



TRANSDERMAL PATHWAY FOR ANTIPSYCHOTIC THERAPY: A REVIEW

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ABSTRACT

Transdermal drug delivery system is topically administered medicaments. Transdermal patches are pharmaceutical preparation of varying sizes, containing, one or more active ingredient, intended to be applied to the unbroken skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers, and it avoid first pass effect. Transdermal patches deliver the drugs for systemic effects at a predetermined and controlled rate. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow. Characterization of transdermal patch is used to check its quality, size, time of onset & duration, adhesive property, thickness, weight of patch, moisture of content, uniformity & cutaneous toxicological studies. The market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future. An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world. Psychosis refers to an abnormal condition of the mind described as involving a "loss of contact with reality". People with psychosis are described as psychotic.

KEYWORDS: Transdermal patches, Transdermal system; Drug delivery; Patch; Adhesion.

INTRODUCTION

Transdermal patches are designed to deliver a therapeutically effective amount of drug across a patient's skin to the systemic circulation. Usually, today's patches are drug in adhesive (DIA) systems where a drug is dispersed or dissolved in a pressure sensitive adhesive (PSA) matrix. The typical components of a transdermal patch besides the API are the PSA, the backing membrane, the release liner and if required certain excipients. The most common^[1], form of delivery of drugs is the oral route. It has the notable advantage of easy administration, but also have significant drawbacks – namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and / or frequent dosing, which can be both cost prohibitive and inconvenient.^[2]

To overcome these difficulties there was a need for the development of new drug delivery system; which can improve the therapeutic efficacy and safety of drugs by more precise spatial and temporal placement within the body thereby reducing both the size and number of doses. Transdermal drug delivery system are topically administered medicaments. In the form of patches that deliver drugs for systemic effects at a predetermined and

controlled rate. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. Transdermal patches are flexible pharmaceutical preparation of varying sizes, containing, one or more active ingredients. They are intended to be applied to the unbroken skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers. These devices allow for pharmaceuticals to be delivered across the skin barrier. Theoretically, transdermal patches work in a very simple way. A drug is applied in a relatively high dosage to the inside of patch, which is worn on the skin for an extended period of time. Though a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow. Nicotine patch was the very first transdermal patch in market of India. The first transdermal patch, scopolamine was approved in 1979.^[3]

Psychosis and Antipsychotics

Schizoaffective disorder most commonly in conjunction with either an antidepressant (in the case of the depressive subtype) or a mood stabiliser (in the case of the bipolar subtype). Bipolar disorder (acute mania and mixed episodes) may be treated with either typical or atypical antipsychotics, although atypical antipsychotics are usually preferred because they tend to have more favourable adverse effect profiles and, according to a recent meta-analysis, they tend to have a lower liability for causing conversion from mania to depression.

Psychotic depression. In this indication it is a common practice for the psychiatrist to prescribe a combination of an atypical antipsychotic and an antidepressant as this practice is best supported by the evidence. Treatment-resistant (and not necessarily psychotic) major depression as an adjunct to standard antidepressant therapy. They are not recommended for dementia or insomnia unless other treatments have not worked. They are not recommended in children unless other treatments are not effective or unless the child has psychosis.^[3-6]

Advantages and Disadvantages of Transdermal drug delivery systems^[3-6]

Advantages	Disadvantages
i) They can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administration drug.	i) Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
ii) They can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhea.	ii) Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's imperability.
iii) To avoid the first pass effect e.g. Transdermal Nitroglycerin. It is rapidly metabolized by the liver when taken orally.	iii) Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable.
iv) They are noninvasive, avoiding the inconvenience of parenteral therapy.	iv) Long time adhere is difficult.

COMPONENTS OF TRANSDERMAL PATCHES^[7-9]

Polymer Matrix

The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in transdermal patches.

- Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
- The polymer should be stable.
- The polymer should be nontoxic
- The polymer should be easily of manufactured
- The polymer should be inexpensive
- The polymer and its degradation product must be non toxic or non-antagonistic to the host.
- Large amounts of the active agent are incorporated into it.

Types of polymer^[10-13]

(a) Natural polymers

Cellulose derivative, Gelatin, Waxes, Proteins, Gum, Shellac, Natural rubber, starch.

(b) Synthetic Elastomers

Hydrin rubber, silicone rubber, Nitrile, Acrylonitrile, Neoprene.

(c) Synthetic polymers

Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamide, polyurea, epoxy.

Drug

Drug solution in direct contact with release liner.

Physiochemical properties^[14-16]

- The drug should have a molecular weight less than 1000 Daltons.
- The drug should have affinity for both lipophilic and hydrophilic phases.
- The drug should have a low melting point.

