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Review Article

Transdermal drug delivery system: An overview

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ABSTRACT

Today three fourth of the drugs manufactured are taken orally and are not found to be effective as desired. When compared to oral route of administration, transdermal route has numerous advantages over the more traditional drug delivery systems. Drug delivery through the skin to attain systemic circulation is known as transdermal drug delivery system (TDD).TDDS are the dosage forms which involves penetration of the drug substances through the outermost layer of skin that is stratum corneum to show its therapeutic effect, where major part of drug is transported into systemic circulation. A Transdermal Patch is an adhesive patch that has a coating of medicine (drug) that is placed on the skin to deliver specific dose (drug) into the blood over a period of time. This review describes about recent advancements in TDD enhancement techniques, skin morphology & mechanism of penetration, components of Transdermal patches, types of patches, and its physicochemical methods of evaluation is described.

Keywords: Transdermal delivery; types of patches; skin penetration; Evaluation.

INTRODUCTION

Transdermal drug delivery systems (TDDS) or transdermal therapeutic Systems (TTS) or patches are convenient dosage forms in terms of application, patient compliance and readily withdrawal of drug (if desired). (Chein et al., 1992) Several CNS medications have been formulated into various transdermal systems for local and prolonged delivery and this delivery system offer an advantageous alternative to common delivery methods such as injections or oral delivery.

Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation, oestradiol (alone or in combination with levonorgestrel or norethisterone) for hormone replacement and testosterone for hypogonadism. The first Transdermal system, Transderm-SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with ravel, particularly by sea (Loyd V. Allen Jr et al., 2005). Before any drug applied topically can act either locally or systemically it must penetrate the barrier layer of the skin, the stratum corneum. This behaves like a passive diffusion barrier with no evidence of metabolic transport processes, drugs being absorbed by transcellular or intercellular pathways. Quantity and area of application and dosage frequency obviously affect therapeutic efficacy, but the most significant factors are inter- and intra individual variations in skin permeability. The seminal work of Scheuplein and Blank (1971) opened a floodgate of research into skin permeation, which has ultimately resulted in the development of modern controlled transdermal drug delivery.

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Advantages of Transdermal drug delivery systems

Absorption of medication can be rapidly terminated whenever therapy must be interrupted.

Reduced dosing frequency and production of controllable and sustained plasma levels tend to minimize risks of undesirable side-effects which may be observed after oral dosage.

The avoidance of hepatic first-pass metabolism is an obvious advantage.

Improved patient compliance and comfort via non-invasive, painless and simple application.

Constant and continuous administration of drugs may be achieved by a simple application to the skin surface.

Transdermal medications deliver a steady infusion of a drug over an extended period of time adverse effects.

Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., GI irritation, low absorption, decomposition due to hepatic„"first- pass" effect, formation of metabolites that cause side effects, short half - life necessitating frequent dosing etc.

Provides ease of rapid identification of medication in emergencies - non-responsive patients, unconscious or comatose patients.

The activity of drugs having short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.

Disadvantages of Transdermal drug delivery systems

Some patients develop contact dermatitis at the site of application from one or more of the system components, which require discontinuation.

Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation

Irritation may be possible at the site of action.

Heat can slightly compromise the barrier function of the skin.

Barrier function of the skin changes from one site to another on the same person, from person to person and with age.

If the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult.

The molecular size of the drug should be reasonable so that the drug should enter percutaneously.

Limitations of transdermal drug delivery systems (Govil, S.K et al., 1998)

- Transdermal delivery is neither practical nor affordable when required to deliver large doses of drugs through skin
- Cannot administer drugs that require high blood levels
- Drug of drug formulation may cause irritation or sensitization
- Not practical, when the drug is extensively metabolized in the skin and when molecular size is great enough to prevent the molecules from diffusing through the skin.
- Not suitable for a drug, which doesn't possess a favorable, o/w partition coefficient
- The barrier functions of the skin of changes from one site to another on the same person, from person to person and with age. (Monkhouse et al., 1988).

Basic components of Transdermal drug delivery systems (Bernar B et al., 1994)

1. **Polymer matrix:** The polymer controls the release of the drug from the device. Types of polymers used.

