



Research Article

DEVELOPMENT AND EVALUATION OF TRANSDERMAL THERAPEUTIC SYSTEM OF AN ANTIHYPERTENSIVE DRUG

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ABSTRACT

Transdermal drug delivery offers potential alternative to conventional techniques employed for administration of systemic therapeutics. The present study was aimed at the formulation of matrix type transdermal system of Diltiazem hydrochloride using blends of ethyl cellulose and polyvinyl pyrrolidone in different ratios and selecting the suitable formulation for the development of transdermal system. Transdermal patches of the drug employing different ratios of ethyl cellulose and polyvinylpyrrolidone were developed and evaluated for physicochemical properties and potential drug delivery using freshly excised abdominal skin of rat. The drug excipient interactions were carried out using Fourier transform infrared spectroscopy and differential scanning calorimetry. *In vitro* permeation study was conducted for 11 hours using Franz diffusion cell. Interaction studies showed absence of any significant interaction between the drug and polymer as evidenced by the absence of additional peaks in the FTIR spectra. The *in vitro* permeation study revealed that formulation F4 showed sustained and maximum release over a period of 11 h. The results obtained from *in vitro* release studies were subjected to various kinetic models and the formulations were found to follow zero order release mechanism. Thus the blends of Ethyl cellulose and Polyvinyl Pyrrolidone can be incorporated in other transdermal delivery systems also to produce sustained release.

Keywords: Transdermal drug delivery; Diltiazem hydrochloride; polyvinyl pyrrolidone; Ethyl cellulose.

INTRODUCTION

The flaws governing the traditional methods of drug delivery that has been used for a long time and continue to overwhelm the novel drug delivery system even today have forced the biologists to look for the alternatives beyond the obvious. Although being the most common route of drug administration, the oral route had significant disadvantage of low bioavailability due to hepatic first pass metabolism which results in high and low blood level spikes leading to high or frequent dosing making this route inconvenient. Therefore to mimic the benefits of intravenous drug infusion and to address the problems associated with conventional dosage forms transdermal drug delivery system was developed.^{1,2} Transdermal drug delivery system has proved to be an excellent alternative for the systemic delivery as it overcomes the flaws associated with conventional drug therapy including avoidance of first pass biotransformation and metabolism, minimizing absorption and metabolic variations, increasing bioavailability and efficacy of drugs, providing good patient compliance due to simple dosage regimen and enabling fast delivery termination at any point of time simply by removing the patch.³ Diltiazem is a calcium channel blocker, widely employed in the management of angina pectoris and hypertension. Its short biological half life (3.5 hour), low oral bioavailability (40 %) due to hepatic metabolism, high aqueous solubility, and the requirement of continuous delivery, makes it a potential candidate for sustained release preparations. Transdermal drug delivery systems are best suited for the chronic diseases which require continuous and controlled drug delivery.⁴⁻⁶ Formulation of transdermal patch was envisioned for Diltiazem hydrochloride as such a system would bypass hepatic first pass metabolism of the drug thus ensuring the therapeutic concentration of the drug over the required period of time in systemic circulation which is vital for the disease for which the drug is employed. The objective of the present study was the

formulation and evaluation of matrix type transdermal therapeutic system of Diltiazem hydrochloride, followed by the selection of the best formulation on the basis of the physicochemical evaluation parameters and *in vitro* release study.

MATERIAL AND METHODS

Diltiazem hydrochloride was received as a gift sample from Athena Pharma Pvt Ltd, Maharashtra, India. Other chemicals Ethyl cellulose, polyvinyl pyrrolidone, dibutyl phthalate, dimethyl sulfoxide, chloroform (CDH Pvt Ltd, Mumbai, India) were obtained commercially and were used as such. In addition, double beam spectrophotometer (Shimadzu UV 1800 Japan), magnetic stirrer (Macro scientific works, Delhi, India), pH meter (Labtronics, India), digital balance (Citizen scale CY220), screw gauge (Sterling manufacturing company, India), Franz diffusion cell (Bhanu scientific instruments CO, Bangalore, India) were also employed in this study. FTIR of the patches was done at Punjab technical university. DSC was carried out at S.N. Bose National centre for basic sciences, Kolkata, India.