Biological properties

- The drug should be potent with a daily dose of the order of a few mg/day.
- The half life ($t_{1/2}$) of the drug should be short.
- The drug must not produce allergic response.
- Tolerance to the drug must not develop under the near zero-order release profile of transdermal patches.

Permeation Enhancer

The flux J , of drug across the skin can be write as, $J = D \frac{dc}{dx}$, J = The Flux, D = diffusion coefficient, C = Concentration of the diffusing species, X = Spatial coordinate

Solvent

These compounds increase penetration possibly by swelling the polar pathway. e.g: Water, alcohols–Methanol & ethanol, / Dimethyl acetamide Propylene glycol and Glycerol.

Surfactants

The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.

- Anionic surfactant: Sodium lauryl sulphate Diacetyl sulphosuccinate

- ii) Nonionic Surfactant :-Pluronic F127, Pluronic F68
- iii) Bile Salt:-Sodium taurocholate, Sodium deoxycholate.

Other excipients

(a) Adhesives

The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device.

- i) It should not be irritant
- ii) It should be easily removed
- iii) It should not leave an un washable residue on the skin
- iv) It should have excellent contact with the skin.
- v) Physical & chemical compatibility with the drug
- vi) Permeation of drug should not effected.

Backing

Protect the patch from the outer environment.

Types of Transdermal Patches^[17-19]

There are four types of transdermal patches:

Single-layer drug in-adhesive

The adhesive layer of this system also contains the drug. In this type patches the adhesive layer not only serves to adhere the various layer together, along with entire system to the skin but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

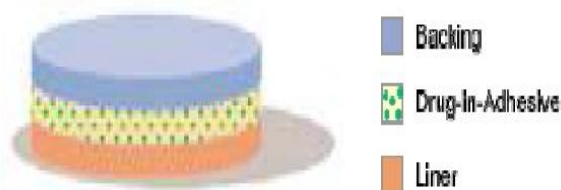


Fig. 1: Single-layer drug in-adhesive

Multi-layer drug in adhesive

The multi layer drug in adhesive is similar to the single layer system in that both adhesive layer are also responsible for the releasing of the drug. But it is different however that it adds another layer of drug in – adhesive, usually separated by a membrane. This patch also has a temporary liner – layer and a permanent backing.

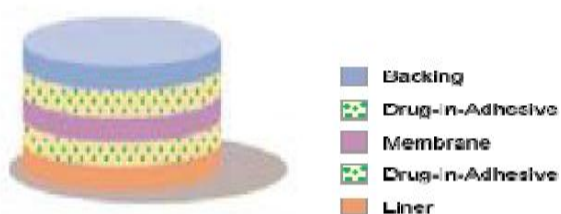


Fig.2: Multi-layer drug in adhesive

Drug reservoir-in-adhesive

Reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug soln or suspn separated by the backing layer. In this type of system the rate of release is zero order.



Fig. 3: Drug reservoir-in-adhesive

Drug Matrix-In-Adhesive

This matrix system has a drug layer of semisolid matrix containing a drug soln or suspn.

The adhesive layer in this patch surrounds the drug layer partially overlaying it.



Fig.4: Drug matrix-in-adhesive

Vapour Patch^[20,21]

In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapour patches release essential oils and is used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market.

FORMULATION OF TRANSDERMAL PATCHES^[22-25]

Membrane permeation – controlled system

These system can be multilaminate process e.g. Transdermal Nitro. These products consist of three substrates held together by two layers of drug containing adhesive. First the drug is processed into the physical / chemical form required for incorporation into the product. Then the drug adhesive components and excipients are mixed with a solvent to achieve uniform solution.

These adhesive composition are deposited as a thin film on moving substances rate which are subsequently dried to remove solvent. Then lamination of the dried adhesive film and other layer to form the five layer product

consisting of release liner, adhesive control membrane, drug reservoir and backing substrate.

The lamination then printed and die cut into final dosage form.

The production are then packed in individual foil pouches. After inspection the products are automatically inserted into a continuously moving web of pouch stock which is sealed around the dosage form.

