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EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy. Transdermal drugs are self-contained, discrete dosage form. It delivers a drug through intact skin at a controlled rate into the systemic circulation. Delivery rate is controlled by the skin or membrane in the delivery system. A sophisticated complex drug delivery system difficult to formulate. It requires specialized manufacturing process/equipment. Formulated to meet specific biopharmaceutical and functional characteristics. Transdermal patch were evaluated for various parameters like thickness, tensile strength, folding endurance, % elongation, % moisture content, % moisture uptake, % drug content, in vitro drug release, in vitro permeation, and drug excipient compatibility. The most commonly used transdermal system is the skin patch using various types of technologies. Transdermal technologies may be applied for several categories of pharmaceuticals used for the treatment of disorders of the skin or for systemic effect to treat diseases of other organs. Several transdermal products and applications include hormone replacement therapy, management of pain, angina pectoris, smoking cessation and neurological disorders such as Parkinson's disease.

Keywords: Transdermal Patch; Peel Test; Skin Irritation Test; Evaluation.

INTRODUCTION

Drug delivery technologies are now receiving considerable attention from pharmaceutical companies. The main purpose of developing alternative drug delivery technologies is to increase efficiency and safety of drug delivery and provide more convenience for the patient. Substantial research conducted during the past several years has lead to the development of technologies that meet the requisite criteria for delivering the drug through a non-invasive route. One of such technologies is transdermal drug delivery. Transdermal drug delivery is the non-invasive delivery of medications from the surface of the skin the largest and most accessible organ of the human body through its layers, to the circulatory system. Medication delivery is carried out by

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a patch that is attached to the body surface. Transdermal patch is a medicated adhesive pad that is designed to release the active ingredient at a constant rate over a period of several hours to days after application to the skin. It is also called skin patch. A skin patch uses a special membrane to control the rate at which the drug contained within the patch can pass through the skin and into the bloodstream. The first transdermal patch was approved by the FDA in 1979. It was a patch for the treatment of motion sickness. In the mid-1980s, the pharmaceutical companies started the development of a nicotine patch to help smokers quit smoking, and within a few months at the end of 1991 and beginning of 1992 the FDA approved four nicotine patches [(1)].

Advantages of Transdermal Drug Delivery System (TDDS) [(2, 3, 4, 5, 6)]

The advantages of transdermal delivery over other delivery modalities are as follows:

- Avoidance of 'first-pass' metabolism of drugs.
- Peak plasma levels of drugs are reduced, leading to decreased side effects.
- Reduction of fluctuations in plasma levels of drugs.
- Utilization of drug candidates with short half-life and low therapeutic index
- Easy termination of drug delivery in case of toxicity.
- Reduction of dosing frequency and enhancement of patient compliance.

Limitations for a drug candidate to be incorporated into a transdermal delivery system are: - [(7, 8, 9)]

- Higher molecular weight candidates (>500Da) fail to penetrate the stratum corneum.
- Drugs with very low or high partition coefficient fail to reach systemic circulation.
- High melting drugs, due to their low solubility both in water and fat.

BASIC COMPONENTS OF TDDS

- Liner - Protects the patch during storage. The liner is removed prior to use.
- Drug - Drug solution in direct contact with release liner.
- Adhesive - Serves to adhere the components of the patch together along with adhering the patch to the skin.
- Membrane - Controls the release of the drug from the reservoir and multilayer patches.
- Backing - Protects the patch from the outer environment. [(10, 11)]

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FACTORS AFFECTING TRANSDERMAL BIOAVAIBILITY Two major factors affect the bioavaibility of the drug via transdermal routes: (1)Physiological factors (2) Formulation factors

Physiological factors include

• Stratum corneum layer of the skin

• Anatomic site of application on the body

• Skin condition and disease

• Age of the patient

• Skin metabolism

• Desquamation (peeling or flaking of the surface of the skin)

• Skin irritation and sensitization

• Race

Formulation factors include[10]

• Physical chemistry of transport

• Vehicles and membrane used

• Penetration enhancers used

• Method of application

• Device used

PRODUCT DEVELOPMENT

Because of the uniqueness of this dosage form, the following questions need to be answered to define the final product. [12,13]

- Target therapeutic concentration
- Dose to be delivered
- Maximum patch size acceptable
- Preferred site of application
- Preferred application period (daily, biweekly, weekly, etc)

Once the preferred final product description has been established, an evaluation of the drug candidate begins. Because of the limitation of loading dose in a patch and a practical patch size, not all drugs can be candidate for transdermal drug delivery (Table 1)

