Transdermal Therapeutic System of Carvedilol: Effect of Hydrophilic and Hydrophobic Matrix on In Vitro and In Vivo Characteristics

Submitted: April 24, 2006; Accepted: June 28, 2006; Published: January 19, 2007

Udhumansha Ubaidulla,[1,2] Molugu V.S. Reddy,[2] Kumaresan Ruckmani,[2] Farhan J. Ahmad,[1] and Roop K. Khar[1]

[1]Faculty of Pharmacy, Jamia University, Department of Pharmaceutics, New Delhi, India
[2]Periyar College of Pharmaceutical Sciences, Tiruchirapalli, Tamil Nadu, India

ABSTRACT

The purpose of this research was to develop a matrix-type transdermal therapeutic system containing carvedilol with different ratios of hydrophilic and hydrophobic polymeric combinations by the solvent evaporation technique. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy and differential scanning calorimetry. The results suggested no physicochemical incompatibility between the drug and the polymers. In vitro permeation studies were performed by using Franz diffusion cells. The results followed Higuchi kinetics (r = 0.9953-0.9979), and the mechanism of release was diffusion mediated. Based on physicochemical and in vitro skin permeation studies, patches coded as F3 (ethyl cellulose:polyvinylpyrrolidone, 7.5:2.5) and F6 (Eudragit RL:Eudragit RS, 8:2) were chosen for further in vivo studies. The bioavailability studies in rats indicated that the carvedilol transdermal patches provided steady-state plasma concentrations with minimal fluctuations and improved bioavailability of 71% (for F3) and 62% (for F6) in comparison with oral administration. The antihypertensive activity of the patches in comparison with that of oral carvedilol was studied using methyl prednisolone acetate–induced hypertensive rats. It was observed that both the patches significantly controlled hypertension from the first hour ($P < .05$). The developed transdermal patches increase the efficacy of carvedilol for the therapy of hypertension.

KEYWORDS: Transdermal, antihypertensive, carvedilol, polyvinylpyrrolidone, ethyl cellulose, Eudragit.

INTRODUCTION

Carvedilol is the most widely prescribed drug in the long-term treatment of hypertension. Following oral administration, carvedilol is rapidly absorbed from the gastrointestinal tract (80%), but the oral bioavailability remains low (eg, 23%) because of significant first-pass hepatic metabolism by cytochrome P450 (urinary recovery as unchanged carvedilol is less than 0.3% of the oral administered dose).[1] Carvedilol also has a short plasma half-life of 6 hours.[2] Long-term therapy of hypertension by carvedilol oral administration may result in poor patient compliance because of low bioavailability and short plasma half-life, leading to increased frequency of administration. An alternate route of administration is needed.

The transdermal route is an alternative for administration of such drugs. This route offers many advantages over the oral dosage form, such as improving patient compliance in long-term therapy, bypassing first-pass metabolism, sustaining drug delivery, maintaining a constant and prolonged drug level in plasma, minimizing inter- and intrapatient variability, and making it possible to interrupt or terminate treatment when necessary.[3,4] Carvedilol possesses ideal characteristics—such as a low molecular weight (406.5), a favorable logarithmic partition coefficient (log octanol/water: 0.58 ± 0.02; log octanol/buffer pH 7.4: 0.61 ± 0.06), smaller dose range (25-50 mg), short plasma half-life, and poor oral bioavailability[2]—for formulation as a transdermal patch.

There are reports describing the use of Eudragit RL (ERL) and Eudragit RS (ERS) transdermal delivery systems as well as other dosage forms for controlled release of drugs.[5] ERL is freely permeable to water, whereas ERS is slightly permeable.[6] These transdermal delivery systems are neither extremely hydrophobic nor extremely hydrophilic. Therefore, varying the ratio of these polymers in the composition of the films provides control of drug release characteristics.[7]

The aims of the present study were to (1) develop different matrix patches with various ratios of hydrophilic and hydrophobic polymer combinations such as (a) ethyl cellulose (EC) and polyvinylpyrrolidone (PVP), and (b) ERL 100 and ERS 100 containing carvedilol; (2) perform physicochemical characterization and in vitro permeation studies through rat skin; and (3) evaluate the efficacy of transdermal patches against hypertension-induced rats. 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.