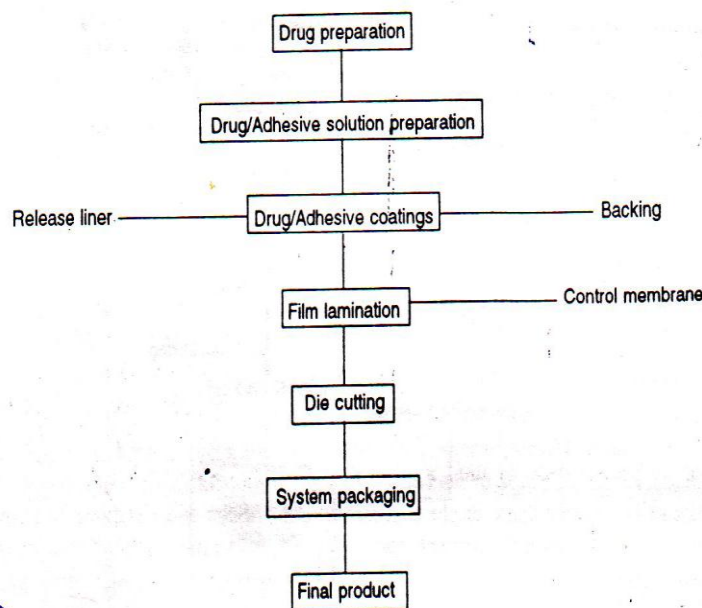


Fig.5: Multilaminate transdermal dosage from manufacturing process flow diagram

Evaluation Parameters^[26-32]

Thickness of the patch

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and the average thickness and standard deviation is determined to ensure the thickness of the prepared patch. The thickness of transdermal film is determined by traveling microscope dial gauge, screw gauge or micrometer at different points of the film.

Weight uniformity

The prepared patches are dried at 60°C for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Folding endurance

A strip of specific area is to be cut evenly and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

Percentage Moisture content

The prepared films are to be weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Content uniformity test

10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

Moisture Uptake

Weighed films are kept in desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in desiccators until a constant weight is achieved. % moisture uptake is calculated as given below 11, 13.

$$\% \text{ moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Final weight}} \times 100$$

Drug content

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyze the drug content with the suitable method (UV or HPLC technique). Each value represents average of three different samples.

Tensile Strength:

To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation.

$$\text{Tensile strength} = F/a.b (1+L/l)$$

F is the force required to break;

a is width of film;

b is thickness of film;

L is length of film;

l is elongation of film at break point

In another study, Tensile strength of the film was determined with the help of texture analyzer. The force and elongation were measured when the films broke.

Shear Adhesion test

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of cross linking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength.

Peel Adhesion test

In this test, the force required to remove an adhesive coating from a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180° angle, and the force required for tape removed is measured.

Water vapor transmission studies (WVT)

For the determination of WVT, weigh one gram of calcium chloride and place it in previously dried empty vials having equal diameter. The polymer films are pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then, the vials are accurately weighed and placed in humidity chamber maintained at 68 % RH. The vials are again weighed at the end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch. In other reported method, desiccators were used to place vials, in which 200 mL of saturated sodium bromide and

saturated potassium chloride solution were placed. The desiccators were tightly closed and humidity inside the desiccators was measured by using hygrometer. The weighed vials were then placed in desiccators and procedure was repeated. $WVT = W/ST$, W is the increase in weight in 24 h; S is area of film exposed (cm^2); T is exposure time.

Microscopic studies

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.

Adhesive studies

The therapeutic performance of TDDS can be affected by the quality of contact between the patch and the skin. The adhesion of a TDDS to the skin is obtained by using PSAs, which are defined as adhesives capable of bonding to surfaces with the application of light pressure. The adhesive properties of a TDDS can be characterized by considering the following factors:

Peel Adhesion properties

It is the force required to remove adhesive coating from test substrate. It is tested by measuring the force required to pull a single coated tape, applied to substrate at 180° 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.

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 tackifying resins in polymer.

Thumb tack test

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

Rolling ball tack test

This test measures the softness of a polymer that relates to tack. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

Quick Stick (peel-tack) test

In this test, the tape is pulled away from the substrate at 90°C at a speed of 12 inches/min. The peel force required breaking the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

Probe Tack test

In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams.

Drug release studies^[33-35]

Dissolution studies

The drug dissolution studies were carried out to see drug release from the medicated patches. The studies were done using apparatus similar to USP Dissolution Apparatus Type V (Paddle over Disk). The transdermal patches were cut with area 4.0 square cm. The patch was pressed on one side of double-sided adhesive tape for one minute so that it could firmly stick to the slide. Then, in temperature maintained dissolution apparatus, the slide was slowly released such that the slide will be flat and the release surface will be positioned upward and parallel to bottom of blade. Air bubble, if any, were removed and the test was carried out at 50 rpm. The distance between slide and paddle was 25.5mm. Interference from adhesive tape was determined by carrying out dissolution test with adhesive tape only.

Methods for determination of drug release rate of TDDS

The Paddle over Disc

(USP apparatus 5/PhEur 2.9.4.1) 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 $32 \pm 5^\circ\text{C}$.

