FORMULATION AND EVALUATION OF CARVEDILOL TRANSDERMAL PATCHES

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ABSTRACT

The present study was carried out to develop and evaluate matrix-type transdermal formulations containing carvedilol with different ratios of hydrophilic (HPMC) and hydrophobic polymeric (Eudragit RS100) combinations plasticized with glycerin and dibutyl phthalate by the solvent evaporation technique. Effect of surfactant (PEG-400 and Tween 80) and permeation enhancers (DMSO and DMF) were studied. The interference of the polymers were ruled out by infrared and uv spectroscopic methods. Viscosity of the polymers was determined using Brookfield viscometer (LVDV-E). The partition coefficient study was performed using n-octanol as the organic phase and phosphate buffer pH 7.4 as an aqueous phase. The prepared patches were tested for their physicochemical characteristics such as thickness, weight, and drug content uniformity, swelling index, water vapour transmission, folding endurance, and tensile strength. In vitro release studies of carvedilol-loaded patches in phosphate buffer (pH, 7.4) exhibited drug release in the range of 80.70 to 98.56 % in 24 h. Data of in vitro release from patches were fit in to different equations and kinetic models to explain release kinetics. The models used were zero and first-order equations, Hixon-Crowell, Higuchi and Korsmeyer-Peppas models. Based on physicochemical and in vitro release studies, patches containing HPMC and Eudragit RS 100 (DMSO as permeation enhancer) were chosen for in vitro skin permeation studies which were performed using a modified diffusion cell across rat abdominal skin and showed first order release mechanism. Skin studies for the transdermal patches were assessed and were found to be free of irritation. The patches were subjected to short term stability studies and were found stable. Good correlation was observed (R² = 0.810) with in vitro release Vs in vitro skin permeation studies.

KEYWORDS: Carvedilol; Transdermal; HPMC; Eudragit RS100, In vitro permeation.

INTRODUCTION

Transdermal drug delivery systems (TDDS) are adhesive drug containing devices of defined surface area that delivers predetermined amount of drug to the intact skin at a preprogrammed rate.1 The transdermal delivery has gained importance in recent years. The transdermal drug delivery system has potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood levels for longer period of time resulting in a reduction of dosing frequency, improved bioavailability, decreased gastrointestinal irritation that occur due to local contact with gastric mucosa and improved patient compliance.2 Some of the antihypertensive drugs have already been formulated and evaluated as transdermal patches but most of them still been unexplored. Transdermal formulation of anti hypertensive drug is promising aspect in near future. A few anti hypertensive drugs like propranolol, metoprolol, mepindolol, captoril, verapamil, diltiazem, and nifedipine have been incorporated in transdermal dosage form and been evaluated.3

Carvedilol is a nonselective β-adrenergic blocking agent with α1-blocking activity and is well absorbed from gastrointestinal tract but is subjected to high first pass metabolism in liver; the absolute bioavailability is about 25%. Peak plasma concentration occurs in 1-2 h after drug administration. It has
high lipid solubility. Carvedilol is more than 98% bound to plasma proteins. The elimination half-life is about 6 h.4,5

Carvedilol was chosen as the model candidate 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. It also means multiple daily administrations with subsequent lack of patient compliance. The present investigation is concerned with the development of the unidirectional transdermal films of carvedilol to increase the bioavailability of the drug and half life. In this article the term “patch” refers to 1 x 1 cm² size formulations and the term “film” refers to the formulations of bigger size than patch.

MATERIALS AND METHODS
Carvedilol and Eudragit RS 100 were obtained as gift samples (Dr. Reddy’s Labs, Hyderabad, India). Polymers and solvents were purchased from S.D. Fine Chem Ltd., Mumbai. Distilled water was prepared in laboratory using all glass distillation apparatus. Other materials used in the study were of analytical grade.