Corresponding Author: Udhumansha Ubaidulla, Faculty of Pharmacy, Jamia University, Department of Pharmaceutics, New Delhi, India. Tel: 91-11-26089688-5605; Fax: 91-11-2605-9663; E-mail: ubaidnkl@gmail.com

Materials and Methods

Materials

Carvedilol was received as a gift sample from Sun Pharmaceuticals Ltd (Baroda, India). ERL 100, ERS 100, and PVP were procured from Madras Pharmaceuticals (Chennai, India). EC (ethoxy content of 47.5%-53.5% by weight and viscosity of 14 cps in a 5% wt/vol, 80:20 toluene:ethanol solution at 25°C) was purchased from SD Fine Chemicals Ltd (Mumbai, India). Methyl prednisolone acetate (MPA) was purchased from Sigma Chemical Co (St Louis, MO). Other materials used in the study (chloroform, sodium hydroxide, phosphoric acid, diethyl ether, and potassium dihydrogen phosphate) were of analytical grade. Double-distilled water was used throughout the study.

Investigation of Physicochemical Compatibility of Drug and Polymer

The physicochemical compatibility between carvedilol and polymers used in the patches was studied by using differential scanning calorimetry (DSC, Perkin-Elmer–Pyris 6 DSC, Salem, MA) and fourier transform infrared (FTIR) spectroscopy. In DSC analysis, the samples were weighed (5 mg), hermetically sealed in flat-bottom aluminum pans, and heated over a temperature range of 50 to 250°C in an atmosphere of nitrogen (20 mL/min) at a constant increasing rate of 10°C/min. The thermograms obtained for carvedilol, polymers, and physical mixtures of carvedilol with polymers were compared.

The infrared (IR) spectra were recorded using an FTIR spectrophotometer (FTIP-800, Biorad, Munich, Germany) by the KBr pellet method and spectra were recorded in the wavelength region between 4000 and 400 cm^{-1}. The spectra obtained for carvedilol, polymers, and physical mixtures of carvedilol with polymers were compared.

Preparation of Transdermal Films

The matrix-type transdermal patches containing carvedilol were prepared using different ratios of EC:PVP and ERL 100:ERS 100 (Table 1). The polymers in different ratios were increased to a total weight of 400 mg and dissolved in chloroform. Carvedilol (2.5% wt/wt) was added slowly to the polymer solution and mixed thoroughly to obtain a uniform solution. Di-*n*-butyl-phthalate was used as a plasticizer. The polymeric solution of drug was poured onto the mercury surface (25 cm^2) and dried at room temperature in a dust-free environment. After 24 hours, the films were cut into a 5 cm^2 piece and a backing membrane of polypropylene film was glued on. The transdermal films were stored in a desiccator until further use.

Evaluation of Physicochemical Properties of Patches

Weight Variation

Weight variation was studied by individually weighing 10 randomly selected patches. Such determination was performed for each formulation.

Drug Content

A 5-cm^2 film was cut into small pieces, put into a 100-mL buffer (pH 7.4), and shaken continuously for 24 hours. Then the whole solution was ultrasonicated for 15 minutes. After filtration, the drug was estimated spectrofluorometrically at an excitation wavelength of 240 nm and an emission wavelength of 340 nm. The preliminary studies indicated that there was no interference of polymers in the excitation and emission wavelengths of the drug.

Flatness

Three longitudinal strips were cut out from each film: 1 from the center, 1 from the left side, and 1 from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.[8]

Folding Endurance

Folding endurance was determined by repeatedly folding the film at the same place until it broke. The number of times

Table 1. Composition and Physicochemical Properties of Carvedilol Transdermal Patches*

Code	Ratio of EC:PVP	Ratio of ERL:ERS	Weight (mg)	(%) Drug Content	% MU	% MC	Folding Endurance
F1	9:1	—	92.02 ± 1.6	99.0 ± 0.3	4.65 ± 3.4	3.24 ± 1.6	12 ± 1.9
F2	8:2	—	92.22 ± 2.0	98.3 ± 0.4	5.84 ± 2.2	5.18 ± 2.4	8 ± 2.1
F3	7.5:2.5	—	91.24 ± 2.3	99.8 ± 0.1	7.98 ± 3.6	6.32 ± 3.8	6 ± 1.4
F4	—	5:5	93.44 ± 2.6	98.2 ± 0.3	3.68 ± 3.1	2.36 ± 2.2	9 ± 3.6
F5	—	7:3	93.46 ± 3.8	99.0 ± 0.4	5.02 ± 2.9	3.98 ± 3.8	10 ± 3.0
F6	—	8:2	93.68 ± 3.5	100.0 ± 0.6	6.74 ± 2.0	5.22 ± 3.7	10 ± 3.2

*All values are expressed as mean ± SD (n = 10). EC indicates ethyl cellulose; PVP, polyvinylpyrrolidone; ERL, Eudragit RL; ERS, Eudragit RS; MU, moisture uptake; MC, moisture content.

the film could be folded at the same place without breaking was the folding endurance value.

