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Analytical Methods, Preformulation Study and Physicochemical Evaluation Techniques for Transdermal Patches of Antihypertensive Drug

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ABSTRACT

Since early 1980s, this dosage form of transdermal therapeutic system has been available in the pharmaceutical market. The discovery of transdermal drug delivery systems (TDDS) is a breakthrough in the field of controlled drug delivery systems. The ability of TDDS to deliver drugs for systemic effect through intact skin while bypassing first pass metabolism has accelerated transdermal drug delivery research in the field of pharmaceutics. Over a decade of such extensive research activities, many transdermal patches have been developed and successfully commercialized.

The present study was carried out to evaluate transdermal formulation containing carvedilol with different ratios of hydrophilic (Eudragit RL100,HPMC) and hydrophobic polymeric (Eudragit RS100,Ethyl Cellulose) combinations plasticized with triethyl Citrate and dibutyl phthalate by the solvent evaporation technique. The prepared patches were tested for their physicochemical characteristics such as thickness, weight and drug content uniformity, water vapour transmission, folding endurance, and tensile strength.

In vitro release studies of carvedilol-loaded patches in 30% v/v Methanolic Isotonic Phosphate Buffer(MIPB) of pH 7.4 . The antihypertensive activity of the patches was studied using methyl prednisolone acetate induced hypertensive rats. This article describes various methods of evaluation of transdermal dosage form containing Antihypertensive drug Carvedilol.

KEYWORDS

Transdermal drug delivery system, Patch, evaluation of transdermal system, *in-vivo* study.

INTRODUCTION

Recent trends in pharmaceutical dosage forms, transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. Transdermal patches are polymeric formulations which when applied to skin deliver the predetermined amount drug at a predetermined rate across dermis to achieve systemic effects. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a time-released dose of medication systemically for treating illnesses.

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Since early 1980s, this dosage form of transdermal therapeutic system has been available in the pharmaceutical market[3]. The discovery of TDDS is a breakthrough in the field of controlled drug delivery systems. The ability of TDDS to deliver drugs for systemic effect through intact skin while bypassing first pass metabolism has accelerated transdermal drug delivery research in the field of pharmaceutics.

Transdermal dosage forms, though a costly alternative to conventional formulations, are becoming popular because of their unique advantages. Controlled absorption, more

uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application and flexibility of terminating drug administration by simply removing the patch from the skin are some of the potential advantages of transdermal drug delivery. Development of controlled release transdermal dosage form is a complex process involving extensive efforts.

The Skin Site for Transdermal Drug Administration[1,2]

The skin is one of the most extensive and readily accessible organs of the human body. The skin of an average adult body covers a surface area of approximately $2m^2$ (or 3000 $inch^2$) and receives about one third of the blood circulating through the body.

Drug Transport Through Human Skin[3,4]

Human skin is an effective, selective barrier to chemical permeation. Most small water-soluble non-electrolytes diffuse into the systemic circulation a thousand times more rapidly when the horny layer is absent.

Among the various skin layers, stratum corneum (SC) is the rate-limiting barrier to percutaneous drug transport due to its desquamating 'horny' properties comprising about 15–20 rows of flat partially desiccated dead keratinized epidermal cells. Due to the lipid - rich nature of the SC layer (40% lipids, 40% protein and only 20% water) and its low water content transport of hydrophilic or charged molecules across SC is low while transport of lipophilic drug molecules.

Skin Absorption Pathways: [1,2,]

Skin absorption pathways can be divided into the transport:

(1) Across the intact stratum corneum and

(2) Along the skin appendages.

The physicochemical properties of the drug as well as the nature of the formulation are the main factors influencing the choice of pathway.

Transport Across the Intact Stratum Corneum

Originating from the structure of the stratum corneum two permeation pathways are possible:
(a) The intercellular route and

(b) The transcellular route.

The intercellular route is considered to be the predominantly used pathway in most cases especially when steady-state conditions in the stratum corneum are reached. Substance transport occurs in the bilayer-structured continuous intercellular lipid domain within the stratum corneum, the intercellular pathway provides hydrophilic and lipophilic regions allowing more hydrophilic substances to use the hydrophilic and vise versa.

Under normal conditions the transcellular route is not considered as the preferred way of dermal invasion the reason being the very low permeability through the corneocytes and the obligation to partition several times from the more hydrophilic corneocytes into the lipid intercellular layers in the stratum corneum and vice versa.