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Table 1: Ideal Properties of a Transdermal Drug Delivery System

Properties	**Comments**
Patch size	< 40 cm^2
Shelf life	Up to 2 years
Aesthetic appeal	Clear, tan or white color
Dose frequency	Once a daily to once a week
Packaging	Easy removal of release liner and minimum number of steps required to Apply

Table 2: Ideal Properties of Drug Candidate for Transdermal Drug Delivery

Parameter	**Properties**
Dose	Should be low
Half-life in hr	10 or less
Molecular weight	< 400
Partition coefficient	Log P (octanol-water) between –1.0 to 4
Skin permeability coefficient	> 0.5 x10-3cm/hr
Skin reaction	Non irritating and non-sensitizer
Oral bioavailability	Low
Therapeutic index	Low

SELECTION OF DRUG

The transdermal route of administration cannot be employed for a large number of drugs, only a small number of drug products are currently available via transdermal delivery. In many cases, a drug's physical properties, including molecular size and polarity, have limited its capacity to be delivered transdermally. Similarly, the biological properties of drug molecules, including dermal irritation and insufficient bioavailability, have been problematic. In the product development the focus must be on the rationality of drug selection based on pharmacokinetic parameters and physicochemical properties of the drug. Physiochemical factors such as solubility, crystallinity, molecular weight <400, polarity, melting point <200, partition coefficient Log P (octanol-water) between -1.0 to 4 must be considered. Biological factor should also be considered such as skin irritation, site of application of the patch e.g. scopolamine patch for motion sickness is applied

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backside of the ear and Transderm-Nitro is applied on the chest. When a pharmacologically active material has to be presented to the skin, an occlusive or allergic response is significant, limits have to be determined for the acceptability of the undesired effect. The pharmacokinetic information of the drug is a critical factor in deciding its suitability for delivery by the transdermal route as it is suitable only for drugs whose daily dose is in few milligrams. The resulting plasma concentration of active agent depends on the clearance; however, if one assumes a small volume of distribution and relatively long half-life, plasma level in excess of few micrograms per milliliter is very unlikely.

Another important factor is the half-life, (e.g., nitroglycerin t1/2 is 3 min) which provides information on the disposition of a drug in our body other parameters such as effective plasma level Table 2. [14, 15]

EVALUATION OF TRANSDERMAL PATCHES

PHYSICOCHEMICAL EVALUATION

A) Physical Appearance

All the prepared patches were visually inspected for color, clarity, flexibility and smoothness. [16, 17]

B) Thickness Uniformity

The thickness of the formulated film was measured at 3 different points using a digital caliper and average thickness of three reading was calculated.

C) Weight Uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated.

D)Folding Endurance

The folding endurance of patches was determined by repeatedly folding one film at the same place till it tends to break. The number of times the film would be folded at the same place without breaking was taken as the value of folding endurance. [18, 19]

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E)Percentage Moisture Absorption [20, 21]

The films were weighed accurately and placed in the desiccators containing 100 ml of saturated solution of potassium chloride, which maintains 80-90% RH. After 3 days, the films were taken out and weighed. The study was performed at room temperature. The percentage moisture absorption was calculated using the formula:

$$\text{Percentage moisture absorption} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100$$

F)Percentage Moisture Loss

The films were weighed accurately and kept in the desiccator containing anhydrous calcium chloride [22]. After 3 days the film were taken out and weighed then moisture loss was calculated using the formula:

$$\text{Percentage moisture loss} = \frac{\text{Initial weight-Final weight}}{\text{Initial weight}} \times 100$$

G) Drug Content Uniformity

A fabricated film was cut into small pieces and put in a 100ml of phosphate buffer 7.4 pH solution. This is then stirred in a mechanical stirrer to get a homogenous solution and filtered. The filtrate of 1ml was withdrawn and made up to 100ml, again from this 1ml was pipetted out and made up to 10 ml with buffer 7.4 pH. The drug content was analyzed at 251.2nm by UV spectrophotometer. [23, 24]

H) Drug Content Determination

An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution. [17, 19]

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I) Tensile Strength

A small film strip (40 x 15 mm) was used. One end of the strip was fixed between adhesive tapes to give support to the film when placed in the film holder. Another end of the film was fixed between the adhesive tapes with a small pin sandwiched between them to keep the strip straight while stretching. A small hole was made in the adhesive tape near the pin in which a hook was inserted. A thread was tied to this hook, passed over the pulley and a small pin attached to the other end to the hold the weights. A small pointer was attached to the thread, which travels over the graph paper affixed on the base plate. To determine the tensile strength, the film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force till the film was broken. The weight required to break the film was noted as break force. [24]