Percentage of Moisture Content

The films were weighed individually and kept in a desiccator containing activated silica at room temperature for 24 hours. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.[9]

Percentage of Moisture Uptake

A weighed film kept in a desiccator at room temperature for 24 hours was taken out and exposed to 84% relative humidity (a saturated solution of aluminum chloride) in a desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

In Vitro Skin Permeation Studies

In vitro skin permeation studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 20 mL. The excised rat abdominal skin was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were placed over the skin and covered with paraffin film. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 32 ± 0.5°C. The samples were withdrawn at different time intervals and analyzed for drug content spectrofluorometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. The cumulative amounts of drug permeated per square centimeter of patches were plotted against time.

In Vivo Studies

The animals used for in vivo experiments were adult male Wistar albino rats (230-250 g) procured from the central animal house of the Periyar College of Pharmaceutical Sciences (Tiruchirapalli, India). The animals were kept under standard laboratory conditions, at 25 ± 1°C and 55 ± 5% relative humidity with a 12-hour light/dark cycle. The animals were housed in polypropylene cages, 4 per cage, with free access to a standard laboratory diet (Lipton Feed, Mumbai, India) and water ad libitum. Guidelines of the institutional animal ethics committee were followed for in vivo experiments.

Pharmacokinetic Evaluation of Patches on Animals

Wistar albino rats were used as the animal models for the bioavailability studies. The animals were selected after superficial examination of the skin surface for abnormalities. Only rats weighing between 230 and 250 g were selected for the study. About 10 cm^2 of skin was shaved on the dorsal side. Before application of the patches, rats were kept under observation for 24 hours for any untoward effects of shaving; they were fasted over this period. The rats were divided into 3 groups (n = 6). Group I was administered carvedilol orally (5 mg/kg), group II received transdermal patch F3, and group III received transdermal patch F6. The blood samples were withdrawn at different time intervals (1, 2, 3, 5, 8, 12, and 24 hours). Plasma samples were separated by centrifugation (Sorvall Centrifuge, Hertfordshire, UK) and stored in vials at –70°C until they were analyzed.

The plasma carvedilol concentration was measured according to the Reverse Phase - High Performance Liquid Chromatography (RP-HPLC) method[10] with a slight modification. The plasma samples were made alkaline by adding 1N NaOH (50 μL) and extracted with diethyl ether (5 mL). The analytes were back-extracted into 250 μL of 0.2% phosphoric acid. Exactly 50 μL of analytes were injected into the RP-HPLC system. The chromatographic assembly consisted of a model LC-10A Liquid Chromatograph (Shimadzu, Japan), a Rheodyne 7125 injector, and a model RF-10A fluorometry detector set at an excitation wavelength of 278 nm with a 320-nm emission filter. The column used was (5 μm, 150 × 20 mm) C18 base-deactivated. The binary mobile phase consisted of (1) 20 mM pH 2.5 potassium phosphate buffer, and (2) a mixture of methanol, acetonitrile, and isopropanol (7:2:1). The starting mobile phase composition was 31% of mobile phase (2) and increased to 47% in 8 minutes. This percentage was held for 3 minutes; then, the composition returned to initial conditions in 12 minutes.

Efficacy of Transdermal Patches Against Hypertension in Rats

A blood pressure (BP) measuring instrument (Stoelting, Wood Dale, IL) with a non-invasive tail cuff and a digital BP display panel was used. The rats were trained to stay in the rat holder in a calm and non-aggressive state during BP measurement. After rats' initial BPs were recorded, hypertension was induced by injecting MPA (20 mg/kg/week subcutaneously).[11,12] Two weeks later, rats with a minimum mean BP of 150 mmHg were selected. The animals were divided into 4 groups (n = 6). Group I served as control, group II received carvedilol 5 mg/kg orally, group III received transdermal patch F3, and group IV received transdermal patch F6. BP was measured at different time intervals (1, 2, 4, 6, 10, and 24 hours).

Skin Irritation Test

The hair on the dorsal side of Wistar albino rats was removed by clipping 1 day before this portion of the experiment.[13] The rats were divided into 4 groups (n = 6). Group I served as the control, group II received transdermal patch F3, group III received transdermal patch F6, and group IV received an 0.8% vol/vol aqueous solution of formalin as a standard irritant.[14] A new patch, or new formalin solution, was applied daily for 7 days. Finally, the application sites were graded according to a visual scoring scale, always by the same investigator.