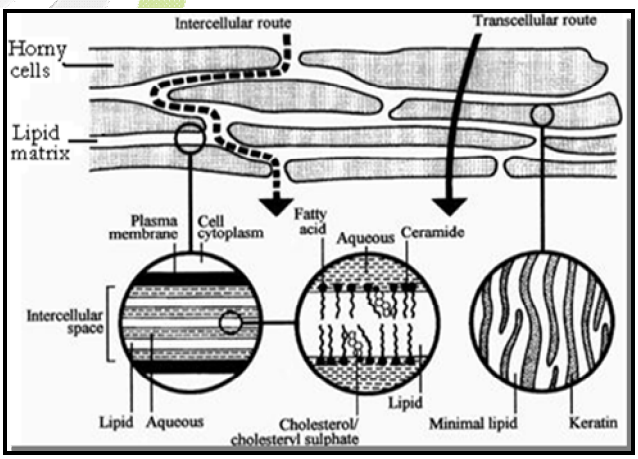


Figure 1: Transport of drugs through stratum.

The appendages route:

The appendages route consists of the glandular and the follicular pathways with the latter one being the more important. However, since appendages cover only 0.1% of the whole skin surface area these pathways do not contribute significantly to dermal absorption.

MATERIALS AND METHODS

Analytical Methods of Carvedilol

Determination of λ_{max} of Carvedilol in 30% v/v Methanolic Isotonic Phosphate Buffer (MIPB) of pH 7.4 [5]

Carvedilol exhibits absorption maxima at 242 nm in 30% v/v Methanolic isotonic phosphate buffer (MIPB) pH 7.4.

A. Preparation of standard solution

100 mg of Carvedilol was accurately weighed into a 100 ml volumetric flask and dissolved in small volume of MIPB pH 7.4 with sonication. The volume was made up to 100 ml with MIPB to get a concentration of 1000 µg/ml (SS-I). From the above solution 10 ml was pipetted in a 100 ml volumetric flask and the volume was made up with MIPB to get a concentration of 100 µg/ml (SS-II). From this, working standard solutions were prepared.

B. Preparation of working standard solutions

From (SS-II) aliquots of 0.2, 0.4, 0.6, 0.8., 1.0, 1.2, 1.4, 1.6, 1.8 and 2.0 ml were pipetted out into a series of 10 ml volumetric flasks and the volume was made with MIPB to get a concentration ranging from 2-20 µg/ml.

The absorbance of the resulting solutions was then measured at 242 nm using UV spectrophotometer against respective parent solvent as a blank. The standard curve was obtained by plotting absorbance v/s concentration in µg/ml.

Beer's range: 2 to 20 µg/ml.

Calibration Curve of Carvedilol in 30% v/v Methanolic Isotonic Phosphate Buffer (MIPB) of pH 7.4

Preformulation Studies

Prior to the development of the dosage form preformulation studies were carried out on parameters like solubility, partition coefficient, melting point and diffusion rate constant of Carvedilol.

Determination of Melting Point

Melting point of drug was determined by taking a small amount of drug in a capillary tube closed at one end and was placed in melting point apparatus and temperature at which the drug melts was noted.

Determination of Partition Coefficient [1]

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.

Procedure: The Carvedilol was added little at once into 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 *n*-octanol. In total 5 ml of *n*-octanol containing Carvedilol was mixed with 15 ml of water. Then two phases were allowed to equilibrate at 37°C for 24 h, on 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.

Permeability Studies through Porcine Ear Skin

Preparation of the Skin Barrier

From a local abattoir, ears were obtained from freshly slaughtered pigs. The ears were cleaned with water to remove blood stains. The fresh full thickness (0.95 mm) porcine ear skin was used for the study. The epidermis was prepared by soaking the ear in water at 60°C for 1 min. The intact epidermis from the dorsal side was subsequently teased off from dermis with forceps, rapidly rinsed with isopropyl alcohol to remove the fat adhering to the dermal side, washed with water & used immediately.

Determination of Drug Permeability Through Porcine Ear Skin [1,6,7,8,9]

The permeability study of the drug was carried out across the porcine ear skin using a Keshary-Chien diffusion cell. A 5 mg/ml drug suspension was prepared in phosphate buffer pH 7.4 and sonicated to ensure uniform drug distribution. One ml of the above suspension was taken in the donor compartment. The barrier was mounted between the donor & the receptor compartments in a way that, the dermal side of the skin was facing receptor compartment. The receptor cell contained MIPB of pH 7.4 as the elution medium. The medium was magnetically stirred for uniform drug distribution and was maintained at 37 ± 1^0C. The samples were withdrawn every hour upto 8 hours and estimated spectrophotometrically (UV) at 242 nm after suitable dilutions to determine the amount of drug diffused.