J) Solubility Studies

The solubility studies were performed in phosphate buffer solution, pH 7.4 by adding excess amounts of drug in each case and keeping the excess drug containing phosphate buffer flasks on awater bath shaker NSW-133 (REMI Equipment, Mumbai, India) for 24 h at 328C.7 After 24 h, solutions were analyzed spectrophotometrically at 275 nm, which was the absorption maxima determined earlier and drug concentrations were calculated. [25]

K) Determination of Partition Coefficient of Drug

The partition coefficient study was performed using n-octanol as oil phase and phosphate buffer, pH 7.4, as aqueous phase. The two phases were mixed in an equal quantity and were saturated with each other on a mechanical water bath shaker NSW-133 at 328C for 24 h. The saturated phases were separated by centrifugation at 2000 rpm on a REMI R-23 centrifuge. Standard plots of drug were prepared from both the phosphate buffer and octanol. Equal volumes (10 ml each) of the two phases were taken in hexaplicate in conical flasks and, to each, 100 mg of weighed amount of drug was added. The flasks were shaken at 328C for 6 h to achieve a complete partitioning at 100 rpm. The two phases were separated by centrifugation at 1000 rpm for 5 min and they were then analyzed for respective drug contents. The partition coefficient of drug Ko/w was calculated using the following formula: [26]

Ko/w = Concentration in octanol/ Concentration in phosphate buffer pH 7.4

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L) Water Vapor Transmission Rate

For water vapor transmission studies glass vials of equal diameter were used as transmission cell. These transmission cells were washed thoroughly and dried in an oven. About 1 gm of anhydrous calcium chloride was taken in the cell and the polymer film was fixed over the brim with the help of the solvent. The cell were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride to maintain a humidity of 84% RH. The cells were taken out and weighed after 1, 2, 3, 4, 5, 6 and 7th day. Water vapor transmission rate usually expressed as the number of grams of moisture gain/hours/ sq.cm. W V T = WL/S Where, W is water vapor transmitted in mg, L is thickness of the film in mm, S is exposed surface area in cm^{2}[27]

M) Flatness and Elongation brake

Longitudinal strips were cut out from the prepared transdermal patches. The flatness was determined at various points by using vernier calipers. The percentage elongation brake was determined by noting the length just before the break point and substituted in the eq.1. Elongation (%) = L1 – L2 X 100/ L2 (1) Where L1 = final length of each strip L2 = initial length of each strip [28, 29].

N) Tack Properties

It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of pacifying resins in polymer.

O) Thumb Tack Test

The force required to remove thumb from adhesive is a measure of tack.

P) Rolling Ball Test

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

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Q) Quick Stick (Peel Tack) Test

The peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90° at the speed of 12 inch/min.

R) Probe Tack Test

Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack. [30]

S) Stability Studies:

The stability studies are conducted to investigate the influence of temperature and relative humidity on the drug content in different formulations. The transdermal formulations are subjected to stability studies as per ICH guidelines. [31]

IN VITRO DRUG RELEASE STUDIES

Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage forms. The dissolution test was performed using a six-spindle Chinese Pharmacopoeia apparatus employing glass vessels containing 900 ml phosphate buffer (pH 7.4) and a paddle speed of 50 r/min. The patch assembly was carefully placed at bottom of the vessel and centered using a glass rod. The paddles were lowered to a height 2.5 cm above the patches. The apparatus was equilibrated to 32 ± 0.5°C, the temperature of the skin surface. Five milliliters samples were collected at appropriate time intervals up to 10 h then an equal volume of fresh media was added and the determination of the drug content was performed by HPLC. The dissolution data isfitted to these models and the best fit is obtained to describe the release mechanism of the drug[18, 24,32,33]. There are various methods available for determination of drug release rate of TDDS.