Preparation of Transdermal Films
Transdermal films containing carvedilol were prepared by the solvent evaporation technique6 for the formulations shown in Table 1. Solution of HPMC and Eudragit were prepared separately in ethanol and acetone, respectively. The two polymeric solutions were mixed to which weighed amount of carvedilol was added slowly. To the mixture, 4 drops of glycerin (117.6 mg), 1 drop of dibutyl phthalate (27.4 mg), and 0.25 ml of surfactant (PEG 400 / Tween 80) and permeation enhancer (DMF / DMSO) were added and mixed. The drug-polymer solution was casted in a glass mould of 4 cm² (4 × 10 cm²). The mould was kept aside for drying at room temperature for 24 h. Inverted plastic funnel was placed over the mould to prevent the current of air. After drying, the films were peeled from glass mould, wrapped in aluminium foil, and preserved in desiccator for further studies.

Determination of Viscosity
Aqueous solutions containing both polymer and plasticizer were prepared in the same concentration as that used for preparation of patches.7 A Brookefield viscometer (LVDV-E, Brookfield Engineering Labs. Inc, USA) attached to the helipath spindle number 18 and small sample adaptor was used. The viscosity was measured at 20 rpm at room temperature. The recorded values were the mean of three determinations.

Determination of Partition Coefficient
The oil-water partition coefficient is a measure of lipophilicity of a molecule, which can be used to predict its capability to cross biological membrane. One of the most common ways of measuring partition coefficient is shake flask method.8,9 The carvedilol was added little at once in to 5 ml of n-octanol until saturated solution was obtained. This solution was filtered to get a clear solution. Three ml of the saturated solution was mixed with 2 ml of fresh octanol. In total, 5 ml of octanol containing carvedilol was mixed with 15 ml of water. Then, two phases were allowed to equilibrate at 37 °C for 24 h, in cryostatic constant temperature shaker bath (Research and Test Equipments, Bangalore, India). The concentration of the drug in the aqueous phase and organic phase was determined by UV spectroscopic method after necessary dilution. The apparent partition coefficient (Kp) was calculated as the ratio of drug concentration in each phase by the following equation.

\[
K_p = \frac{C_{org}}{C_{aq}}
\]  

where, \( C_{org} \) is concentration of drug in organic phase and \( C_{aq} \) is the concentration of drug in aqueous phase.

Drug–Excipient Compatibility Studies
In the preparation of film formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer
interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between carvedilol and the selected polymers. The pure drug and drug with excipient were scanned separately. The potassium bromide was mixed with drug and/or polymer and the spectra were taken. FT-IR spectrum of carvedilol was compared with FT-IR spectra of carvedilol with polymer. Disappearance of carvedilol peaks or shifting of peak in any of the spectra was studied.

**Evaluation of Patches**
Formulated patches were subjected to the preliminary evaluation tests. Patches with any imperfections, entrapped air, or differing in thickness, weight (or) content uniformity were excluded from further studies.

**Thickness Uniformity**
The thickness of each film was measured by using screw gauze. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the film.

**Folding Endurance**
Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times manually, which is considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on all the patches for three times.

**Uniformity of Weight**
Patches of size 1 x 1 cm² were cut. The weights of three patches were taken using Shimadzu balance of sensitivity 0.0001 g (Shimadzu, Tokyo, Japan) and the weight variation was calculated.

**Drug Content Uniformity**
The films were tested for the content uniformity. A film of size 2 x 2 cm² was cut and placed in a volumetric flask. Ten ml of methanol was added and the contents were stirred in a shaker bath for 24 h to dissolve the film. Subsequent dilutions were made with phosphate buffer (pH 7.4). The absorbance of the solution was measured against the corresponding blank solution at 241 nm using UV-VIS spectrophotometer (UV-1601, Shimadzu Corporation, Tokyo, Japan).

**Swelling Studies**
Weight and area increase due to swelling were measured.

**Weight increase due to swelling:** The drug-loaded patch of size 1 x 1 cm² was weighed on a pre-weighed cover slip. It was kept in a petridish and 50 ml of phosphate buffer (pH 7.4) solution was added. After every five min, the cover slip was removed, wiped with tissue paper, and weighed up to 30 min. The difference in the weights gives the weight increase due to absorption of water and swelling of patch.

**Area increase due to swelling:** A drug loaded patch of size 1 x 1 cm² was cut and placed in a petridish containing 50 ml of phosphate buffer (pH 7.4) solution. A graph paper was placed beneath the petridish and was clearly visible, which facilitated the measurement of increase in the area. An increase in the length and breadth of the patch was noted at five min intervals for 60 min and the area was calculated. The percent swelling, % S was calculated using the following equation;

\[
\% S = \left( \frac{X_t - X_o}{X_o} \right) \times 100
\]

where \(X_t\) is the weight or area of the swollen patch after time \(t\) and \(X_o\) is the original patch weight or area at zero time.