Preparation of Matrix Type Transdermal Patch

Matrix type transdermal patches containing Diltiazem hydrochloride were prepared using solvent casting technique. The required proportion of polymers (Ethyl cellulose and polyvinyl pyrrolidone) were weighed and dispersed in 10 ml of casting solvent (chloroform) by continuous stirring on a magnetic stirrer for 6 h. Then dibutyl phthalate (30 % w/v of polymer weight) was incorporated a plasticizer and dimethyl sulfoxide (15 % w/w of polymer weight) was incorporated as a penetration enhancer in the above solution. At last Diltiazem hydrochloride (100 mg) was added to the solution with continuous stirring. After complete mixing, the

solution was allowed to stand for 30 min to ensure the removal of air bubbles and then the resulting solution was poured on mercury placed in a glass petridish (9.4 cm diameter) and dried at room temperature for 24 h. The rate of evaporation was controlled by inverting a funnel over the petridish. The solvent completely dried in 24 hrs whereas dibutyl phthalate and dimethyl sulfoxide remained in drug polymer matrix. After drying the films were peeled off from the glass petridish and were then cut to yield the patch of 1.0 cm in diameter. The patches were then stored in a dessicator containing fused calcium chloride to maintain integrity and elasticity until further use. The composition of various formulations is given in Table 1.

Evaluation of Transdermal Patches

Physical appearance

The patches were visually examined for color, clarity, flexibility and smoothness.⁷

Interaction studies

The interaction studies were carried out by FTIR and DSC.

Fourier transform infrared spectroscopy (FTIR)

The FTIR analysis of Diltiazem hydrochloride was carried out for qualitative identification of the compound. The potassium bromide pellet of approximately 1 mm in diameter incorporating Diltiazem hydrochloride was prepared by grinding 3-5 mg of Diltiazem hydrochloride with 100-150 mg of potassium bromide in pressure compression machine. The resulting pellet was then mounted in the FTIR compartment and was scanned at a wavelength ranging from 4000 cm^{-1} - 400 cm^{-1} . The observed peaks were reported for functional groups.

Differential scanning calorimetry (DSC)

DSC was carried out to determine the exact melting point of Diltiazem hydrochloride employed in the present investigation. It was carried out at a temperature of 50-450° C at 5°C/min using duplicate samples of 5 mg in crimped aluminum pans. The DSC instruments were calibrated using indium samples.⁸

Thickness

Five patches were randomly selected and the thickness was assessed at three different places using a screw gauge. Then from the average value thickness of one patch was determined.^{9,10}

Weight variation

The individual weight of five patches was determined using digital balance and average weight was determined. The individual weight should not deviate significantly from the average weight.^{11,12}

Drug content uniformity

The drug content uniformity was determined on the basis of dry weight of the drug and polymer used, by means of UV/VIS spectrophotometer method. Five strips were cut from the prepared patch and were taken in separate stoppered conical flasks containing 100 ml of suitable dissolution medium (0.1 N HCl:CH₃OH) and stirred vigorously for 6 h using magnetic stirrer. The above solution was then filtered and suitable dilutions were made. Absorbance was observed using UV-Visible spectrophotometer at 236 nm against a blank solution prepared by the same protocol but not containing the drug.¹³

Folding endurance

Folding endurance was determined by repeatedly folding the patch at the same place until it breaks. The number of times the patch could be folded without breaking gave the folding endurance value.^{14,15}

Surface pH

The surface pH was determined by allowing the patches to swell by keeping them in contact with 0.5 ml of phosphate buffer saline for 1 h. Then the pH paper was brought in contact with the surface of the swollen patch. Then mean of three readings was recorded.¹⁶

Percentage flatness

Longitudinal strips were cut from the prepared medicated patches and the length of each strip was measured and the variation in length due to non uniformity in flatness was measured. Flatness was determined by measuring constriction of strips and a zero percent constriction indicated 100 % flatness.

$$\text{Constriction \%} = (I_1 - I_2) / I_1 \times 100$$

Where I_1 is the initial length of the strip and I_2 is the final length.¹⁷

Swellability

The drug loaded patch was weighed and then placed in a petridish to which 50 ml of phosphate buffer (pH 7.4) was added. The patches were weighed after every 10 minutes until constant weight was attained. The difference in weight gives the weight increase because of absorption of water. The percentage swelling is given by the following equation

$$\%S = (X_t - X_0) / X_0 \times 100$$

Where X_0 is the weight of the patch at zero time and X_t is the weight of the patch after time t .^{18,19}

In vitro drug permeation study

In vitro study was carried out to predict the delivery and permeation of the drug molecule through the skin surface in the body of the living animal. This was achieved by using a Franz diffusion cell.²⁰

Preparation of rat abdominal skin

The male wistar rats weighing 170-190 g were sacrificed using anesthetic ether. The full thickness skin was removed from the abdominal region and abdominal hairs were removed by depilatory. The dermal side of the skin was washed thoroughly with distilled water to remove the blood vessels and adhering tissues. The skin of the test animal was then wrapped in aluminum foil and stored in freezer until further use. Prior to the experiment the skin was equilibrated for 15 minutes in the dissolution medium (phosphate buffer pH 7.4).²¹

