film was low, which maintains suppleness, thus preventing drying and brittleness. The moisture absorption of the transdermal formulations was also low, which protects the film from microbial contamination as well as bulkiness of transdermal patch. Due to moisture absorption from the atmosphere, significant changes in properties like increased

porosity, increased pore diameter, and reduced crushing strength have been reported for matrix film containing hydrophilic polymers.

Table 3: Data for %Moisture absorbed and %Moisture content of Diltiazem hydrochloride transdermal patches

Formulation Code	% Moisture absorbed	% Moisture content
M1	9.68±1.97	5.79±0.42
M2	12.3±2.12	6.52±0.47
M3	16.65±2.84	7.98±0.58
M4	8.18±1.37	5.02±0.54
M5	9.35±1.66	5.86±0.69
M6	15.56±2.57	7.03±0.82
M7	7.56±1.55	4.93±0.47
M8	6.92±1.26	4.52±0.45
M9	5.85±1.05	2.98±0.35
M10	8.93±1.56	5.12±0.65
M11	7.32±1.46	4.98±0.49
M12	6.91±1.25	3.42±0.39

mean ± S.D (n=6)

3.5 In vitro drug release studies from transdermal Patches

The in vitro release profile is an important tool that predicts in advance how a drug will behave in vivo. Release studies are required for predicting the reproducibility of rate and duration of drug action. The in vitro drug release profiles of the formulations prepared from the HPMC K15, HPMC K100, Eudragit RL 100 and Eudragit RS 100 are shown in Figure1,2,3,4. The cumulative percentage of the drug released in 24 h was found to be satisfactory for all types of transdermal films and drug release ranged from 62.61 (M12) to 81.63% (M1).The formulations containing HPMC K15 and HPMC K100 shown greater release profiles when compared with the formulations containing Eudragit RL100 and Eudragit RS 100. The results indicated that the release of drug from patches increases with increasing concentration of HPMC K15M. The drug release was found to increase with the increasing concentration of hydrophilic polymer in the polymer matrix. This is due to the fact that dissolution of an aqueous soluble fraction of the polymer matrix leads to the formation of gelataneous pores. The formulation of such pores leads to decreasing mean diffusion path length of drug molecules to release into the diffusion medium and hence, to cause higher release rate. It was observed that the drug release rate was high in Eudragit RL100 compared to Eudragit RS100 formulations. it might be attributed to the high permeability of Eudragit RL100.

The release profiles of Diltiazem hydrochloride from Transdermal patches presented in Figure. 7, 8, 9 and 10.FormulationsM2, M5, M7 and M10 exhibited greatest percentage of drug release values 93.3±3.03, 97.8±3.98, 80.9±2.416 and 80.75±2.44 respectively than the rest of the formulations.