**Tensile Strength**
Tensile strength of the film was determined with Universal Strength Testing Machine (Hounsfield, Slinfold, Horsham, U.K). The sensitivity of the machine was 1 g. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (4 x 1 cm²) was fixed between these cell grips and force was gradually applied till the film broke. The tensile strength of the patch was taken directly from the dial reading in kg.

**Water Vapour Transmission Rate (WVTR)**
For this study, vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven, about 1 g of fused calcium chloride was taken in cells and the polymeric patches measuring 1 cm² area were fixed over the brim with the help of an adhesive. The cells were washed.
weighed accurately and initial weight was recorded, and then kept in a closed desiccator containing saturated solution of potassium chloride to maintain 63 % RH. The cells were taken out and weighed after 72 h.\textsuperscript{15} The amount and rate of water vapor transmitted was calculated by the difference in weight using the following formula.

\[
WVTR = \frac{W}{L/S} \quad (3)
\]

where, W is the water vapor transmitted in g, L is the thickness of the film in cm, and S is the exposed surface area in square cm.

**In vitro Release Studies of Carvedilol Patches in Phosphate Buffer (pH 7.4)**

The drug release was determined using U.S.P. dissolution tester (TDT-08L, Electrolab, Bombay, India) thermostated at 37 ±1 \(^{\circ}\)C and stirred at a rate of 50 rpm.\textsuperscript{16,17} Sink condition was maintained throughout the study.

Each film was fixed on a glass slide with the help of cyanoacrylate adhesive, so that the drug could be released only from upper face. The slide was immersed in the vessel containing 900 ml of phosphate buffer (pH 7.4) solution. Aliquots of 5 ml of samples were withdrawn with graduated pipette at every one hour time intervals up to 24 h replacing with equal volume of phosphate buffer (pH 7.4) solution. The sample was analyzed spectrophotometrically at 241 nm and the cumulative amount of drug released at various time intervals was calculated. The test was carried out in triplicate.

**In vitro Skin Permeation Studies**

Male Wistar rats (140 ± 20 g) free from any visible signs of disease were selected for the *in vitro* skin permeation studies.\textsuperscript{14,18} The hair on abdominal region was removed using a depilatory preparation one day prior to experiment. On the day of experiment, the animals were sacrificed by cervical dislocation and the abdominal skin was excised. The fatty material adhered to the dermis was carefully peeled off. Freshly excised rat skin was mounted on donor compartment. Transdermal film containing DMSO as permeation enhancer was placed.

A modified diffusion cell was used for drug release from the transdermal patches. The transdermal film of area 4 cm\(^2\) was placed on the rat skin, which was then tied to the diffusion cell. This diffusion cell was immersed in a beaker (receptor compartment) containing 100 ml phosphate buffer (pH 7.4) solution, which was used as the receptor fluid. The receptor compartment was stirred by using a magnetic stirrer at 100 rpm and the whole assembly was maintained at 37 ± 1 \(^{\circ}\)C. The amount of the drug released was determined by withdrawing 5 ml of samples at specific time intervals up to 24 h. The volume withdrawn was replaced with equal volume of fresh phosphate buffer (pH 7.4) solution. The absorbance of the withdrawn sample was measured after suitable dilution at 241 nm to estimate carvedilol. The experiment was carried out in triplicate and average values were reported.

**In vitro Skin Irritation Studies**

A primary skin irritation test was performed since skin is a vital organ through which drug is transported. The test was carried out on 3 healthy male rabbits (1.4 ± 1 kg). Drug free polymeric films of size 4 cm\(^2\) were used as control. The dorsal surface of rabbits was cleared well and the hair was removed by using a depilatory preparation. The skin was cleared with rectified sprit. Transdermal films containing carvedilol (60 mg equivalent) were placed over the skin with the help of adhesive tape. The films were removed after 24 h and the skin was examined for erythema. All the experimental protocols involving laboratory animals were approved by the Institutional Animal Ethics Committee.\textsuperscript{6}

**Stability Studies**

Optimized medicated films were subjected to short term stability testing. Films were placed in a glass beaker lined with aluminium foil and kept in a humidity chamber maintained at 40 ± 2 \(^{\circ}\)C and 75 ± 5% RH for 1 month as per ICH guidelines.\textsuperscript{19} Changes in the appearance and drug content of the stored films were investigated after storage at the end of every week. The data presented were the mean of three determinations.

