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TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT
Transdermal drug delivery system/TDDS are topically administered drugs in the form of patches that deliver drugs for systemic circulation at a predetermined and controlled rate. TDDS works very easily and drug is applied within the patch and it is worn on skin for long period of time by this constant concentration of drug remain in blood for long time. It is many types varying from single layer drug in adhesive to multi-layer drug in adhesive and others are reservoir and the matrix systems. Drug delivery through the skin has been always a challenging area for research due to barrier properties exhibit by the outermost layer of skin stratum corneum. In the few decades, TDDS has become a proven technology that offers significant clinical benefits over other dosage forms. Because it offers controlled as well as predetermined rate of release of the drug into the patient, it able to maintain steady state blood concentration. This system is a desirable form of drug delivery because of the obvious advantages like it painless and self-administration, avoidance of hepatic first-pass metabolism and the GI tract for poorly bioavailable drugs over other routes of delivery.

KEYWORDS: Transdermal drug delivery system, bioavailability, Iontophoresis, Electroporation, microscopic projection.

INTRODUCTION
Transdermal drugs (Transdermal patches) applied are typically administered in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. A TDDS device, which design like active or passive design, a device that provides an alternative route of oral drug delivery for administering medication. These devices allow for drugs to be delivered across the skin barrier and transdermal patches work very simply and easily. A high dosage of drug is applied inside of a patch. By diffusion process, the drug enters to the bloodstream directly through the skin. It Moves high concentration to low concentration because patch have high concentration and blood have low concentration, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.[1] Some popular drugs administered through skin patches like scopolamine, nicotine, estrogen, nitroglycerin, and lidocaine to relieve the pain of shingles (herpes zoster). Since the beginning of life on the earth, humans have applied a lot of substances to their skin as cosmetics and therapeutic agents.[2] However, it was the 20th century when the skin became used as a route for long-term drug delivery. Amongst all techniques which were used for release drugs in a controlled way into the human body, transdermal drug delivery system is widely recognized as one of the most reliable, appealing as well as effective technique. Transdermal drug delivery system in last few decade had become an appealing and patient acceptance technology as it is minimized and avoids the limitations allied with conventional as well as the parenteral route of drug administration such as peak and valley phenomenon i.e., exhibit fluctuation in plasma drug concentration level, pain and inconvenience of injections, and the limited controlled release options of both.[3]

Transdermal patche
The patch is medicated as an adhesive patch that placed on topical (skin) to deliver a specific dose of medicament into the bloodstream through the skin.

Advantage of transdermal patches[4-9]
- Transdermal drug delivery enables the avoidance of gastrointestinal absorption, with its associated pitfalls of enzymatic and pH-associated deactivation.
- This method also allows for reduced pharmacological dosing due to the shortened metabolization pathway of the transdermal route versus the gastrointestinal pathway.
- The patch also permits constant dosing rather than the peaks and valleys in medication level associated with orally administered medications, Multi-day therapy with a single application.

- Rapid notification of medication in the event of an emergency, as well as the capacity to terminate drug effects rapidly via patch removal.
- As a substitute for the oral route
- Transdermal medication provides safe, convenient, and pain-free self-administration for patients.
- Transdermal delivery may be useful in those patients who are poly-medicated.
- Transdermal drug delivery provides a constant rate of release of medicine to maintain concentration level of drug for a longer period of time to avoid peak and valley associated with oral dosing and parenteral administration.
- Transdermal patches improved therapeutic effect s of various drugs by avoiding specific problems associated with drugs such as pre-systemic metabolism, the formation of toxic metabolites, low absorption, gastro-intestinal irritation, etc.
- Useful in drugs possesses short half-life to avoid frequent dosing administration.
- Reduced inter & intra-patient variability by simplified medication regimen.
- Greater advantage in those patients who are unconscious, dysphagia, or constipation.
- Elimination of pre-systemic metabolism results in a reduction in the amount of drug administered, resulting in the reduction of adverse effects and hence safer in hepato-compromised patients,
- Fruitful in especially when long-term treatment is required, as in chronic pain treatment e.g., hormone replacement, etc., and smoking cessation therapy.
- The drug input can be terminated at any point in time by removing the transdermal system.
- Transdermal systems are generally inexpensive and economical when compared with other therapies on a cost basis, as patches are designed to deliver drugs from 1 to 7 days.
- The general acceptability of transdermal products by patients is very high, which is also proved by the increasing market for transdermal products.
- Topical patches are easier to use and remember
- Topical patches over an alternative to people who cannot, or prefer not to take medications or supplements orally.
- Provide a relatively large area of application in comparison with the buccal or nasal cavity.