The flux (µg/cm^2/hr) of Carvedilol was calculated from the slope of the plot of cumulative amount of drug permitted per square centimeter of skin at steady state against the time using linear regression analysis.

The steady state permeability coefficient (Kp) of the drug diffused through the porcine skin was calculated using the equation:

$$Kp = \frac{J}{C} \text{---------- (15)}$$

Where, J = Steady state flux

C = Concentration of Carvedilol in donor compartment.

Optimization of Transdermal Patches with Different Plasticizers and in Different Concentrations [1,7,10]

Drug free patches of Eudragit RL : RS 100 and HPMC 6cps : Ethyl cellulose were prepared by casting on mercury surface (mercury substrate method) along with two different plasticizers i.e. dibutyl phthalate (DBP) and triethyl citrate (TEC).

Polymer solutions were prepared by dissolving in respective solvents by sonication with the aid of a sonicator for 12 mins. For Eudragit and HPMC : Ethyl cellulose patches acetone and a mixture of methylene chloride & methanol were used as solvents respectively. Plasticizers like DBP and TEC at different concentrations based on dry weight of polymer were used to optimize the patches. The prepared patches were then evaluated for physical appearance and folding endurance.

Polymer-Skin Compatibility [1,11,12]

Compatibility of polymers with skin was determined by performing skin irritation test. The skin irritation test was performed on two healthy albino rabbits weighing between 2.0 to 3.5 kg. Aqueous solution of formalin 0.8% was used as standard irritant. Drug free polymeric patches of 4.5 cm^2 were used as test patches. 0.8% of formalin is applied on the left dorsal surface of each rabbit, where as the test patches were placed on identical site, on the right dorsal surface of the rabbit. The patches were removed after a period of 24 hrs with the help of alcohol swab. The skin was examined for erythema /oedema.

Determination of Drug-Excipient Compatibility Studies

A) FTIR Studies [10,13,14,15]

The application of infrared spectroscopy lies more in the qualitative identification of substances either in pure form or in the mixtures and as a tool in establishment of the structure. Since I.R. is related to covalent bonds, the spectra can provide detailed information about the structure of molecular compounds. In order to establish this point, comparisons were made between the spectrum of the substance and the pure compound. The infrared data is helpful to confirm the identity of the drug and to detect the interaction of the drug with the polymers. Infrared spectra of drug & polymers, alone and in physical mixtures were taken. Then it was investigated for any possible interaction between polymer and drug.

B) DSC Studies[10,11]

The physicochemical compatibility between drug and polymers to be used in the formulation of transdermal patches was also studied by using differential scanning calorimetry (DSC). The thermograms obtained for drug, polymers and their physical mixtures were compared to ascertain any interactions.

Evaluation of Film

Physical Appearance

All the transdermal systems were visually inspected for colour, clarity, flexibility and smoothness.

Thickness Uniformity[7,17]

The thickness of the patches was measured at three different places by using a Digital Screw Gauge micrometer (Mitutoyo, Japan) and mean thickness was calculated.

Weight Uniformity[1,11,17]

The dried patches were weighed on electronic balance (Sartorius UK). The average of 3 observations was calculated.

Tensile Strength[1,11,17]

Tensile strength of the film was determined with Universal Strength Testing Machine (Hounsfield, Slinfold, Horsham, U.K.) as shown in Figure 7. The sensitivity of the machine was 1 gram. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (4 × 1 cm^2) was fixed between these cell grips and force was gradually applied till the film broke. The tensile strength of the film was taken directly from the dial reading in kg.

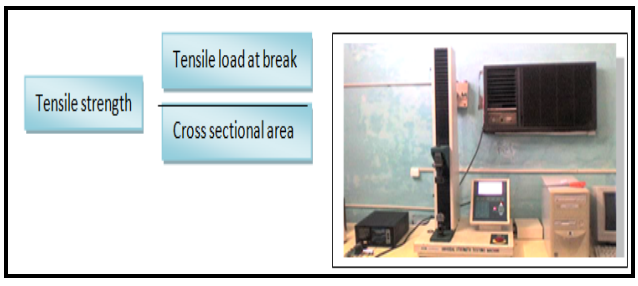


Figure 2: Universal Strength Testing Machine (Courtesy: B.I.E.T., Davangere)

Folding Endurance[11,12]

Folding endurance of the film was determined manually by folding a small strip of the film (4×3 cms) at the same place till it breaks. The maximum number of folding operation done at the same place of the film without breaking, gives the value of folding endurance, where the cracking point of the films were considered as the end point.