**RESULTS AND DISCUSSION**

Calibration curves of carvedilol in 0.1 N HCl and phosphate buffer (pH 7.4) solutions were constructed at \(\lambda_{\text{max}}\) 241 nm with a UV-VIS spectrophotometer (UV-1601PC, Shimadzu Corporation, Tokyo, Japan).
Beer’s law obeyed to construct the calibration curve in the concentration range of 1 – 10 μg/ml. Analyses were done in triplicate.

The viscosities of the solutions were 20.19 cps (patch F₁), 19.17cps (patch F₂), and 18.55 cps (patches F₄ to F₇). Viscosity of film F₁ was high when compared to others. It could be because of complete solubility of polymers in ethanol or more amount of the polymer, where as viscosity was least in films F₃ to F₇ probably due to dispersion of polymer in acetone. However, there is a need to explore the relation between viscosity and other properties of films.

The swelling of the drug loaded patches of size 1 x 1 cm² was studied up to 30 min in case of change in weight and 60 min in case of change in area. The swelling was more pronounced in patch F₁ which contain more of HPMC (hydrophilic polymer). This is in agreement with the uniformity of the thickness. Perusal to Table 2 indicates, addition of Tween 80 in the formulation F₂ increased the thickness of film. Tween 80 decreases interfacial tension and increases wetting of polymer by solvent. This results indicated that carvedilol is not involved in any chemical reactions with the polymer used. Further, the interference was also verified using UV-spectrophotometric method.

The patches of selected polymers were prepared. Addition of the plasticizer produced a patch of good strength. The patches were translucent and visually smooth surfaced. The developed procedure to prepare the patches was reproducible.

In the present study, transdermal patches of carvedilol were formulated using the hydrophilic polymer matrix of hydroxypropyl methylcellulose and the effect of Eudragit RS100 as rate-controlling polymer was studied. The prepared patches were characterized for physicochemical properties, in vitro release, in vitro permeation profile across excised hairless rat abdominal skin, and skin irritation studies in rabbits.

The physicochemical properties of carvedilol transdermal patches are presented in Table 2.

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FT-IR spectra of carvedilol alone and its combination with polymers are shown in Fig. 1. FT-IR spectra of the pure carvedilol and the drug-polymer mixture showed characteristic bands at 3344.93 cm⁻¹ (N-H stretching), 2922.59 cm⁻¹ (O-H stretching), 2630.43 cm⁻¹ (C-H stretching), and 1891.83 cm⁻¹ (C=O stretching) due to functional groups, indicating the chemical stability of carvedilol in the chosen polymeric mixture. This also indicated that carvedilol is not involved in any chemical reactions with the polymer used. Further, the interference was also verified using UV-spectrophotometric method.

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All the patches had uniform thickness throughout with the standard deviation of ± 0.005 μm. The thickness results are given in Table 2. The result indicated that there was no much difference in the thickness within the formulations. The order of the thickness of films is F₆ < F₄ < F₃ < F₁ < F₇ < F₂ < F₅. Perusal to Table 2 indicates, addition of Tween 80 in the formulation F₃ increased the thickness of film. Tween 80 decreases interfacial tension and increases wetting of polymer by solvent. This results in more swelling during casting. Even after complete drying, the swollen polymer gave thicker film.

Drug loaded patches (1 x 1 cm²) were tested for uniformity of weight and the results of weight uniformity are given in Table 2. The weight was found to be uniform in the prepared batches with standard deviation of ± 0.416 mg per patch. The order of the weight of films is F₆ < F₁ < F₄ < F₃ < F₁ < F₇ < F₂ < F₅. This is in agreement with the uniformity of the thickness. Perusal to Table 2 indicates that patch F₅ exhibited highest weight. It could be because of the reason explained in the thickness uniformity.