   A) Natural polymers: zein, gelatin, shellac

   B) Synthetic polymers: polyurea, polyethylene

   C) Synthetic elastomers: butyl rubber, neoprene

2. **Drug**: Desirable properties of the drug are
   - Mol wt should be less than 1000 Daltons
   - Oil solubility should be greater than 1mg/ml
   - Water solubility should be greater than 1mg/ml
3. **Permeation enhancers**: Which facilitate the transport of drug molecules across skin by temporarily altering permeability. Ex: Terpenes, Terpenoids, Pyrrolidones. Solvents like alcohol, Ethanol, Methanol. Surfactants like Sodium Lauryl sulfate, Pluronic F127, Pluronic F68.
4. **Adhesives**: Serves to adhere the patch to the skin for systemic delivery of the drug Example: acrylates, polyisobutylene, silicones.
5. **Backing membrane**: protect the drug in the patch from outer environment and also prevent drug from leaving the top. Should be flexible, impermeable membrane and accept printing. Ex: metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminum foil)
6. **Release liner**: protect patch during storage. It is removed prior to use. Ex: non occlusive base layer and a release coating layer made of silicon or Teflon.

FACTORS THAT INFLUENCE TRANSDERMAL DRUG DELIVERY

Biological factors include

1. Skin condition
2. Skin age
3. Blood flow
4. Regional skin sites
5. Skin metabolism
6. Species differences

Physiological factors include

1. Skin hydration
2. Temperature and pH
3. Diffusion coefficient
4. Drug concentration
5. Partition coefficient
6. Molecular size and shape

Skin morphology

Before the discussion of transdermal transport, it is essential to understand the anatomy and barrier properties of skin. Skin is multilayered organ comprised of

many histological layers. Mainly dived into three categories epidermis, dermis and hypodermis. Microscopically, the epidermis further divided into five anatomical layers with stratum corneum forming the outer most layer of the epidermis, exposing to the external environment.

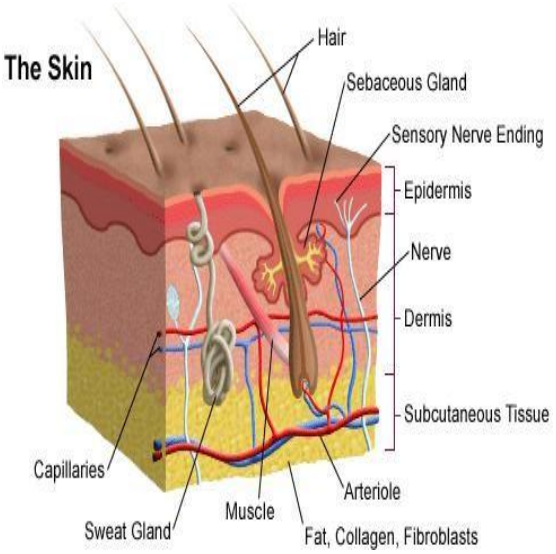

Figure 1: Structure of layers of skin

Stratum corneum is a passive diffusion barrier with no evidence of metabolic transport processes, drugs being absorbed by transcellular or intercellular pathways. The more common pathway through the skin is via the intercellular route. Drugs crossing the skin by this route must pass through the small spaces between the cells of the skin, making the route more tortuous. A less important pathway of drug penetration is the follicular route. Hair follicles penetrate through the stratum corneum, allowing more direct access to the dermal microcirculation. However, hair follicles occupy only 1/1,000 of the entire skin surface area. Consequently, very little drug actually crosses the skin via the follicular route.

Mechanisms of transdermal permeation

Penetration of water and low molecular weight nonelectrolytes through the epidermis is proportional to their concentration, and to the partition coefficient of the solute between tissue and vehicle. A form of Fick's law describes steady-state transport through the

Skin: J= (dp/ δ) ΔCv

Where J is the solute flux, D is the solute diffusion coefficient in the stratum corneum P is the solute partition coefficient between vehicle and skin, and δ is the thickness of the stratum corneum. ΔCv_ is the difference in solute concentration between vehicle and tissue. This relation is obtained.

Fick's law of diffusion shows that JαΔCv

A proportionality constant κ_p may be added. Thus J=κpΔCv

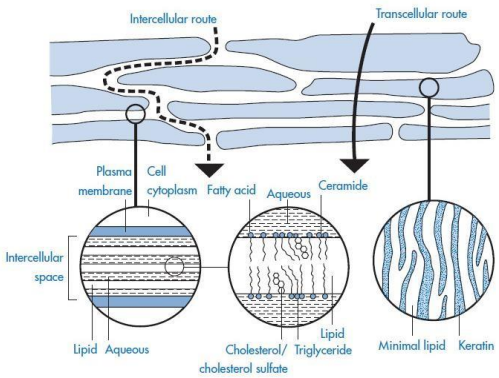

Figure 2: 'Bricks and mortar' model of the stratum corneum, illustrating possible pathways of drug permeation through intact stratum corneum (transcellular and tortuous intercellular pathways) and the lamellar structure of intercellular lipids