Limitation

- The drug moiety must possess some physicochemical properties for penetration through the skin and if the dose of the drug is large i.e., more than 10- 25mg/day transdermal delivery is very difficult. a daily dose of drug preferred less than 5mg/day.
- Local irritation at the site of administration such as itching, erythema, and local edema may be caused by drugs or the excipients used in the formulations.
- Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.
- Some patients develop contact dermatitis at the site of application due to system components.
- The barrier function of the skin changes from one site to another, from person to person, and with age.
- Poor skin permeability limits the number of drugs that can be delivered in this manner.
- A high drug level cannot achieve by this system.
- Transdermal drug delivery is unable to deliver ionic drugs.
- Transdermal drug delivery system is restricted to the potent drug.
- It cannot deliver drugs in a pulsatile fashion.
- Tolerance inducing drugs or those (e.g., hormones) requiring chrono-pharmacological management are not suitable candidates.
- Required significant lag time.
- Drug molecules having a large molecular size (>1000 Dalton) cannot develop for transdermal delivery.

Basic component of transdermal system[9-16]

Polymer matrix or matrices

Polymers are the foundation of the transdermal system. The selection of polymer and design are of prime importance considerations for polymer selection in the transdermal delivery system:

- Should be stable and non-reactive with the drug moiety.
- Easily available, fabricated, and manufactured into desired formulations.
- The properties of polymer e.g., molecular weight glass transition temp. Melting point and chemical functionality etc. should be that the drug can easily diffuse through it and with other components of the system.
- Mechanical properties should not change if a large amount of drug incorporated.
- Should provide a consistent release of the drug throughout the life of the system

The polymers used in the transdermal system are

Natural polymers: e.g., zein, gelatin cellulose derivatives, gums, natural rubber, shellac, waxes, and chitosan, etc.

Synthetic elastomers: e.g., polyisobutylene, polybutadiene, silicon rubber, nitrile, neoprene, butyl rubber, hydrino rubber, acrylonitrile, etc.

Synthetic polymers: e.g., polyvinylchloride, polyethylene, polyvinyl alcohol, polypropylene, polyamide, polyacrylate, polyurea, polyvinylpyrrolidone, polymethylmethacrylate, etc.

Polymers used in a transdermal system such as

Rate controlling membrane

It controls the release of drugs by dispersing through an inert polymer matrix. The polymer powder blended with

drug moiety in a physical manner and then molded into the desired shape with the required thickness and surface area.

Adhesive
It makes intimate contact between the skin and the transdermal system. It carries the drug which is dissolved or dispersed in solution or suspension form. The drug diffused into the skin depending on the holding power.

Pressure-sensitive adhesive
The rapidity of the transdermal system can be done by pressure-sensitive adhesive. The 3 most commonly used adhesives are polyisobutylene, polyacrylate, and silicones in TDD devices.

Release liners
A transdermal patch is covered by a protective liner during storage until it is used. The release liner removed and discarded just before the application of the patch over the skin since the release liner is in intimate contact with the transdermal system hence it should be physically as well as chemically inert.