Patches did not show any cracks even after folding for more than 300 times. Hence it was taken as the end point. Folding endurance did not vary when the comparison was made between dummy patches and drug-loaded patches.

The results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 82.1 to 93.78% for formulations F₁ to F₇. The drug content analysis of the prepared formulations had shown that the process employed to prepare films in this study was capable of giving films with a uniform drug content and minimum batch variability.

The swelling of the drug loaded patches of size 1 x 1 cm² was studied up to 30 min in case of change in weight and 60 min in case of change in area. The swelling of the patches were observed in phosphate buffer solution (pH 7.4). The data for increase in weight due to swelling are given in Table 2. Swelling was more pronounced in patch F₁ and F₂ which contain more of HPMC (hydrophilic polymer). Patches F₃ to F₇ showed lesser swelling (weight basis), may be due to the presence of higher concentrations of Eudragit RS 100, hydrophobic polymer. The order of patches for their increase in
weight due to swelling is $F_3 < F_6 < F_5 < F_7 < F_4 < F_2 < F_1$. Further, it should be verified with increase in area due to swelling.

The data for the increase in area due to swelling are given in Table 2. Swelling was more pronounced in patches $F_1$ and $F_2$ which contain more of HPMC, which is hydrophilic polymer. Patches $F_3$ to $F_7$ showed lesser increase in area due to swelling. This must be due to the presence of higher concentrations of Eudragit RS 100. The order of patches for their increase in area due to swelling is $F_4 < F_7 < F_3 < F_6 < F_5 < F_2 < F_1$. This was almost in agreement with the increase in weight due to swelling.

The tensile strengths of drug-loaded films were higher than dummy films (Table 2). The order of tensile strength of the films is $F_3 < F_4 < F_5 < F_6 < F_7 < F_2 < F_1$. The tensile strengths of drug loaded films were higher than dummy films. This is justified because dissolved carvedilol strengthened the bonding of polymer chains. With increase in HPMC proportion the tensile strength of films was increased. It reflects that the soluble polymer develops cross linking better than insoluble polymer. This is in agreement with the viscosity determinations. More the solubility of the polymer higher will be the tensile strength.

The patch formulated with HPMC alone showed maximum WVTR of $0.167 \pm 0.039$ mg cm$^{-2}$ h$^{-1}$, which can be attributed to the hydrophilic nature of the polymer. The casting of the HPMC with the rate-controlling polymer of Eudragit RS100 decreased the values of the water vapour transmission rate.

Drug release profiles from formulations $F_1$ and $F_2$ are shown in Fig. 2, whereas formulations $F_3$ to $F_7$ are shown in Fig. 3. Perusal to Fig. 3 indicates that 98.02% of drug was released within 3 h from $F_1$ and followed zero-order kinetics. This means the film has to be applied several times a day to maintain therapeutic levels constant. The faster drug release rate is due to the use of hydrophilic polymer (HPMC) alone. To get sustained release, copolymer that decreases the drug release rate is needed to be added. Therefore, rate-controlling membranes of Eudragit RS 100 were cast with the aim to achieve controlled release of carvedilol from drug reservoirs of HPMC.

Perusal to Fig. 2 indicates that, the cumulative amount of drug released after 10 h from $F_2$ was found to be 98.98%. When compared to $F_1$ the drug release from $F_2$ was delayed from 3 h to 10 h. This effect was because of the copolymer, Eudragit RS 100, which acted as the rate-controlling polymer. However, the target is to get drug release up to 24 h. Hence there is a need to delay the drug release further.

The sustained drug release could be achieved by increasing the copolymer concentration in the formulation by maintaining the total polymer concentration same i.e., 500 mg. In the formulations $F_3$ to $F_7$, HPMC was decreased to 250 mg and Eudragit was increased to 250 mg. From Fig. 3, it was found that only 81.00% of carvedilol was released from $F_3$ at the end of 24 h. Though sustained effect was achieved to a greater extent but complete drug was not released in 24 h. Further there was a need to improve the formulation.

In the formulations $F_4$ and $F_5$, an attempt was made by adding surfactant to get the required release rate. In the formulation $F_4$, the surfactant, PEG 400, was added in addition to the ingredients of $F_3$ formulation. This increased the drug release rate from 81.00 % of $F_3$ to 91.53%. This was appreciable improvement. Still there was a need for further improvement to achieve the target.