In Vitro and In Vivo Data Analysis

The cumulative amount of carvedilol permeated per unit area was plotted against time, and the slope of the linear portion of the plot was estimated as steady-state flux (Jss). The permeability coefficient (Kp) was calculated by using the equation Kp = Jss/Cv, where Cv is the total concentration of the patches.

The plasma concentration of carvedilol at different time intervals was subjected to pharmacokinetic analysis to calculate various parameters: maximum plasma concentration (C_{max}), time to reach maximum concentration (T_{max}), and area under the plasma concentration-time curve ($AUC_{0\rightarrow\infty}$). The values of C_{max} and T_{max} were read directly from the arithmetic plot of time vs plasma concentration of carvedilol. The AUC was calculated by using the trapezoidal rule. The elimination rate constant (K_e) was calculated by regression analysis from the slope of the line, and the half-life ($t_{1/2}$) was obtained by $0.693/K_e$. The relative bioavailability of the carvedilol after the transdermal administration versus the oral administration was calculated as follows:

$$F(\%) = \left(\frac{\text{Sample AUC}}{\text{Oral AUC}}\right)\left(\frac{\text{Oral}}{\text{Sample}}\right) \qquad (1)$$

The statistical significance of the differences between the formulations was analyzed by Student *t* test using Graph Pad InStat 3 software. A difference below the probability level of .05 was considered statistically significant.

Results and Discussion

Investigation of Physicochemical Compatibility of Drug and Polymer

The DSC analysis of pure carvedilol showed a sharp endothermal peak at 116.91°C, corresponding to the drug's melting point (Figure 1). The DSC analysis of the physical mixture of the drug and the polymers revealed a negligible change in the melting point of carvedilol in the presence of the polymer mixtures studied (115.34°C for the mixture of carvedilol, EC, and PVP, and 118.23°C for the mixture of carvedilol, ERL, and ERS). The IR spectral analysis of carvedilol alone showed that the principal peaks were observed at wavenumbers 3348, 1630, 1503, 980, and 958 cm^{-1}, confirming the purity of the drug. In the IR spectra of the physical mixture of carvedilol, EC, and PVP, the major peaks of carvedilol were observed at wavenumbers 3343, 1633, 1502, 984, and 958 cm^{-1}; for the physical mixture of carvedilol, ERL, and ERS, they were observed at 3344, 1632, 1503, 984, and 958 cm^{-1}. However, some additional peaks were observed with the physical mixture, possibly because of the presence of polymers. The DSC and IR results suggest that the drug and polymers are compatible. Wade and Weller reported that EC, PVP, ERL, ERS, and other common polymers are popular in controlled- and sustained-release matrix-type patches because of their compatibility with several drugs.[6]

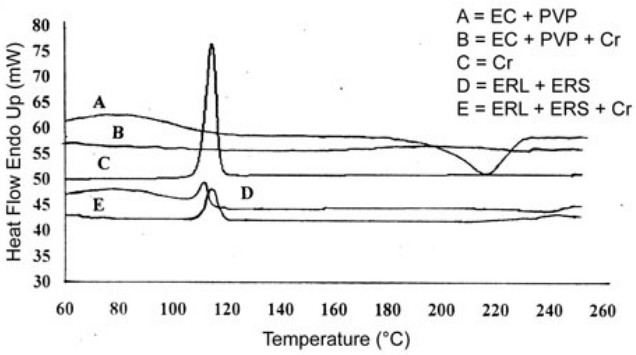

Figure 1. DSC thermograms of carvedilol, polymers, and the physical mixtures. Cr indicates carvedilol.

Physicochemical Characterization of Patches

The results of the physicochemical characterization of the patches are shown in Table 1. The weights ranged between 91.24 mg and 93.68 mg, which indicates that different batches' patch weights were relatively similar. Good uniformity of drug content among the batches was observed with all formulations and ranged from 98.24% to 100.04%. The results indicate that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability. The flatness study showed that all the formulations had the same strip length before and after their cuts, indicating 100% flatness. Thus, no amount of constriction was observed; all patches had a smooth, flat surface; and that smooth surface could be maintained when the patch was applied to the skin. Folding endurance test results indicated that the patches would not break and would maintain their integrity with general skin folding when applied.