Procedure

The receptor compartment of the Franz diffusion cell was filled with 65 ml of phosphate buffer pH 7.4. The contents of the diffusion cell were stirred using a teflon coated bead at a constant speed of 50 rpm on a magnetic stirrer. The isolated rat skin was mounted on the diffusion cell and the transdermal patch was placed over the skin. The temperature of the medium in the receiver compartment was maintained at $37 \pm 1^\circ\text{C}$ with the water jacket. The donor compartment was kept open to maintain the exposure of system to ambient conditions. The amount of drug permeated in the receptor solution was determined by withdrawing 1 ml at hourly intervals

and each time equal volume of buffer was supplemented in the receptor compartment to maintain sink condition. The samples were then diluted to 10 ml and analyzed for drug content at 236 nm using UV spectrophotometer. The permeation study was carried out for 11 hours.²² The complete assembly of Franz diffusion cell has been shown in Figure 1.

RESULTS

The monolithic transdermal patches of Diltiazem hydrochloride using ethyl cellulose and polyvinyl pyrrolidone were prepared by solvent evaporation and solvent casting technique and were flexible, smooth and transparent.

Drug excipient interaction study

FTIR characterization

The FTIR spectra of the drug and the drug loaded patch depicted in the Figures 2 and 3 respectively indicated absence of interaction between the drug and the polymer. The principal peaks of the drug due to the carbonyl groups showed the values around 1679 and 1742 cm^{-1} . These peaks were found intact in the drug polymer mixture which indicated the compatibility of the drug with the polymer. The infrared spectral assignment of the drug has been shown in Table 2.

Thermal characterization

The DSC analysis of Diltiazem hydrochloride showed a sharp peak at 213°C corresponding to its melting point. The melting endotherm

of drug polymer mixture showed no considerable change in the melting point of drug. The DSC thermo grams of drug and drug polymer mixture have been shown in Figures 4 and 5. The transdermal patches were also evaluated for the physical parameters which have been depicted in Table 3.

In vitro permeation studies

The permeation study was carried out for 11 hours and maximum permeation was obtained for formulation F4 (96.009) and minimum permeation was obtained for formulation F1 (64.93). Formulation F1 contained higher proportion of Ethyl cellulose and it showed comparatively sustained release pattern. Hence for obtaining sustained release high concentration of ethyl cellulose is required. The cumulative percentage of drug permeated for all the formulations have been shown in Table 4. The plot of cumulative percent of drug permeated v/s time has been shown in Figure 6.

Drug release kinetics

The *in vitro* permeation data obtained for all the formulations was fitted to various kinetic models to elucidate the permeation profile. The drug permeation profile for all the formulations was found to follow zero order kinetics as evidenced by the straight line and higher regression value depicted in Figure 6. Thus the release rate was independent of the concentration of the drug. The kinetic models for various formulations have been shown in the Table 5.

Table 1: Composition of transdermal patches

S. No.	Formulation code	Polymers EC:PVP (500 mg)	Plasticizer dibutyl phthalate %w/v	Penetration enhancer dimethyl sulfoxide %w/w	Casting solvent	Drug (mg)
1.	F1	8:1	30	15	Chloroform	100
2.	F2	6:1	30	15	Chloroform	100
3.	F3	4:1	30	15	Chloroform	100
4.	F4	2:1	30	15	Chloroform	100

Volume of the casting solvent for each formulation is 10 ml, *Based on the polymer weight

Table 2: Infrared Spectral assignment of Diltiazem Hydrochloride

S. No.	Functional groups	Frequency
1.	Aromatic C-H _{str}	3034 cm^{-1}
2.	Aliphatic C-H _{str}	2926 cm^{-1}
3.	Acetate C=O _{str}	1742 cm^{-1}
4.	Lactum C=O _{str}	1679 cm^{-1}
5.	O- substituted C-H _{def}	837 cm^{-1}
6.	p-substituted C-H _{def}	779 cm^{-1}