Water Vapour Transmission Rate[12,17]

MVT is defined as the quantity of moisture transmitted through unit area of film in unit time.

For this study glass vials of equal diameter were used as transmission cells. These cells were washed and dried in an oven. About 1gm of fused calcium chloride was taken in the cells and the polymeric patches (1.30 cm^2 area) were fixed over the brim with the aid of an adhesive. Then the cells were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride (200 ml). The humidity inside the desiccator was measured by a digital Hygro thermometer and found to be 84% RH. The cells were taken out and weighed after 1st, 2nd, 3rd, 4th, 5th, 6th & 7th days of storage and weighed accurately. The amount of water vapour transmitted and rate of WVT were calculated and plotted.

The rate of water vapour transmission (WVT) was calculated using the formula:

$$\text{WVT Rate} = \frac{WL}{S} \longrightarrow \quad (18)$$

Where, W = gm of water transmitted

L = Thickness of the film in cm

S = Exposed surface area of the film in cm^2.

Drug Content Uniformity of Films[11,17]

Transdermal systems of specified area (5.088 cm^2) was cut into small pieces and taken into 50 ml volumetric flask, 25ml of MIPB pH 7.4 was added and gently heated to 45^0 C for 15 min and kept for 24 hrs with occasional shaking. Then the volume was made up to 50ml again with

MIPB pH 7.4 and further dilutions were made from this solution. Similarly, a blank was carried out using a drug free patch. The solutions were filtered and absorbances were read at 238 nm by UV spectrophotometer.

Moisture Content[11,15,16]

The prepared films were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 hours. The films were weighed repeatedly until they showed a constant weight. The percentage moisture content was calculated using the following formula:

Percentage moisture content =

[Initial wt.−Final wt./Final wt.]×100------ (17)

Moisture uptake[11,15,16]

The weighed films were kept in a dessicator at room temperature for 24 hours. They were then taken out and exposed to 84% relative humidity using a saturated solution of potassium chloride in a dessicator until a constant weight was achieved. Then the films were weighed and percentage moisture uptake was calculated by using the following formula:

Percentage moisture uptake =

[Final wt.−Initial wt./Initial wt.]×100 -----(16)

Flatness

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

$$\% \text{ constriction} = \frac{I_1 - I_2}{I_1} \times 100$$

I_2 = Final length of each strip

I_1 = Initial length of each strip

Microscopic Studies: Scanning Electron Microscopy (SEM)[1,17]

The surface morphologies of the transdermal patches were analyzed by using a JEOL, JSM-6360A, Japan scanning electron microscope. The samples placed on the stubs were coated finely with gold palladium alloy and examined under the microscope. fig no 3.

Figure 3: JEOL, JSM-6360A, Japan scanning electron microscope

Distribution of drug and polymer in the film can be studied using scanning electron microscope. For this study, the sections of each sample are cut and then mounted onto stubs using double sided adhesive tape. The sections are then coated with gold palladium alloy using fine coat ion sputter to render them electrically conductive. Then the sections are examined under scanning electron microscope.

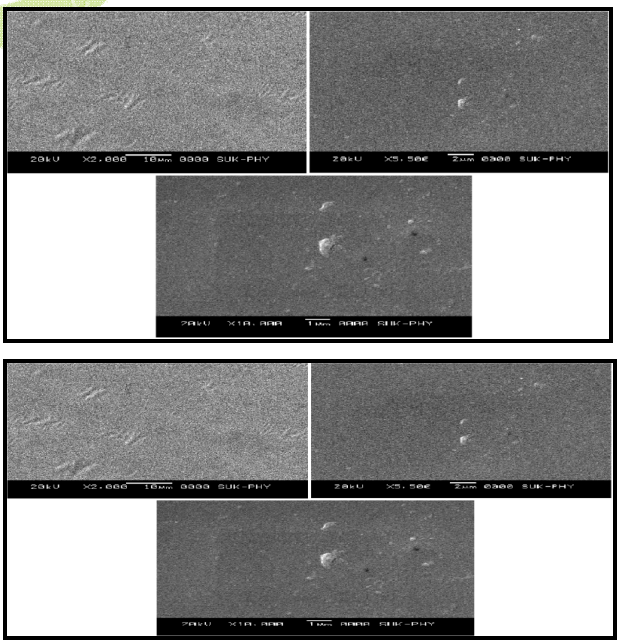


Figure 4: Scanning electron microscopy (SEM)