Moisture content and moisture uptake studies indicated that the increase in the concentration of hydrophilic polymer was directly proportional to the increase in moisture content and

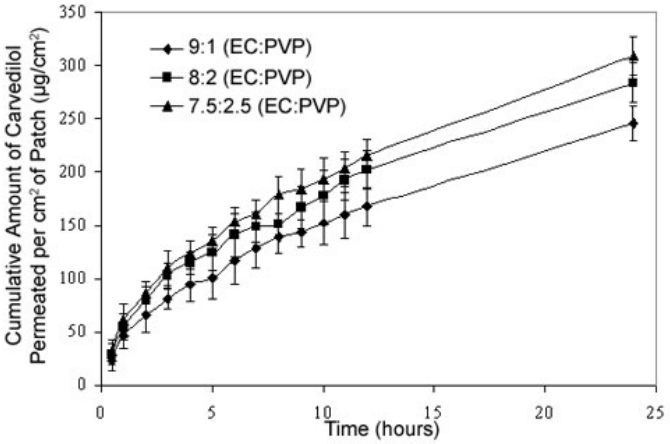

Figure 2. In vitro skin permeation profile of carvedilol from transdermal patches with different proportions of ethyl cellulose: polyvinylpyrrolidone. Data are mean ± SE (n = 6).

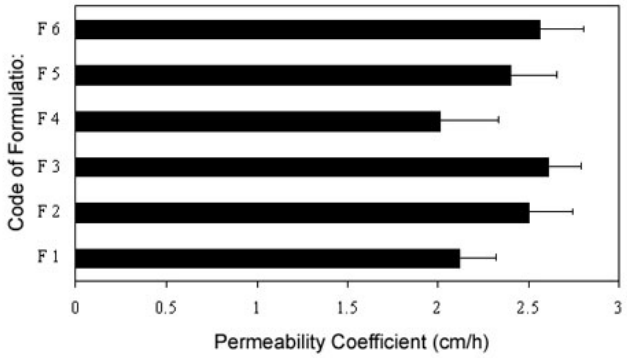

Figure 4. In vitro skin permeation coefficient (cm/h) from transdermal patches through rat abdominal skin, in phosphate buffer pH 7.4. Data are mean ± SE (n = 6).

moisture uptake of the patches. The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long-term storage. The moisture uptake of the formulations was also low, which could protect the formulations from microbial contamination and reduce bulkiness.[14]

In Vitro Skin Permeation Studies

The in vitro release profile is an important tool that predicts in advance how a drug will behave in vivo.[15] The results of in vitro skin permeation studies of carvedilol from transdermal patches are shown in Figures 2 and 3. The cumulative amount of drug released from formulations (1 cm^2) F3 and F6 (309.02 and 304.201 µg) was high when compared with release from other formulations. When the cumulative amount of drug permeated per square centimeter of patches through rat skin was plotted against time, the permeation profiles of the drug followed mixed zero-order/first-order kinetics. The in vitro release profiles of the formulations did not fit into zero-order kinetics (r^2 = 0.9206-0.9282) or first-order kinetics (r^2 = 0.6615-0.6782). However, the release profile of the formulated patches followed Higuchi's equation (r^2 = 0.9953-0.9979), which indicates that the permeation of the drug from the patches was governed by a diffusion mechanism. Since many release processes can be represented by a coupling of a Fickian and non-Fickian mechanism, Ritger and Peppas introduced the power law equation $M_t/M_\infty = Kt^n$ to characterize the controlled-release behavior of a drug from polymer matrices.[16] The value of n can be calculated from the slope of In $M_t/M\infty$ vs In t and can be indicative of the operating release mechanism. The n values ($0.5022 < n > 0.5268$) obtained by this equation indicated that the amount of drug released by Fickian diffusion predominated with all formulations. In this context, the results obtained from the Fickian mechanism support the results of Higuchi's equation and the theory that the patches release the drug by a diffusion-dominated mechanism.

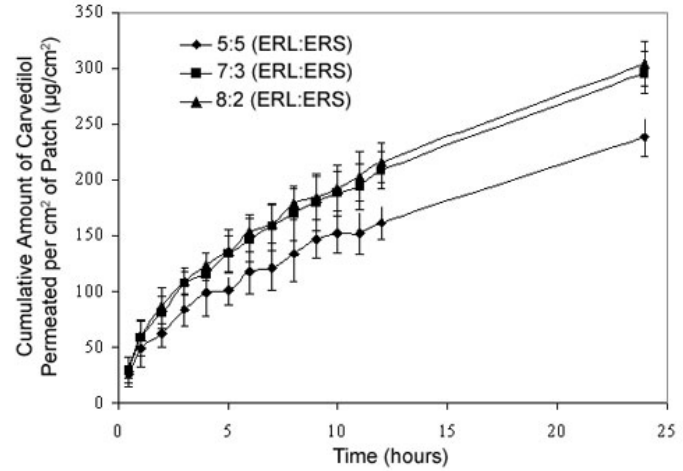

Figure 3. In vitro skin permeation profile of carvedilol from transdermal patches with different proportions of Eudragit RL: Eudragit RS. Data are mean ± SE (n = 6).