Table 3: Physical parameters and drug content of transdermal patches

Batch codes	Physical appearance	*Weight (mg)	*Thickness (mm)	*Drug content	*Surface pH	*Folding endurance	Flatness (%)	%Swellability
F1	++	8.6 ± 0.002	0.170 ± 0.001	97.4 ± 0.30	6.7 ± 0.15	296 ± 0.52	100	12.2
F2	++	8.8 ± 0.050	0.175 ± 0.001	97.7 ± 0.10	6.8 ± 0.10	299 ± 0.01	100	15.4
F3	++	8.26 ± 0.001	0.172 ± 0.005	98.0 ± 0.52	6.7 ± 0.11	297 ± 0.57	100	16.2
F4	++	9.20 ± 0.001	0.178 ± 0.007	99.6 ± 0.11	6.9 ± 0.10	299 ± 0.15	100	18.6

++ Satisfactory; *Average of three determinations for each parameter

Table 4: % Cumulative drug permeated for the formulations F1 –F4

Time (min)	Cumulative % of Drug permeated (F1)	Cumulative % of drug permeated (F2)	Cumulative % of drug permeated (F3)	Cumulative % of drug permeated (F4)
60	5.853	8.95	11.70	7.85
120	9.853	18.82	19.70	17.90
180	13.98	26.55	26.69	26.53
240	20.72	34.61	36.19	34.28
300	24.54	41.42	43.68	41.28
360	31.56	46.98	49.71	46.76
420	37.93	54.00	56.40	56.36
480	43.06	60.51	62.43	68.81
540	47.13	68.10	69.73	75.79
600	53.24	78.35	77.67	85.15
660	64.93	81.32	85.97	96.01

Table 5: Value of R² for different kinetic models for Formulations F1-F4

Formulation code	R ²				
	Zero order	First order	Higuchi	Korsmeyer Peppas's	n value
F1	0.991	0.887	0.887	0.991	0.121
F2	0.995	0.942	0.942	0.991	0.114
F3	0.994	0.946	0.946	0.980	0.108
F4	0.996	0.908	0.908	0.966	0.711



Figure 1: Complete assembly of Franz diffusion cell for *in vitro* release study

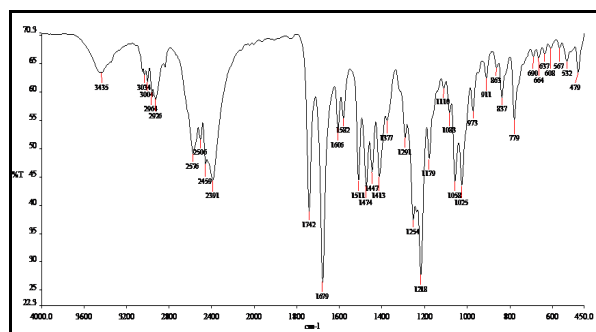


Figure 2: IR spectra of Diltiazem hydrochloride

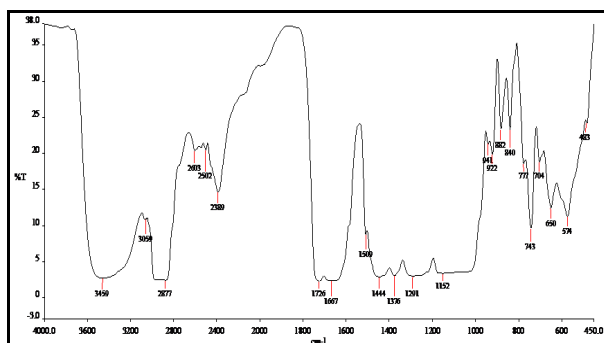


Figure 3: IR spectra of the drug loaded patch containing Ethyl cellulose and Polyvinyl pyrrolidone

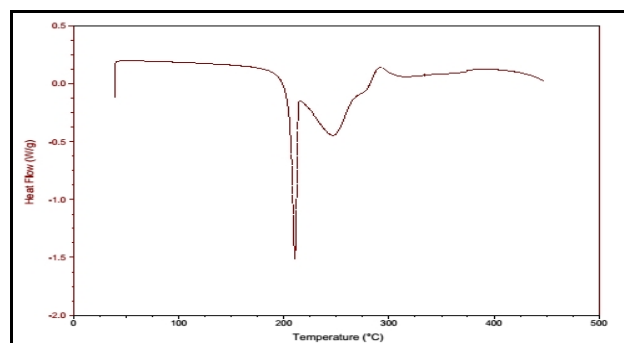


Figure 4: DSC thermogram of Diltiazem hydrochloride

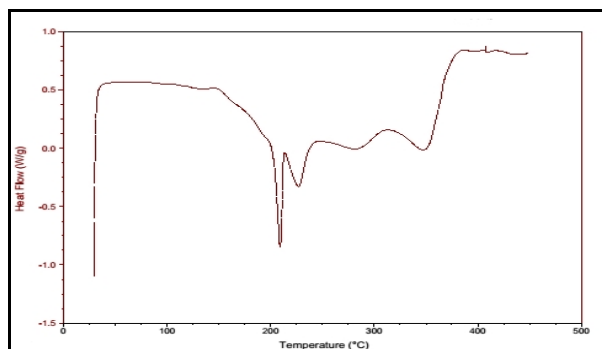


Figure 5: DSC thermogram of the drug loaded patch containing Ethyl cellulose and Polyvinyl pyrrolidone