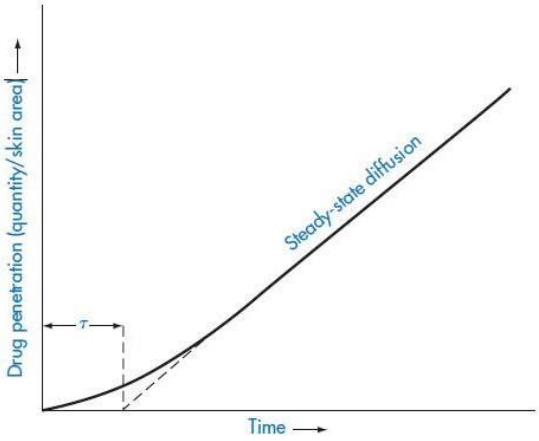

Figure 3: Drug penetration–time profile for an idealized drug diffusing through human skin

Where κp is the permeability constant, which provides a means of expressing absorption measurements for comparing different vehicles and conditions. The units of permeability constant are m s^{-1}, the concentration term being mol m^{-3}, so that J has the correct units of-Mol m^{-2} s^{-1}. It has been shown that κp =PD/δ, so that equation is readily obtained.

Types of transdermal patches

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

In this type the drug reservoir is formed by dispersing the drug in adhesive polymer and then spreading the medicated polymer by solvent casting or melting on a impervious backing layer. The rate of release of drug from this type of system is dependent on the diffusion across the skin. The intrinsic rate of drug release from this type of drug delivery system is defined by

$$dQ/dT = \frac{Cr}{1/Pm + 1/Pa}$$

Where Cr is the drug concentration in the reservoir compartment and Pa and P m are the permeability coefficients of the adhesive layer and the rate control-

ling membrane,Pm and Pa, respectively, are defined as follows.

$$Pm = \frac{Km}{r}.Dm/hm$$

$$Pa = \frac{Ka}{m}.Da/ha$$

where Km/r and Ka/m are the partition coefficients for the interfacial partitioning of drug from the reservoir, Dm and Da are the diffusion coefficients, hm and ha are the thicknesses of the rate controlling membrane and adhesive layer, respectively.

2. Multi layer drug in adhesive

It is similar to the Single-layer Drug-in-Adhesive in that the drug is incorporated directly into the adhesive. However, the multi-layer encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film. The rate of drug release in this system is defined by,

$$\frac{dQ}{dT} = Cr.\frac{Ka}{r}.\frac{Da}{ha}$$

Where Ka/r is the partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer.

3. Drug reservoir in adhesive

Characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the release liner or in a concentric configuration around the membrane.

$$Rate\ of\ drug\ release\ is\ given\ by \frac{dQ}{dt} = \frac{\frac{Ka}{r}.Da}{ha\ (t)} A\ (ha)$$

4. Drug matrix in adhesive

In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive Rim.

$$\frac{dQ}{dT} = ACpDp½/2t$$

A is the initial drug loading dose dispersed in the polymer matrix

Cp and Dp are the solubility and diffusivity of the drug in the polymer respectively

Cp is essentially equal to CR, where CR is the drug concentration in the reservoir compartment

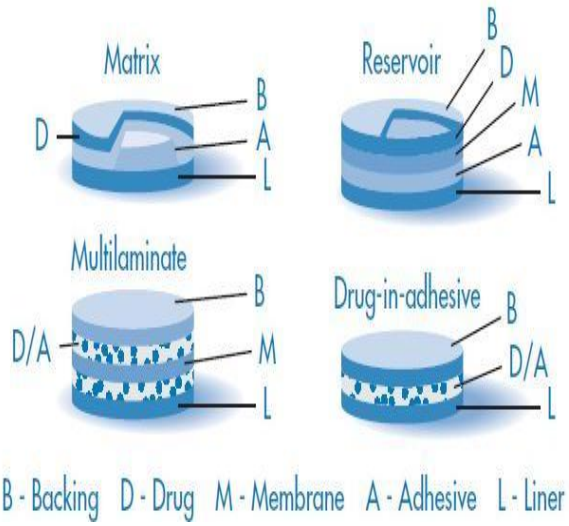

Figure 4: Types of transdermal patches a) matrix, b) reservoir, c) multilaminate, d) drug in adhesive

Evaluation of Transdermal drug delivery systems

Interaction studies: The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. Excipients are integral components of almost all pharmaceutical dosage forms. (Singh j et al., 1993) The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physiochemical characters such as assay, melting endotherms, characters wave numbers, absorption maxima etc.,

Thickness of the patch: (Aarti N et al., 1995) The thickness of the drug loaded patch is measured by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

Weight uniformity: (Rhaguram reddy k et al., 2003) The prepared patches are to be 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 weight

Folding endurance: (Rhaguram reddy k et al., 2003) A strip of specific are is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance

Peel adhesion test: In this test force required to remove an adhesive coating from a test substrate known

as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. (Aarti N et al., 1995) 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 180º angle, and the force required for tape removed is measured.