In the formulation $F_5$, Tween 80 was added replacing PEG 400 of $F_4$. The drug release from this film was found to be 95.02%. When compared to $F_4$, % drug release was improved by 3.5%. Hence, the use of surfactant was a successful attempt. But the thirst for improving the formulation continued to develop further.

Literature study gave us an idea of using permeation enhancer as an alternative to surfactant to improve the formulation as the former helps in the permeation of drug through the skin. DMF and DMSO were the most popularly used permeation enhancers in the research work reported for transdermal drug delivery. As a first attempt, DMF was tried in the formulation $F_6$. In vitro drug release pattern shown in Fig. 3 indicates 96.74% of drug was released in 24 h. The drug release was improved by 1.7% when compared to $F_5$. This was a significant improvement as DMF alone improved the performance without any surfactant.

In the formulation $F_7$, DMSO was used instead of DMF as permeation enhancer and observed the response. It was clearly indicated from the Fig. 3 that 98.56% of the carvedilol was released in 24 h.
When compared to all the earlier formulations, this formulation gave maximum drug release in 24 h. Thus, the target was achieved.

All the formulations (F2 to F7) released drug in a biphasic pattern, i.e. a faster release that occurred for first half an hour, after which the release rate slowed down. This result can be explained from the theoretical point of view. Eudragit RS100 being an inert polymer, solvent penetration in to the film was rate-limiting factor for the release of the active principle. At the beginning of the process, the active substance at and near the surface of the film dissolves quickly. When the dissolution process advances, there is a greater resistance to the penetration of the solvent in the inside of the matrix film, due to the non-hydrophilicity of the polymer and the decreasing length of the solvent front. The drug, easily accessible by water immediately dissolves and diffuses from the interface between the film surface and surrounding media after which diffusion process slows down. The formulations can be arranged in order of release rate as: F1 > F2 > F3 > F4 > F5 > F6 > F7.

The regression values of films F1 and F2 are higher with zero order and therefore the release kinetics followed zero order from these two patches and films F3 to F7 are higher with first order and therefore the release kinetics followed first order.

Hixon-Crowell cube root law was applied to test the release mechanism. R2 values are higher for Higuchi’s model compared to Hixon – Crowell for the films F1, F2 and F3. Hence carvedilol release from these films (F1, F2 and F3) followed diffusion rate controlled mechanism. Carvedilol release from films F4, F5, F6 and F7 followed dissolution rate controlled mechanism.

According to Korsmeyer–Peppas model, a value of slope between 0.5 and 1 indicates an anomalous behavior (Non-Fickian). So, it indicates that release mechanism from all the films follows Non-Fickian diffusion (anomalous behavior). However, film F1 follows case II transport (n > 1).

The in vitro permeation study was performed across hairless rat abdominal skin using modified diffusion cell. It was found that about 89.16% of the drug permeated through hairless skin from film F7. The permeation kinetics was studied by regression analysis (R2 =0.935). The permeation of carvedilol followed first order. Drug permeation profile from formulation F7 is shown in Fig. 4.

In vitro release studies and their correlation with in vitro skin permeation studies will be helpful to predict therapeutic efficiency of the dosage form. So correlation between in vitro release behavior of a drug and its in vitro permeation in rat skin is demonstrated experimentally to reproduce therapeutic response. The data of in vitro release and in vitro skin permeation of carvedilol from film F7 was regressed using MS-Excel statistical program to understand in vitro release and in vitro permeation correlation. A good correlation was observed (since R2 value was 0.810) for patch F7 (Fig. 5).

No erythema was observed from a primary skin irritation test carried out on rabbits after the application of transdermal films. The absence of erythema indicated that these polymeric patches of carvedilol were compatible with skin and hence can be used for the transdermal application.

Films that were placed in humidity chamber for short time stability studies were withdrawn every week and analysed for their drug content. Percentage drug present in the patches were determined spectrophotometrically. Decrease in the drug content from the films ranged from 3.131 to 4.298 %. It was found that the drug loss is less though the films were stored for one month. The films were also observed for their appearance and texture. These properties did not change in films during the period of study. Transdermal films containing carvedilol using HPMC and Eudragit RS100 polymers showed satisfactory characteristics without being drastically influenced by ageing.