The Cylinder modified USP Basket

(USP apparatus 6 / PhEur 2.9.4.3) 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 $32 \pm 5^\circ\text{C}$.

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 (PhEur 2.9.4.2) may be used.

Diffusion studies^[36-38]

Diffusion studies were done to get an idea of permeation of drug through barrier from the transdermal system. Usually, two types of diffusion cells are used as horizontal and vertical. The Franz and Keshary Chien (K-C) type of diffusion cells are of vertical type of cells. In this work, K-C type of diffusion cell was used. Fig.: 6 shows schematic diagram of KC diffusion cell.

Diffusion cells generally comprises of two compartments, one containing the active (active

compartment) and the other containing receptor solution (receptor compartment), separated by barrier i.e. dialysis membrane. The cell consisted of sampling port and temperature maintaining jacket. The outlet and inlet was connected with latex tube so jacket had stagnant water inside and heat was provided by hot plate. A steel pin was used to stir the receptor solution using a magnetic stirrer. The dialysis membrane was placed on receptor compartment and both compartments are held tight by clamps.

Method

Phosphate buffer pH 7.4 was used as receptor solution. The volume of diffusion cell was 40 ml and stirred with bent steel pin. The temperature was maintained $37 \pm 1^\circ$ with the help of hot plate. The diffusion was carried out for 6 hours and 1 ml sample was withdrawn from receptor compartment at an interval of 1 hour and same volume of buffer was added to receptor compartment. The 1ml sample was diluted up to 5 ml. The sample were analyzed with UV.

Formulations with good physical and mechanical properties were chosen for diffusion study.

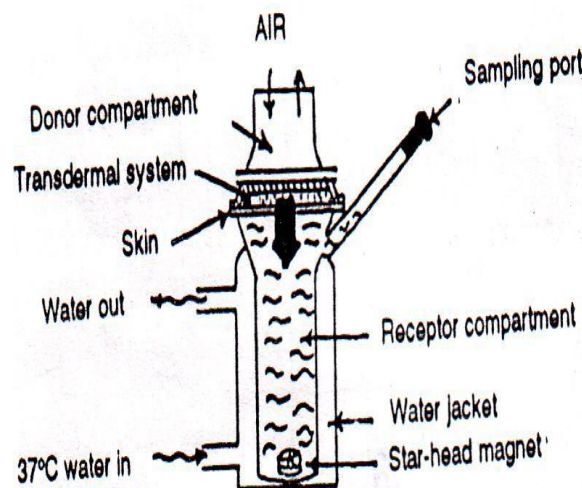


Figure 6: Keshary Chien diffusion cell for Permeation studies.

In vitro permeation studies^[39-40]

The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by penetration through cells of epidermis, between the cells of epidermis through skin appendages. Usually permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment in a vertical diffusion cell such as Franz diffusion cell or keshary-chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophilic side in contact with receptor fluid. The receiver compartment is

maintained at specific temperature (usually $32\pm5^{\circ}\text{C}$ for skin) and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined spectrophotometrically. Then the amount of drug permeated per centimeter square at each time interval is calculated. Design of system, patch size, surface area of skin, thickness of skin and temperature etc. are some variables that may affect the release of drug. So permeation study involves preparation of skin, mounting of skin on permeation cell, setting of experimental conditions like temperature, stirring, sink conditions, withdrawing samples at different time intervals, sample analysis and calculation of flux i.e., drug permeated per cm^2 per second.

Preparation of skin for permeation studies

Hairless animal skin and human cadaver skin are used for permeation studies. Human cadaver skin may be a logical choice as the skin model because the final product will be used in humans. But it is not easily available. So, hairless animal skin is generally favored as it is easily obtained from animals of specific age group or sex.

Intact Full thickness skin:

Hair on dorsal skin of animal are removed with animal hair clipper, subcutaneous tissue is surgically removed and dermis side is wiped with isopropyl alcohol to remove residual adhering fat. The skin is washed with distilled water. The skin so prepared is wrapped in aluminum foil and stored in a freezer at -20°C till further use. The skin is defrosted at room temperature when required.

Separation of epidermis from full thickness skin

The prepared full thickness skin is treated with 2M sodium bromide solution in water for 6 h. The epidermis is separated by using a cotton swab moistened with distilled water. Then epidermis sheet is cleaned by washing with distilled water and dried under vacuum. Dried sheets are stored in desiccators until further use.

In vivo Studies^[41-46]

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

Animal models

Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. 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. Various experiments conducted lead us to a conclusion that hairless animals are preferred over hairy animals in both in vitro and in vivo experiments.