Backing laminate
While design the baking layer following points must be in consideration:

- Must be flexible.
- Having low water vapor transmission rate so as to promote skin hydration and thus greater skin permeability of drug
- Should be compatible with the transdermal system as remain in use while applying.
- Should be chemical resistance.
- Having good tensile strength.

Drug
Transdermal delivery is various physicochemical, pharmacokinetic, and pharmacological properties of the drug that should be considered for transdermal system development. Because of the limited permeability of the skin, drugs have to be trans-dermally delivered by passive diffusion through the skin and are limited by several substantial constraints. The drug moiety for the transdermal system should be potent (dose in mg), having molecular weight ≤ 1000 Da, adequate solubility in the vehicle, a log P value of < 5, melting point of 200 °C and appropriate lipophilicity, undergo extensive pre-systemic metabolism, non-ionic and non-irritant are considered as suitable candidates for delivery via this route.

Penetration enhancers
Penetration enhancers promote the penetration of topically applied drugs are commonly referred to as absorption promoters, accelerants, or penetration enhancers. Penetration enhancers are incorporated into a formulation to improve the diffusivity and solubility of drugs through the skin that would reversibly reduce the barrier resistance of the skin.

Other excipients
Plasticizers
Plasticizers have also been used in many formulations ranging from 5 to 20% (w/w, dry basis). Along with the brittleness and ductility of the film, it is also responsible for adhesiveness of the film with other surfaces or membranes and improvement in strength of film. Some of its examples are glycerol or sorbitol, at 15%, w/w, dry basis, phosphate, phthalate esters, fatty acid esters and glycol derivatives such as PEG 200, and PEG 400.

Solvents
Different solvents like methanol, chloroform, acetone, isopropanol and dichloromethane etc. are used to prepare drug reservoir.

Mechanism of action of transdermal patch[17-19]
The usage of the transdermal patch and the flow of the active drug constituent from the patch to the circulatory system via skin occur through various methods.

1. **Iontophoresis**

The Iontophoresis passes a some milliamperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. Principally used of pilocarpine delivery to induce sweating as part of cystic fibrosis diagnostic test.

2. **Electroporation**

It is method of application of short, high-voltage electrical pulses to the skin. Since electroporation, the permeability of the skin for diffusion of drugs is increased by 4 orders of magnitude. Electroporation is safe and electrical pulses can be administered painlessly using closely spaced electrodes to constrain the electric field within the nerve-free stratum corneum.

3. **Application by ultrasound**

It is, particularly low frequency ultrasound, has been shown to enhance transdermal transport of various drugs including macromolecules. It is also known as sonophoresis. Katz et al. indirect on the use of low-frequency sonophoresis for topical delivery of EMLA cream.

4. **Use of microscopic projection**

This patches with microscopic projections called microneedles were used to facilitate transdermal drug transport. The needles ranging from approximately 10-100 µm in length are arranged in arrays. Surface coated of drug on the microneedles to aid in rapid absorption. Projection are used in development of cutaneous vaccines for tetanus and influenza. Various other methods are also used for the application of the transdermal patches like thermal portion, magnetophoretic, and photomechanical waves.

Types of transdermal patches[20,21]

1. **Single-layer Drug-in-Adhesive**

In this type of patch, the adhesive layer not only serves to adhere the various layers together, along with the 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.

2. Multi-layer Drug-in-Adhesive

Multi-layer drug in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. Its system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases).

3. Reservoir

Single-layer and Multi-layer Drug-in adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system, the rate of release is zero order.

4. Matrix

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. This layer in this patch surrounds the drug layer partially overlaying it.

5. Vapor patch

In this type of patch, the adhesive layer not only serves to adhere the various layers together but also to release vapor. The vapor patches are new on the market and they release essential oils for up to 6 hours. The vapors patches release essential oils and are used in cases of decongestion mainly. Other vapor patches on the market are controller vapor patches that improve the quality of sleep.