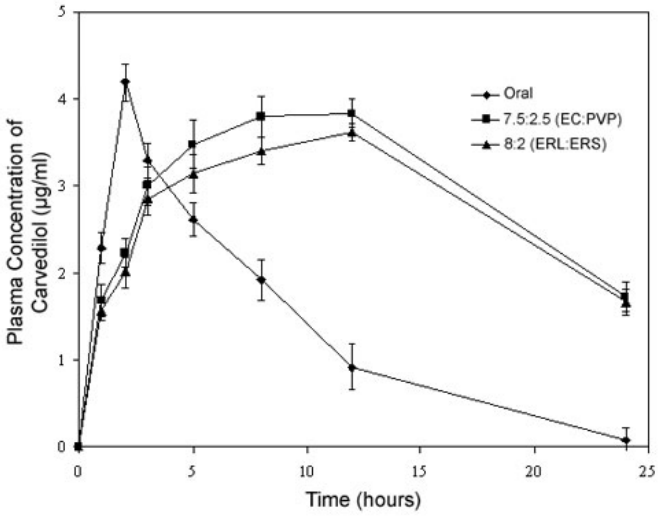

Figure 5. In vitro study profile of carvedilol after oral and transdermal patch treatment in rats. Data are mean ± SE (n = 6).

Table 2. Mean Pharmacokinetic Parameters of Carvedilol After Oral and Transdermal Administration*

Parameters	Oral	F3	F6
C_{max} (μg/mL)	4.198 ± 0.22	3.842 ± 0.16	3.624 ± 0.10
T_{max} (h)	2.0 ± 0.00	12.0 ± 0.00	12.0 ± 0.00
k_e (h^{-1})	0.185 ± 0.012	0.041 ± 0.006†	0.044 ± 0.004†
$t_{1/2}$ (h)	3.75 ± 1.82	16.90 ± 0.68	15.75 ± 0.84
AUC_{0-24} (μg h/mL)	32.62 ± 4.68	71.52 ± 3.84†	65.74 ± 4.38†
$AUC_{0-\infty}$ (μg h/mL)	33.69 ± 3.24	167.41 ± 7.65†	145.42 ± 6.84†
F (%)	—	310.50 ± 10.24	270.17 ± 9.20

*All values are expressed as mean ± SE (n = 6). F3 and F6 are transdermal patches. C_{max} indicates maximum concentration; T_{max}, time of maximum concentration; K_e, elimination rate constant; AUC, area under the plasma concentration-time curve; $t_{1/2}$, elimination half-life; F (%), relative bioavailability.
†$P < .05$; significant compared with control.

The in vitro permeation experiment indicated that when the hydrophilic polymer concentration increased, the amount of drug permeation increased. As described by Rao and Diwan, initial rapid dissolution of the hydrophilic polymers occurs when the patch is in contact with the hydrated skin, resulting in the accumulation of high amounts of drug on the skin surface and thus leading to the saturation of the skin with drug molecules at all times.[17]

Unlike the formulations F1, F2, F4, and F5, the formulations F3 and F6 achieved a high cumulative amount of drug permeation at the end of 24 hours. When the permeability coefficients (Figure 4) of the different formulations were compared, F3 and F6 were found to have similar permeability coefficients and the highest levels of release. Based on physicochemical and in vitro release experiments, F3 and F6 were chosen for further in vivo studies.