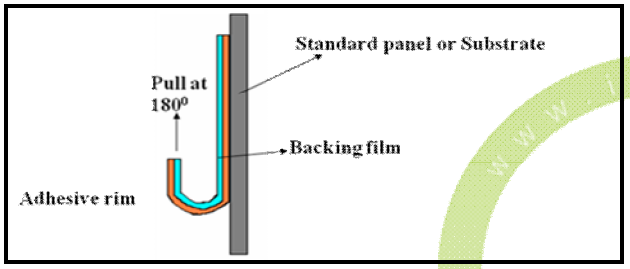
Adhesive Study

Peel Adhesion Property

Peel adhesion is the force required to remove an adhesive coating from the test substance. It is important in transdermal devices because the adhesive should provide adequate contact of the device with the skin & should not damage the skin on removal. Peel adhesion properties are affected by Molecular weight of the adhesive polymer, the type & amount of adhesives added in it and Polymer composition.

Procedure

It is tested by measuring the force required to pull a single coated tape, applied to a substrate, at 180^0 angle.



The test is passed if there is no residue on the substrate. Minghetti *et al.*, (2003) performed the test with a tensile testing machine Acquati model AG/MC 1 (Aquati, Arese, Italy) [20]

Tack Properties

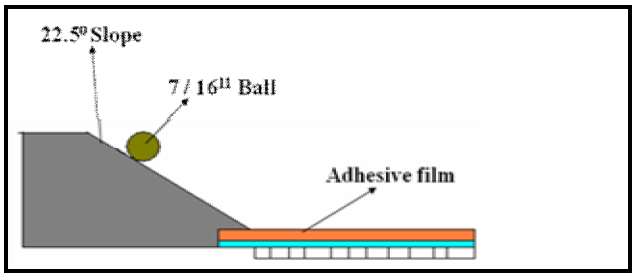
Tack is the ability of the polymer to adhere to the substrate with little contact pressure. It is important in transdermal devices which are applied with finger pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer[20,21.]

Thumb Tack Test[3]

This is a subjective test in which evaluation is done by pressing the thumb briefly on to the adhesive and the force required to remove thumb from adhesive is a measure of tack. Experience is required for this test.

Rolling Ball Test

This test involves the measurement of the distance that a stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the faster the ball will travel.

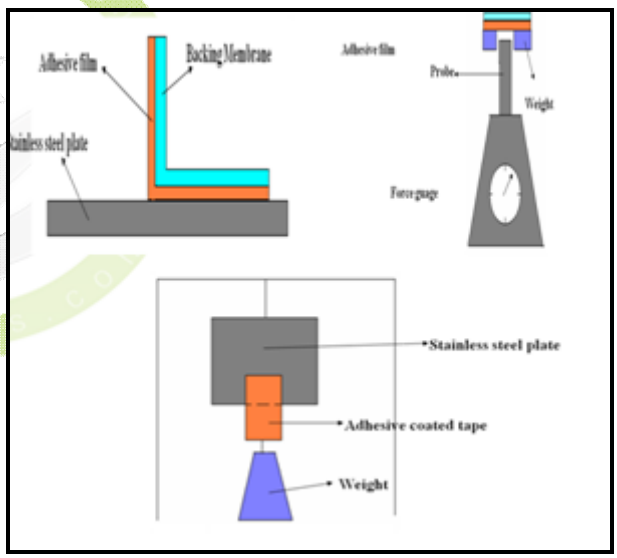


Quick Stick (Peel Tack) Test

The peel force required to break the bond between an adhesive & substrate is measured by pulling the tape away from the substrate at 90^0 at a speed of 12 inch/min.

Probe Tack Test

Here the force required to pull a probe away from an adhesive at a fixed rate is recorded as tack (grams).



Shear Strength Properties (Creep Resistant)

It is a measurement of the cohesive strength of an adhesive polymer. For a polymer the adequate cohesive strength will mean that the device will not slip on application & will leave no residue on removal.