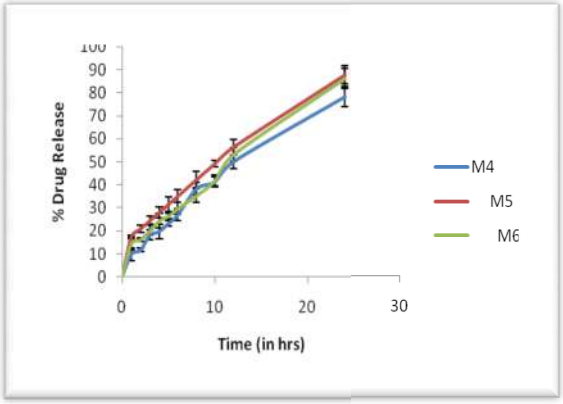

Figure1: In-vitro drug release profile of HPMC K15 formulations

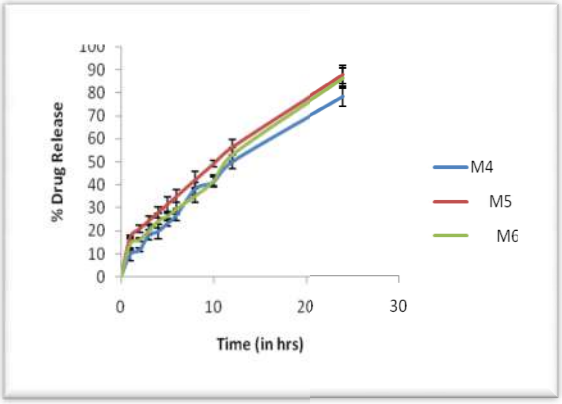

Figure2: In-vitro drug release profile of formulations HPMCK 100

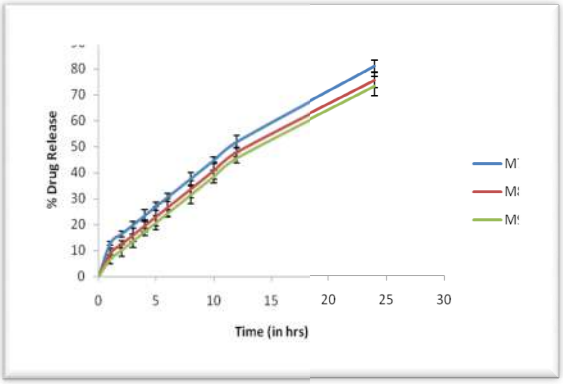

Figure3: In-vitro drug release profile of Eudragit L 100 formulations

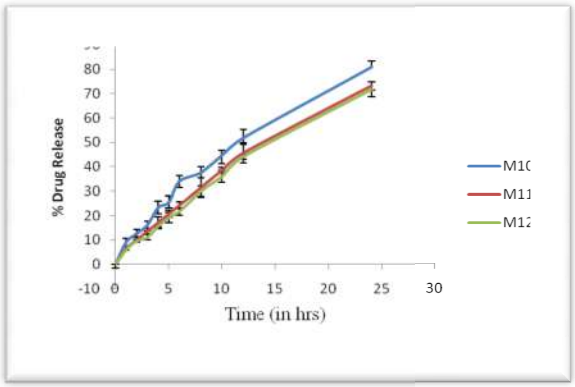

Figure4: In-vitro drug release profile of Eudragit S100 formulations

The results of in vitro skin permeation of Diltiazem hydrochloride from patches of formulations (area of 5.30cm 2) M2, M5, M7 and M10 exhibited the greatest 3691.8±19.25, 2986.6±25.25, 2647.35±16.75 and 2087.65±23.65µg/cm2 respectively. Cumulative amounts of drug permeation for hydrophilic polymers were significantly high when compared with the formulations containing hydrophobic polymers. The mechanical properties of diltiazem transdermal patches were shown in Table 4.

Table 4: Mechanical Properties of Diltiazem transdermal patches

Formulation code	Tensile strength(kg/m2)	Elongation at break (%mm-2)	Elastic modulus (kg/mm2)	Strain
M2	1.52±0.23	77.92±3.07	3.25±0.44	0.52±0.018
M5	1.23±0.25	80.7±3.86	2.54±0.41	0.69±0.024
M7	1.46±0.18	71.16±4.63	3.42±0.40	0.61±0.021
M10	1.35±0.22	73.7±4.76	2.34±0.39	0.59±0.019

Table 5: Kinetic model fitting data for optimized formulations

Formulation code	Zero order	First order	Higuchi	R2 Peppas	n
M2	0.979	0.922	0.954	0.672	0.349
M5	0.962	0.911	0.948	0.973	1.309
M7	0.951	0.909	0.935	0.975	1.315
M10	0.939	0.902	0.929	0.982	1.32

Based on similarity factor results the optimized formulation M2 was fitted into various kinetic models (zero order, first order, Higuchi square root and Korsemeyerpeppas model). The R2 values of zero order plot (0.979) was greater than the R2 values of first order plot (0.9277). Higuchi release kinetic studies R2 value was 0.954 and follows diffusion process. The R2 values reveal that the permeation of diltiazem hydrochloride from the transdermal films followed zero order mechanism and R2 value reveal that it follows diffusion process.

The results of drug permeation from transdermal patches of diltiazem hydrochloride through the rat abdominal skin confirmed that diltiazem hydrochloride was released from the formulation and permeated through the rat skin and hence could possibly permeate through the human skin.

CONCLUSION

Different polymeric films containing diltiazem were prepared and evaluated for physicochemical, in vitro drug release and permeation characteristics. The formulations containing HPMC K15, HPMC K100, ERL 100 and ERS 100 were found to meet the required flux. The transdermal patches of diltiazem with required flux could be prepared with suitable mechanical properties; further studies are recommended to find their therapeutic utility in humans by pharmacokinetic and pharmacodynamic studies.

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AUTHORS CONTRIBUTION STATEMENT

Chandra Shekhar Reddy Bonepally has made a substantial contribution to the concept or design of the article; drafted the article, and revised it critically for important intellectual content. All the authors read and approved the final version of the manuscript.

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