Pharmacokinetic Evaluation of Films on Animals

Figure 5 shows the blood plasma levels of carvedilol after transdermal and oral administration. The pharmacokinetic parameters recorded in Table 2 were calculated from the blood plasma concentrations of the drug. The maximum drug concentration, C_{max}, after oral administration was 4.198 ± 0.22 μg/mL, and T_{max} was 2 hours. For the F3 patch, C_{max} and T_{max} were 3.842 ± 0.16 μg/mL and 12 hours; for the F6 patch C_{max} and T_{max} were 3.624 ± 0.1 μg/mL and 12 hours. All the pharmacokinetic parameters obtained with carvedilol transdermal patches were significantly different from those obtained with oral carvedilol administration. The results indicated that the elimination half-life of carvedilol was prolonged from oral administration (3.75 ± 1.82 hours) to transdermal patches (F3:16.9 ± 0.68 and F6:15.75 ± 0.84 hours) in rats, which means that the drug remains in the body for a longer period and its action is more sustained. The transdermal patches also have a lower elimination rate constant, which further supports sustained action of drug from the patches. The significantly high AUC values observed with transdermal patches also indicate increased bioavailability of the drug from patches compared with oral administration. The F3 and F6 patches were found to enhance the bioavailability of carvedilol by 3.1 and 2.7 times (percent relative bioavailability 310.50 ± 10.24 and 270.17 ± 9.20) with reference to the oral dosage form. The reported mean bioavailability of the oral form is 23%[1], while the patches provided a bioavailability of 71.30% (F3) and 62.1% (F6). This increased bioavailability from transdermal patches may be due to the elimination of hepatic first-pass metabolism.

Table 3. Antihypertensive Effect of Transdermal Patches in Comparison to Oral Route*

		Mean BP (mm Hg)						
Group	Treatment	Initial	1 Hour	2 Hours	4 Hours	6 Hours	10 Hours	24 Hours
I	Control	177.81 ± 7.64	175.59 ± 7.48	175.18 ± 6.95	176.43 ± 6.24	177.67 ± 6.55	177.31 ± 6.73	178.32 ± 6.39
II	Oral	176.82 ± 6.84	125.42 ± 6.84†	89.36 ± 5.84†	99.62 ± 5.32†	106.54 ± 6.32†	114.38 ± 4.84†	170.24 ± 6.28
III	F3	175.67 ± 7.43	151.16 ± 5.58†‡	132.42 ± 5.51†‡	112.47 ± 4.31†	108.69 ± 5.05†	102.51 ± 4.37†	111.38 ± 4.46†‡
IV	F6	179.69 ± 7.52	153.52 ± 5.74†‡	138.61 ± 5.25†‡	114.46 ± 5.11†	110.23 ± 4.36†	105.73 ± 4.45†	115.78 ± 4.27†‡

*All values are expressed as mean ± SEM (n = 6). F3 and F6 are transdermal patches.
†Significant compared with control ($P < .05$).
‡Significant compared with oral ($P < .05$).

Table 4. Skin Irritation Scores Following Transdermal Patch Administration

	Control		F3		F6		Formalin	
Rat No	Erythema*	Edema†	Erythema	Edema	Erythema	Edema	Erythema	Edema
1	0	0	0	1	2	0	2	2
2	0	0	1	0	0	0	3	1
3	0	0	1	0	1	1	3	2
4	0	0	2	1	1	0	2	3
5	0	0	1	0	2	1	3	3
6	0	0	2	0	2	2	3	2
Average	0	0	1.17 ± 0.3073‡	0.33 ± 0.2108‡	1.33 ± 0.3333‡	0.67 ± 0.3333‡	2.67 ± 0.2108	2.16 ± 0.3073

*Erythema scale: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, scar formation.

†Edema scale: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, severe.

‡Significant compared with formalin ($P < .05$).

Efficacy of Transdermal Patches Against Hypertension in Rats

The results in Table 3 indicate that the administration of MPA produced significant hypertension in rats. The oral administration of carvedilol significantly ($P < .05$) controlled the hypertension initially, with the maximum effect observed at 2 hours, but after 2 hours the BP started rising gradually until it was the same as the initial value at 24 hours. In contrast, the administration of carvedilol through transdermal patches F3 and F6 resulted in a gradual decrease of BP, with the maximum effect from both the patches observed at 10 hours ($P < .05$). Despite the fact that the patches produced a peak effect at 10 hours, they decreased the BP significantly ($P < .05$) at the first hour and the effect continued for 24 hours. This clearly indicates that the transdermal patches release the drug gradually over a period of time, which results in prolonged control of hypertension for 24 hours. Oral carvedilol acted quickly and drastically, but then its effect dropped off: the patches did not decrease the BP greatly in the initial phase when compared with the oral form, as indicated by the significant ($P < .05$) difference between the oral- and patch-treated groups at 2 hours, but the effect of oral carvedilol started declining after 6 hours because of its short half-life.[1] Since the administration of carvedilol through patches resulted in sustained and continued drug release for 24 hours, the patches were able to control the hypertension throughout the period. Clearly, the prepared transdermal patches (F3 and F6) are capable of surmounting the shortcomings of oral administration of carvedilol, such as low bioavailability, short half-life, and high first-pass metabolism.