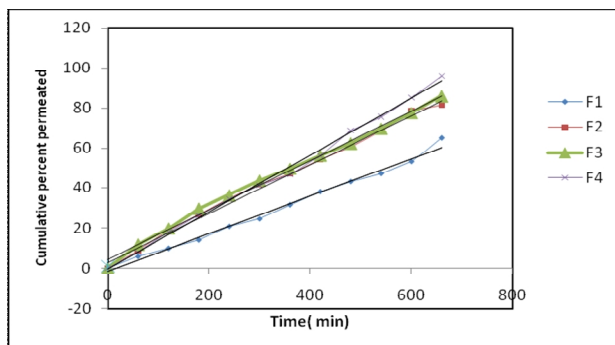


Figure 6: Plot of cumulative percent permeated v/s time across rat abdominal skin for Formulations F1 – F4

DISCUSSION

The Interaction studies for the patch suggested the absence of interaction between the drug and the polymer as observed by the absence of additional peaks in the FTIR spectra of the drug and the polymer. The thickness of the patches ranged from 0.170 ± 0.001 to 0.178 ± 0.007 and weight ranged from 8.26 ± 0.010 to 9.20 ± 0.001 indicating low standard deviation. Good uniformity of drug content among the batches was observed with all formulation and ranged from 97.4 ± 0.30 to 99.6 ± 0.11 . The results indicated that the process employed for the preparation of patches resulted in patches with uniform drug content and minimum patch variability. The surface pH of all the formulations was found to be in the range of 6.7 ± 0.11 to 6.9 ± 0.10 which coincides with the pH range of skin and hence no skin irritation would occur. The folding endurance measures the capacity of the patch to withstand rupture. The results indicated that the folding endurance was in the range of 296 ± 0.52 to 299 ± 0.15 which was satisfactory and ensured that the patches would maintain their integrity when applied to the skin. The results of flatness study indicated that there was no difference in the strip length before and after the longitudinal cuts which indicated 100 % flatness thus ensuring that patch will retain its smooth surface when applied to skin. The hydration study is considered important in sustained release as it affects the release of drug from the controlled release matrix. Water uptake can result in formation of empty spaces thus rendering the structure less resistant and more prone to mechanical stresses. % swellability studies conducted for the Diltiazem hydrochloride patches indicated that increase in concentration of hydrophilic polymer was directly proportional to the increase in % swellability of the patches. The order of % Swellability in different polymeric membranes was found to be $F-4 > F-3 > F-2 > F-1$. The Swellability varied with nature and composition of patches. Hydrophilic polymer showed considerable swelling, as it increased the surface wettability and consequently water penetration within the matrix. The *in vitro* permeation study was conducted for 11 hours and the cumulative percentage permeation was found to be highest in formulation F4 and lowest in formulation F1. (Table 4) Formulations F2, F3 and F4 showed initial burst release which was due to high concentration of hydrophilic polymer. The hydrophilic nature of polyvinyl pyrrolidone results in burst effect as very little time lag is required to establish the concentration profile. Polyvinyl pyrrolidone acts as insoluble film former and Ethyl cellulose tends to increase the release rate of polyvinyl pyrrolidone. The resultant effect of the polymers contributes in leaching the soluble component which leads to pore formation and also the mean diffusion path length of the drug molecule decreases. Polyvinyl pyrrolidone maintains the drug in amorphous form in the matrix hence enhancing the solubility of the drug. The slow permeation observed in case of Formulation F1 can be attributed to the high concentration of the EC which is a

hydrophobic polymer and hence retains the drug in the matrix by avoiding penetration of water.

CONCLUSION

Formulated patches were found to be smooth flexible and transparent and exhibited good physicochemical properties. The *in vitro* permeation study indicated increase in the permeation rate with the increase in the concentration of hydrophilic polymer and formulation F4 was found to depict maximum release as compared to other formulations. The release kinetics was found to follow zero order and non fickian diffusion. The results of evaluation studies indicated that the formulated patches of Diltiazem hydrochloride shows better compliance than conventional drug delivery system. Studies have depicted promising results and it holds scope for further pharmacokinetic and pharmacodynamic evaluation to filter out the potential of this delivery system.

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