Percentage Elongation

Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement by using the following formula.

Percentage elongation = (L_F - L_O) X 100 / L_O.

Where L_F = final length, L_O= initial length

***In Vitro* Drug Release Studies**

***USP Paddle Method*[7,15,16]**

The release rate determination is one of the most important studies to be conducted for all controlled release delivery systems. The dissolution studies of patches are crucial because one needs to maintain the drug concentration on the surface of the stratum corneum consistently and keep it substantially higher than the drug concentration in the body, to achieve a constant rate of drug permeation.

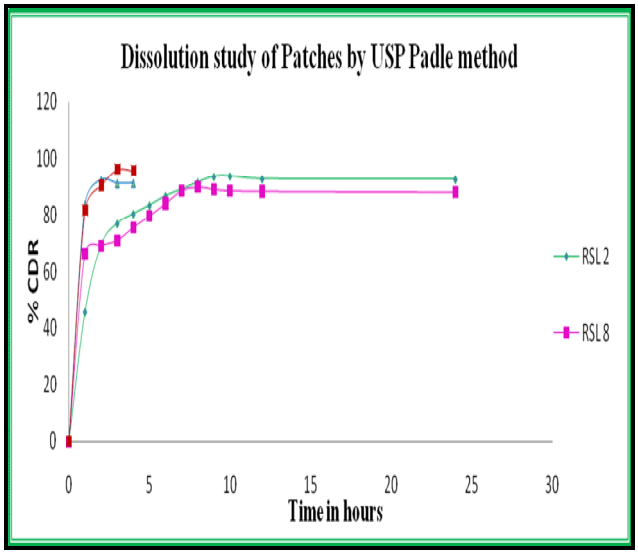
The dissolution study using USP Paddle Type Dissolution Apparatus was carried out at 32±1^{0}C at 50 rpm frequency of the paddle. 500 ml of MIPB of pH 7.4 was used as the dissolution media. The patches were tied with a thin copper wire and then placed in a jar. Samples were withdrawn at different time intervals and then analyzed using a UV Spectrophotometer at 238 nm against blank.

Percentage of drug released was determined using the formula:

% of drug released = Da/Dt × 100 --------- (19)

Where, Dt — indicates the total amount of drug in the patch and

Da — the amount of drug released.



In Vitro Skin Permeation Studies

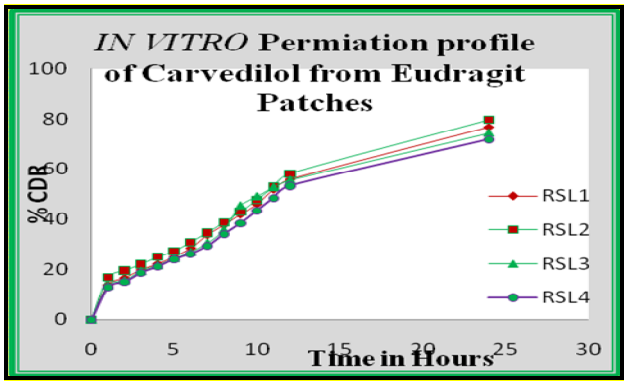
In-vitro permeation studies were carried out for all the formulations using dialysis membrane as barrier. The optimized patches (patches which showed highest release in 8 hours) were further subjected for *in-vitro* release through porcine ear skin.

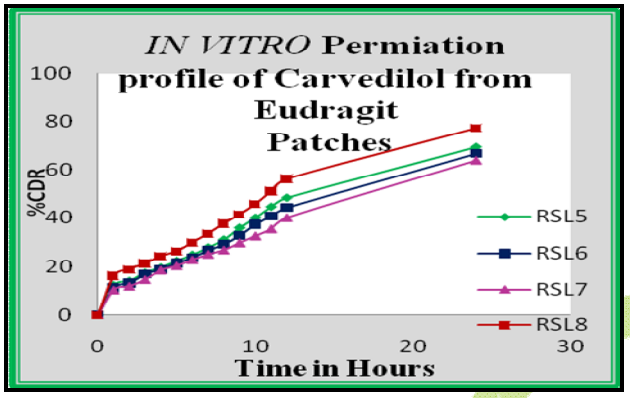
***1. Keshary-Chien Diffusion Cell Using Dialysis Membrane*[1,19]**

The dialysis membrane soaked in phosphate buffer pH 7.4 for overnight was fixed carefully to the receptor compartment of the diffusion cell so that it just touches the receptor fluid surface. The transdermal system of 5.088 cm^2 area was placed above the dialysis membrane fixed to the donor compartment. The receptor compartment was filled with 48 ml of MIPB of pH 7.4 as diffusion medium. The receptor medium was magnetically stirred using a magnetic bead for uniform drug distribution and was maintained at 37±1^{0}C. The samples (3 ml) were withdrawn every hour upto 8 hours and estimated spectrophotometrically (UV) at 238 nm to determine the amount of drug released. The volumes withdrawn at each interval were replaced with an equal volume of fresh, pre warmed buffer solution.