CONCLUSION

On the basis of the in vitro characterization it was concluded that carvedilol could be administered transdermally through matrix type TDDS developed in our laboratory. Transdermal patches consisting of the bioadhesive polymer HPMC and rate-controlling polymer of Eudragit RS100 with DMSO as permeation enhancer demonstrated sustained and controlled release of the drug across rat abdominal skin during in vitro permeation studies. The drug remained intact and stable in the TDDS during storage, with no significant chemical interaction between the drug and the excipients. Further work is to establish the therapeutic utility of this system by pharmacokinetics and pharmacodynamic studies on human beings.
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REFERENCES
### Table 1: Composition of different formulations containing carvedilol

<table>
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<th>F₁</th>
<th>F₂</th>
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<td>0.25</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Tween 80, ml</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>0.25</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>DMF, ml</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>0.25</td>
<td>*</td>
</tr>
<tr>
<td>DMSO, ml</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>0.25</td>
</tr>
</tbody>
</table>

* No ingredient is added; HPMC = Hydroxypropyl methylcellulose; DMSO = Dimethyl sulfoxide; PEG = Polyethylene glycol; DMF; Dimethyl formamide.

### Table 2: Physicochemical characteristics of transdermal patches containing carvedilol

<table>
<thead>
<tr>
<th>PC</th>
<th>TN (mm)</th>
<th>WU (mg)</th>
<th>Swelling</th>
<th>TS (kg)</th>
<th>CU</th>
<th>FE</th>
<th>WVTR (mg cm⁻² h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% weight increase after 30 min</td>
<td>% area increase after 60 min</td>
<td>Dummy patches</td>
<td>Drug loaded patches</td>
<td></td>
</tr>
<tr>
<td>F₁</td>
<td>0.199</td>
<td>19.63</td>
<td>431.31</td>
<td>61.60</td>
<td>2.333</td>
<td>2.830</td>
<td>88.58</td>
</tr>
<tr>
<td>F₂</td>
<td>0.262</td>
<td>21.80</td>
<td>406.11</td>
<td>59.39</td>
<td>1.793</td>
<td>2.460</td>
<td>84.65</td>
</tr>
<tr>
<td>F₃</td>
<td>0.190</td>
<td>17.40</td>
<td>291.93</td>
<td>51.09</td>
<td>1.233</td>
<td>1.306</td>
<td>83.43</td>
</tr>
<tr>
<td>F₄</td>
<td>0.186</td>
<td>18.80</td>
<td>386.07</td>
<td>35.23</td>
<td>1.306</td>
<td>1.816</td>
<td>93.78</td>
</tr>
<tr>
<td>F₅</td>
<td>0.263</td>
<td>22.33</td>
<td>312.667</td>
<td>52.11</td>
<td>1.400</td>
<td>1.856</td>
<td>89.91</td>
</tr>
<tr>
<td>F₆</td>
<td>0.177</td>
<td>14.56</td>
<td>380.23</td>
<td>51.09</td>
<td>1.406</td>
<td>1.876</td>
<td>82.10</td>
</tr>
<tr>
<td>F₇</td>
<td>0.202</td>
<td>20.56</td>
<td>385.09</td>
<td>44.02</td>
<td>1.506</td>
<td>2.076</td>
<td>83.75</td>
</tr>
</tbody>
</table>

PC is patch code (F₁, F₂, F₃, F₄, F₅, Fₛ, and F₇ are formulations). TN, WU, TS, CU, FE and WVTR are thickness, weight uniformity, tensile strength, content uniformity, folding endurance, and water vapour transmission rate, respectively. Each value is an average of three determinations.
Fig 1: FTIR of a) Carvedilol pure b) Carvedilol with hydroxy propyl methylcellulose c) Carvedilol with Eudragit RS100. (top to bottom)
Fig 2: *In vitro* release of carvedilol from patches F₁ to F₂

Fig 3: *In vitro* release of carvedilol from patches F₃ to F₇

Fig 4: *In vitro* permeation of carvedilol from patch F₇ in rat skin
Fig 5: In vitro release Vs in vitro skin permeation of carvedilol from patch F_7

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