Evaluation of transdermal patches[22-26]

- Physicochemical evaluation
- In vitro evaluation
- In vivo evaluation

1. Physicochemical evaluation

Thickness

Transdermal film thickness is determined by travelling microscope, dial gauge, screw gauge or micrometer at different points of the film.

Uniformity of weight

Studied of weight variation by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Drug content determination

Portion of film is accurately weight and 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. Sonication and subsequent filtration, after drug in solution is estimated spectrophotometrically by appropriate dilution.

Content uniformity test

Randomly 10 patches are selected and content is determined for individual patches. When 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. When 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

Moisture content

The film prepared and weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula. % Moisture content = Initial weight – Final weight X 100.

Moisture Uptake

Films after weighed and kept in a desiccator at room temperature for 24 h. These are taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below.

% moisture uptake = Final weight – Initial weight X 100

Flatness

A patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. Flatness determination, one strip is cut from the center and two from each side of patches. The length of some strip is measured and variation in length is measured by determining percent constriction. 0 percent constriction is equivalent to 100 percent flatness.

% constriction = I1 – I2 X 100 I2 = Final length of each strip I1 = Initial length of each strip.

Folding endurance

The evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. The Folding endurance is determined by repeatedly folding the film at the same place until it breaks. Number of times the films could be folded at the same place without breaking is folding endurance value.

Tensile strength

This strength is determined, polymeric films are sandwiched separately by corked linear iron plates. 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 tensile strength can be calculated using the following equation. 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.

Tack properties

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

Rolling ball test
Measurement of this test involve of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.

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.

Probe tack test
Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.

2. In vitro evaluation
The paddle over disc
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.

The cylinder modified USP basket
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.

The reciprocating disc
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.

In vitro permeation studies
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±5°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 cm2 per sec.

Horizontal-type skin permeation system
this has been widely used for the evaluation of drug permeation across skin. The cell is divided in receptor and donor compartments with a low solution volume (3.5ml) for each compartment and a small membrane area (0.64cm2). They are continuously stirred by matched set of star-head magnets, which are rotated at a speed of 600rpm. The system is controlled by thermo-stated water through a water jacket surrounding the two compartments.

Franz diffusion cell
the cell is composed of two compartments: donor and receptor. The receptor compartment has a volume of 5-12ml and effective surface area of 1-5 cm2. The diffusion buffer is continuously stirred at 600 rpm by a magnetic bar. The temperature in the bulk of the solution is maintained by circulating thermo-stated water through a water jacket that surrounds the receptor compartment.

Flow-through diffusion cell
flow through diffusion cells have the advantage that they can be used when the drug has lower solubility in the receptor compartment. This cell can be fully automated and connected directly to HPLC. They have large capacity donor chamber to aloe appropriate loading of the applied compound and a low volume (0.3ml) receiving chamber that ensures rapid removal of penetrant at relatively low pumping rates.

3. In vivo evaluation
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 animal models human volunteers.

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 leads 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 in vivo 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.

Application of transdermal drug delivery

- Nicotine transdermal patch marketed as Nico-dermis to help in smoking cessation. It is the highest selling patch in United State.
- Two opioid medications Fentanyl (marketed as Duragesic) and Buprenorphine (marketed as Bu-Trans) used to provide round-the-clock relief for severe pain available in patch form.
- Estradiol patches available as Estraderm for treat menopausal symptoms as well as postmenopausal osteoporosis. It is also available in combination with levonorgestrel as Climara Pro for menopausal symptoms.
- Nitroglycerin transdermal patches for the treatment of angina pectoris, prescribed in place of sublingual pills.
- Transdermal patch of clonidine available for treatment of hypertension.
- Transdermal patch of the selegiline (MAO inhibiter) became the first transdermal delivery agent for major depressive disorder.

CONCLUSION

Transdermal drug delivery is hardly an old technology, and the technology no longer is just adhesive patches. Due to the recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin membrane transdermal route is becoming the most widely accepted route of drug administration. It promises to eliminate needles for administration of a wide variety of drugs in the future.

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