Figure 5: Magnetic Stirrer with Franz Diffusion cell

The cumulative amount of drug permeated was plotted against time and steady state flux as well as Kp value was determined.





2. *Keshary-Chien Diffusion Cell Using Porcine Ear Skin*[1,7]

The porcine ear skin sample was prepared as described earlier in permeability studies of drug through porcine skin. A Keshary-Chien diffusion cell with a diffusional surface area of 5.088 cm^2 and receptor volume capacity of 48 ml was used for the release study. MIPB of pH 7.4 was used as receptor medium. The transdermal patch was firmly pressed onto the centre of the porcine skin and then the skin along with the patch was mounted on the donor compartment. The donor compartment was then placed in position such that the surface of dermis side skin just touches the receptor fluid surface.

Rest all the experimental set up, procedure and calculations remained similar as described above in release through dialysis membrane.

In Vitro Skin Irritation Studies[1,11,13]

The skin irritation test was performed on two healthy albino rabbits weighing between 2.0 to 3.5 kg. Aqueous solution of formalin 0.8% was used as standard irritant. Polymeric patches containing drug of 5.088 cm^2 were used as test patches. 0.8% formalin is applied on the left dorsal surface of each rabbit, where as the test patches were placed on identical site, on the right dorsal surface of the rabbit. The patches were removed after a period of 24hours with the help of alcohol swab. The skin was examined for erythema/oedema.

In vivo Studies[11]

Procurement, Identification and Housing of Animals

Thirty six male albino rats (8 weeks old) 230-250 g were supplied by Animal House facility in our college and kept under standard laboratory conditions in 12h light/dark cycle at 25 ± 2 °C. Animals were provided with pellet diet (Lipton, India) and water *ad libitum.* Animals were marked with picric acid solution for easy identification.

All the experimental procedures were carried out accordance with committee for the purpose of control and supervision of experiments on animal (CPCSEA) guidelines. All the experimental procedures were approved by the institutional animal ethical committee (IAEC).

Conditioning/Training of Animals

For conducting the BP measurement studies, the animals were required to be kept in a restrainer (rat holder). It had only one side open for entry/exit of the animal with proper ventilation at all other sides. As the rats were unaccustomed to remain in the restrainer in a calm and non-aggressive manner, animals were trained for their stay in the restrainer as a slight movement in and aggression by the animal would have led to variation BP reading. For this, a rat was inserted in the restrainer headlong until the whole body got conveniently accommodated inside. The restrainer was locked by screwing the open side of the apparatus leaving the tail outside. The exercise was repeated several times until the animals learnt to stay in restrainer non-aggressively and familiarized with the conditions.

Measurement of Initial Systolic BP of Rats

The initial BP of all the rats was recorded using Non-invasive blood pressure apparatus (Biopac Systems, Inc Santa Barbara, USA). The restrainer carrying the rat was placed in the rat holder with tail protruding out. Systolic blood pressure was measured indirectly in conscious and slightly restrained, pre-warmed rat by the tail cuff method. An average of ten consecutive readings was noted.

Figure 6: Albino Wistar rats prepared for *in vivo* study

Induction of Hypertension in Normotensive Rats

The animals were divided into six groups' six animals each. Group I was taken as control. Hypertension was induced in the remaining five groups (Groups II to VI) by subcutaneous injection of methyl prednisolone acetate (20 mg/Kg/week). Two weeks later, rats with a minimum mean BP of 150 mmHg were selected.