Thumb tack test: (Aarti N et al., 1995) It is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected.

Rolling ball tack test: (Vyas S.P et al., 2002) 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.

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 900 at the speed of 12inch/min. (Vyas S.P et al., 2002)

Probe Tack test: (Vyas S.P et al., 2002). 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.

Shear strength properties: 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 tackfier added. (Aati N et al., 1995). An adhesive coated tape is applied into 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.

Flatness test: (Wade A et al., 1994). Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

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. (Rhaghuram reddy k et al., 2003).

Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100

Percentage Moisture uptake: Weighed films are to be taken in a desicator at room temperature for 24 hrs. These are then taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in a desicator until a constant weight is achieved. Percentage moisture uptake is calculated as given below (Rhaghuram reddy k et al., 2003)

Percentage moisture uptake=Final weight- Initial weight X 100/Initial weight

Water vapour permeability evaluation (WVP) : Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula. (Shaila L et al., 2006)

$$WVP = W/A$$

Where, WVP is expressed in gm2 per 24 hrs, W is the amount of vapour permeated through the patch expressed in gm/24hrs and A is the surface area of the exposure samples expressed in m2.

Flatness test: (Wade A et al., 1994) Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

Drug content: A 5 cm film should be cut into small pieces; the drug content should be determined by suitable validated analytical method. (Shaila L et al., 2006)

Weight variation: Weight variation should be studied by individually weighing 10 randomly selected patches. Such determination. (Aati N et al., 1995)

Tensile strength: The tensile strength should be determined by using a modified pulley system. Weight was gradually increased so as to increase the pulling force till the patch broke. The force required to break the film was consider as a tensile strength and it was calculated as kg/cm2.

Percentage of moisture uptake: A weighed film kept in a desiccator at room temperature for 24 h was taken out and exposed to 84% relative humidity (a saturated solution of aluminum chloride) in a desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight. (Aati N et al., 1995).

In vitro diffusion studies should be performed by using a Franz diffusion cell with a receptor compartment capacity of 20 m.

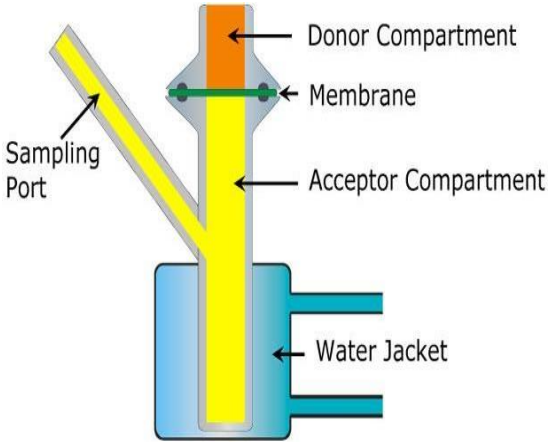

Figure 5: Franz diffusion cell

***In vivo* Evaluation Animal model**: Human skin is difficult to obtain and uniformity is difficult to maintain, since most of human skin comes from cadavers whose sex, age and genetic history are uncontrolled. Whereas, animal skin is easier to obtain and is more uniform. Humans and animals have wide differences in the number of appendageal openings per unit area thickness of skin, structure and porosity of skin, and these factors clearly affect the percutaneous absorption of drugs. (Bronaugh RL et al., 1982).The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig and Brattleboro rat are to be good animal models for skin/ transdermal drug delivery systems. Rhesus monkey is one of the most reliable models for in Vivo evaluation of transdermal drug delivery in man. Standard radiotracer methodology is used. Application site are generally forearm or abdomen. Alternative animal models include weanling pig and human skin grafted nude mouse

Human model: It involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. First described by (Feldman & Maibach). Determination of percutaneous absorption by indirect method of measuring radioactivity in excreta followed by topical application of labeled drug. % dose absorbed = total radioactivity excreted after topical administration divide by total radioactivity excreted after intravenous administration multiplied by 100.14C is generally used for radio- labeling.

***In vitro* drug release studies**: (Singh J et al., 1993) the paddle over disc method can be employed for assessement of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500ml of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32+ 0.50c. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples can be withdrawn at appropriate time intervals up to 24hrs and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

Skin Irritation study: (Shaila L et al., 2006) Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

Stability studies : (Singh J et al., 1993) Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°c and 75±5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content.

CONCLUSION

The TDDS review articles provide valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who is involved in TDDS. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS a realistic practical application as the next generation of drug delivery system.

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