Rhesus monkey is one of the most reliable models for evaluation of transdermal drug delivery in man. 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. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug. Skin irritation studies: White albino rats, mice or white rabbits are used to study any hypersensitivity reaction on the skin. Mutalik and Udupa (2005) carried out skin irritation test using mice. The mice were divided into 5 groups, each group containing 6 animals. On the previous day of the experiment, the hair on the backside area of mice were removed. The animals of group I was served as normal, without any treatment.

One group of animals (group II, control) was applied with marketed adhesive tape (official adhesive tape in USP). Transdermal systems (blank and drug loaded) were applied onto nude skin of animals of III and IV groups. A 0.8% v/v aqueous solution of formalin was applied as standard irritant (group V). The animals were applied with new patch/ formalin solution each day up to 7 days and finally the application sites were graded according to a visual scoring scale, always by the same investigator. The erythema was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for scar formation. The edema scale used was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for severe. After visual evaluation of skin irritation, the animals were sacrificed and skin samples were processed for histological examination. The results of this study showed that the prepared systems (both blank and drug loaded) and USP adhesive tape produced negligible erythema and edema. While standard irritant, formalin produced severe edema and erythema. The histopathologic examination of the skin also indicated that adhesive tape and prepared patches produced mild inflammation and edema.

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.

Regulatory requirements

A transdermal patch is classified by U.S. Food and Drug Administration (FDA) as a combination product,

consisting of a medical device combined with drug or biologic product that the device is designed to deliver. Prior to sale, any transdermal patch product must receive approval from FDA, demonstrating safety and efficacy for its intended use.

Global Overview of the Active Transdermal Drug Delivery Market

Transdermal delivery can nonetheless be viewed in a positive light as a highly attractive route of drug administration. The major challenge of technologies that enable, for example, inhalable and oral delivery, is to deliver sufficient quantities of the drug to the inaccessible surface through which it crosses into the blood. For systemic delivery, inhalers and formulations for inhalation must incorporate advanced designs to allow deposition in the deep lung. Oral technologies must protect the drug from the harsh environment in the stomach just so that it reaches the epithelium intact. In contrast, transdermal formulations can be applied directly to the surface the medication is intended to cross, the skin. The dense capillary bed close beneath the surface tantalizingly suggests easy access to the systemic circulation. Furthermore, patches can readily be designed to release active ingredient over extended periods and thus confer many of the benefits of implants or depot injections, but without the need for an invasive procedure to position a foreign device. Indeed, patients can interrupt dosing from a patch if required simply by removing it. The potential benefits of transdermal delivery have spurred several companies to overcome the challenges the skin presents as a barrier by developing active transdermal delivery technologies. These systems use energy to enhance the extent and rate at which pharmaceutical compounds cross the 10- to 20-micrometer dead layer of the skin, the stratum corneum, which represents the major barrier. The companies developing active transdermal systems aim to open up the transdermal market to the delivery of products that were previously considered undeliverable via this route.

The future of transdermal drug delivery

Transdermal drug delivery is theoretically ideal for many injected and orally delivered drugs, but many drugs cannot pass through the skin because of skin's low permeability. Pharmaceutical companies develop new adhesives, molecular absorption enhancers, and penetration enhancers that will enhance skin permeability and thus greatly expand the range of drugs that can be delivered transdermally. Two of the better-known technologies that can help achieve significant skin permeation enhancement are iontophoresis and phonophoresis (sonophoresis). Iontophoresis involves passing a direct electrical current between two electrodes on the skin surface. Phonophoresis uses ultrasonic frequencies to help transfer high molecular weight drugs through the skin. A newer and potentially more promising technology is micro needle-enhanced delivery. These systems use an array of tiny needle-like structures to open pores in the stratum corneum and facilitate drug

transport. The structures are small enough that they do not reach the nerve endings, so there is no sensation of pain. These systems have been reported to greatly enhance (up to 100,000 fold) the permeation of macromolecules through skin.

CONCLUSION

Transdermal drug delivery systems have been used as safe and effective drug delivery devices since 1981. A lot of progress has been done in the field of Transdermal Patches. Due to large advantages of the Transdermal Drug Delivery System, this system interests a lot of researchers. Many new researches are going on in the present day to incorporate newer drugs via this system. Transdermal dosage forms may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care. In recent years the use of a number of biophysical techniques has aided in our understanding of the nature of the stratum corneum barrier and the way in which chemicals interact with and influence this structure. A better understanding of the interaction of enhancers with the stratum corneum and the development of structure activity relationships for enhancers will aid in the design of enhancers with optimal characteristics and minimal toxicity. This article provides valuable information regarding the transdermal drug delivery systems and its evaluation process in details.

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