Post TDDS Treatment BP Assessment of MPA induced Hypertensive Rats

After MPA treatment, groups III, IV, V and VI were subjected to TDDS (formulations RSL-2, RSL-8, RHE-3 and RHE-7, respectively). Group II served as toxic control and received no further treatment. The TDDS was applied to the previously shaven abdominal area of rat skin with the entire release surface in intimate contact with the stratum corneum. The patch was applied over the stratum corneum, over the patch an aluminum foil was placed for avoid the backward movement of drug through the adhesive tape. A microporous adhesive tape (Johnson and Johnson) was then rolled over to keep the patch secured at the site of application. The rat was then placed in the restrainer and the Systolic BP was recorded upto 12 hours.

XRD Studies[1,20]

Samples of Carvedilol its pure crystalline state and the transdermal patches were assessed for crystallinity using Philips analytica X-Raydiffractometer (Model:PW 3710). The voltage and current was 25 kv and 25 mA, respectively. Measurements were carried out in the angular scan range from 10° to 70° (2θ). The XRD spectral data are shown in spectra 12 to 16.

Stability Studies of the Optimized Formulation[1]

Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life".

Studies are designed to increase the rate of chemical degradation or physical change of an active drug substance or drug product by using exaggerated storage conditions as a part of the formal, definitive, storage program.

ICH specifies the length of study and storage conditions:

- Long term testing: 25^0C ± 2^0C / 60% RH ± 5% RH for 12 months.
- Accelerated testing: 400C ± 20C / 75% RH ± 5% RH for 6 months.

Figure 7: Stability Chamber

Procedure

Optimized formulation of Eudragit RL : RS 100 with TEC as plasticizer (RSL 2) and HPMC : EC with TEC as plasticizer (RHE 3) were selected for accelerated stability studies as per ICH guidelines. These two batches were subjected for $40^0C \pm 2^0C$ / 75% RH ± 5% RH for a period of 3 months. These patches were analyzed for physical appearance, folding endurance, weight variation, content uniformity and finally the patches were studied for interaction studies.

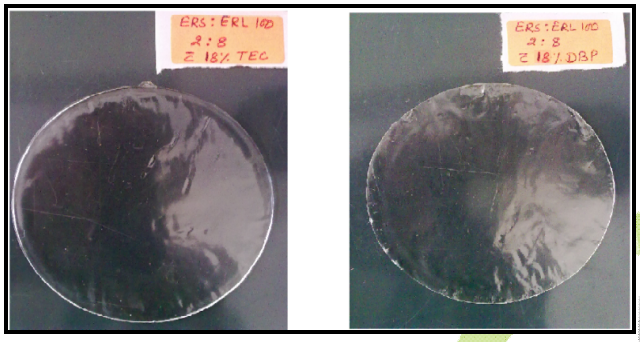


Figure 8 A): Photographs of Eudragit RS: RL100 patches

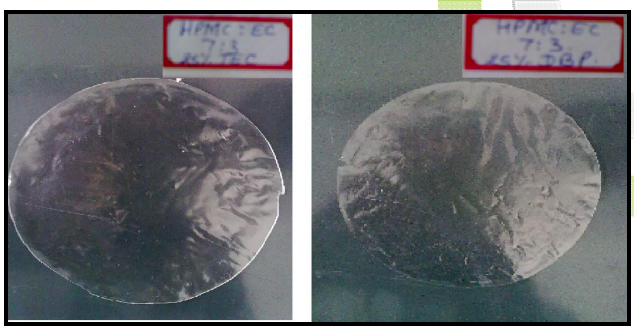


Figure 8 B): Photographs of HPMC: Ethyl cellulose patches

CONCLUSION

Since early 1980s, this dosage form of transdermal therapeutic system has been available in the pharmaceutical market. The discovery of transdermal drug delivery systems (TDDS) is a breakthrough in the field of controlled drug delivery systems. The ability of TDDS to deliver drugs for systemic effect through intact skin while bypassing first pass metabolism has accelerated transdermal drug delivery research in the field of pharmaceutics. As it overcomes the first pass effect and increases bioavailability of drug so this is very much advantages to bypass the degradation of drug. Selection of drug is very important criteria for the formulation of transdermal patches. Recent research is going on to develop and incorporate newer drugs via this system.

For preparation of transdermal patches all the components should undergoes preformulation studies to avoid any further incompatibility in the transdermal patch. After preparation of patches, they must undergo the evaluation studies for the physicochemical, *invitro* permeation, skin irritationstudies, *invivo* studies and stability tastings. If patches give satisfactory result then it approaches for FDA approval. Over a decade of such extensive research activities, many transdermal patches have been developed and successfully commercialized. And after approval from FDA they can be manufactured in large scale for sale in to market.

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