- **The Paddle over Disc**: (USP apparatus 5) This method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains medium at 32 ±5°C. [34]
- **The Cylinder modified USP Basket**: (USP apparatus 6) This method is similar to the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder immersed in medium at 32 ±5°C. [35]

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- **The reciprocating disc**: (USP apparatus 7) In this method patches attached to holders are oscillated in small volumes of medium, allowing the apparatus to be useful for systems delivering low concentration of drug. In addition paddle over extraction cell method may be used. [36]
- **Diffusion Cells e.g. Franz Diffusion Cell and its modification Keshary- Chien Cell**: In this method transdermal system is placed in between receptor and donor compartment of the diffusion cell. The transdermal system faces the receptor compartment in which receptor fluid i.e. buffer is placed. The agitation speed and temperature are kept constant. The whole assembly is kept on magnetic stirrer and solution in the receiver compartment is constantly and continuously stirred throughout the experiment using magnetic beads. At predetermined time intervals, the receptor fluid is removed for analysis and is replaced with an equal volume of fresh receptor fluid. The concentration of drug is determined spectrophotometrically[37, 38].

IN VITRO PERMEATION STUDIES

The skin permeation experiment was carried out according to the method. A side by side (2-chamber) diffusion cell was used for the in vitro permeation experiment. Each cell has a volume of 2.5 ml and an effective diffusion area of 0.95 cm^2. A starhead bar in each cell was driven bya constant speed synchronous motor (MC-301, Scinics, Tokyo, Japan) at about 600 r/min. Wistar rats were anesthetized with sodium pentobarbital (500 mg/kg, I.P.) and the abdomen was carefully shaved using a BRAUN Flex XP BS 5776 shaver (Gillette Japan, Yokohama, Japan) after removed of hair by National ER804 electric clippers (Matsushita Electric Works, Ltd., Osaka, Japan). An area of about 5 cm^2 (circle of 2.5 cm diameter) of skin on the left and right sides of the abdomen was excised and the skin membrane was checked to ensure that no obvious defects were present. Patches with a surface area of 3 cm^2 were cut by a punch, and then applied to the epidermal side of the skin with a slight pressure, and the holders containing the skin and formulation were then placed on diffusion cells using a spring clamp. The temperature of the diffusion cells was maintained at 32 ± 0.5°C by a circulating water jacket. The receiver compartment of each cell was filled with 2.5 ml phosphate buffer (pH 7.4). Samples were withdrawn (2 ml each time) periodically from the receiver cell and an equal volume of phosphate

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buffer was added to keep the volume constant and the diclofenac content determined by HPLC. Each experiment was carried out for 10 h to achieve a steady permeation rate [39, 40].

IN VIVO STUDIES

In vivo evaluations are the true depiction of the drug performance. The variables which cannot betaken into account during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using:

- Animal models
- Human volunteers
- Skin irritation studies

Animal models

The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc.

Human models

The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc[41].

Skin irritation studies

Skin irritation studies were performed on healthy rabbits (average weight: 1.5 to 2.25 kg). The dorsal surface (50 cm^2) of the rabbits was cleaned, and the hair was removed by shaving. The skin was cleansed with rectified spirit. A representative patch (F7) was placed over the skin with the use of adhesive tape and was removed after 24 h [42].

APPLICATION OF TRANSDERMAL DRUG DELIVERY SYSTEM

Ten years ago, the nicotine patch had revolutionized smoking cessation; patients were being treated with nitroglycerin for angina, clonidine for hypertension, scopolamine for motion sickness, and estradiol for estrogen deficiency, all through patches. At that time, bio-

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techmedicinals were still being developed. During the past decade biotech products have come into their own, but transdermals have essentially remained static. The number and there has been little change in the composition of the patch systems. Modifications have been mostly limited to refinements of the materials used. One reason for this undoubtedly is the fact that only certain specialized firms can manufacture transdermal patches. Companies prefer to have full control of their projects and to enjoy the higher profits on products developed and manufactured in house. Another reason is that only a limited numberof drugs fit the molecular weight, lipophilicity, and potency requirements for transdermal absorption [(43)].

FDA REGULATION AND TRANSDERMAL DRUG DELIVERY SYSTEM

The first FDA approved Transdermal Drug Patch was in the year 1979. Since then, the transdermal drug delivery systems have come a long way. Drug gives a chronology of the events in the field of transdermal technology along with the approvals that were obtained atevery stage of this chronology.

The FDA regulation process for Transdermal drug delivery system is very stringent. Transdermal Drug Delivery system is a combinational device as defined in 21 CFR § 3.2(e) by Food and Drug Administration.[(44)]

Transdermal drug delivery system have to undergo premarket approval (PMA) andhence requires substantial evidence including biomechanical testing, animal testing, clinical trials studies before the transdermal patch can get approval for use in the market. The most recent approval in the field of transdermal drug delivery system was the approval of Nuepro patch for treatment of Parkinson's disease.[(45)]

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