Skin Irritation Test

The skin irritation test of the transdermal formulations F3 and F6 showed a skin irritation score (erythema and edema) of less than 2 (Table 4). According to Draize et al, compounds producing scores of 2 or less are considered negative (no skin irritation).[18] Hence, the developed transdermal formulations are free of skin irritation.

CONCLUSION

The carvedilol transdermal patches developed in this study have great utility and are a viable option for effective and controlled management of hypertension. However, pharmacodynamic and pharmacokinetic evaluation of these systems in human volunteers is necessary to confirm these findings.

ACKNOWLEDGMENTS

Professor V. Loganathan, Periyar College of Pharmaceutical Sciences (Trichirapalli, India), is acknowledged for his assistance. Special thanks is given to Sun Pharmaceuticals (Baroda, India) for providing a free gift sample of carvedilol.

REFERENCES

1. Mollendorff EV, Reiff K, Neugebauer G. Pharmacokinetics and bioavailability of carvedilol, a vasodilating beta-blocker. *Eur J Clinical Pharm.* 1987;33:511–513.

2. Dollery C. *Therapeutics Drugs.* Edinburgh, UK: Churchill Livingstone; 1999:75–80.

3. Chien YW. Transdermal therapeutic system. In: Robinson JR, Lee VHL, eds. *Controlled Drug Delivery Fundamentals and Applications.* 2nd ed. New York, NY: Marcel Dekker; 1987:524–552.

4. Keith AD. Polymer matrix consideration for transdermal devices. *Drug Dev Ind Pharm.* 1983;9:605–621.

5. Thassu D, Vyas SP. Controlled transdermal mucolytic delivery system. *Drug Dev Ind Pharm.* 1991;17:561–576.

6. Wade A, Weller PJ. *Handbook of Pharmaceutical Excipients.* Washington, DC: American Pharmaceutical Publishing Association; 1994:362–366.

7. Panigrahi L, Pattnaik S, Ghosal SK. The effect of pH and organic ester penetration enhancers on skin permeation kinetics of terbutaline sulfate from pseudolatex-type transdermal delivery systems through mouse and human cadaver skins. *AAPS PharmSciTech.* 2005;6: E167–E173.

8. Arora P, Mukherjee P. Design, development, physicochemical, and in vitro and in vivo evaluation of transdermal patches containing diclofenac diethylammonium salt. *J Pharm Sci.* 2002;91: 2076–2089.

9. Gupta R, Mukherjee B. Development and in vitro evaluation of diltiazem hydrochloride transdermal patches based on povidone-ethyl cellulose matrices. *Drug Dev Ind Pharm.* 2003;29:1–7.

10. Gehr TWB, Tenero DM, Boyle DA, Qian Y, Sica DA, Shusterman NH. The pharmacokinetics of carvedilol and its metabolites after single and multiple dose oral administration in patients with hypertension and renal insufficiency. *Eur J Clin Pharmacol.* 1999;55:269–277.

11. Aqil M, Ali A, Sultana Y, Dubey K, Najmi KA, Pillai KK. In vivo characterization of monolithic matrix type transdermal drug delivery systems of pinacidil monohydrate: a technical note. *AAPS PharmSciTech.* 2006;7:E1.

12. Aqil M, Sultana Y, Ali A, Dubey K, Najmi KA, Pillai KK. Transdermal drug delivery system of a beta blocker: design, in vitro, and in vivo characterization. *Drug Deliv.* 2004;11:27–31.

13. Namdeo A, Jain NK. Liquid crystalline pharmacogel based enhanced transdermal delivery of propranolol hydrochloride. *J Control Release.* 2002;82:223–236.

14. Mutalik S, Udupa N. Glibenclamide transdermal patches: physicochemical, pharmacodynamic, and pharmacokinetic evaluations. *J Pharm Sci.* 2004;93:1577–1594.

15. Katayose S, Kataoka K. Water-soluble polyion complex associates of DNA and poly(ethylene glycol)-poly(L-lysine) block copolymer. *Bioconjug Chem.* 1997;8:702–707.

16. Ritger PL, Peppas NA. A simple equation for description of solute release, I: Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *J Control Release.* 1987;5:23–26.

17. Rao PR, Diwan PV. Formulation and in vitro evaluation of polymeric films of diltiazem hydrochloride and indomethacin for transdermal administration. *Drug Dev Ind Pharm.* 1998;24:327–336.

18. Draize JH, Woodward G, Calvery HO. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J Pharmacol Exp Ther.* 1944;82:377–379.