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A NOVEL APPROACH FOR TRANSDERMAL DRUG DELIVERY SYSTEM (PATCH) – A REVIEW

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Abstract:
Transdermal drug delivery system are topically applied medication which is used to deliver the specific dose of drug direct entry into systemic circulation after passing through the skin barrier, and it avoid first pass effect. Transdermal patches deliver the drug for systemic effect at a predetermined and control rate through diffusion process. Transdermal drug technology specialists are continuing to search for new methods that can effectively and painlessly deliver large molecule in therapeutic quantities to overcome the difficulties associated with oral route, like poor bioavailability, first pass metabolism and sometime responsible for rapid blood level.
Dermal drug delivery is the dosage form that can transport the drug through viable epidermis and or dermal tissue of the skin for local therapeutic effect. While an important function transport the drug intosystemic blood circulation at controlled rate. Purpose of write the review article provide the overview of transdermal drug delivery like drug delivery route across human skin, permeation enhancer used in TDDS, components used in TDDS, how many type of transdermal patch, advantage and disadvantage and its methods of evaluation.
Keywords: *transdermal patch, Bioavailability, blood circulation, permeation enhancer*

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INTRODUCTION:

Transdermal patch is used to deliver a specific dose of medication through the skin and into bloodstream. Transdermal patches were first approved in 1981 by FDA. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives, and eliminates pulsed entry into systemic circulation which often causes undesirable side effects. Recently, the use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven to be effectively delivered through the skin, typically cardiac drugs such as nitroglycerin and hormones such as estrogen. Since the beginning of life on the earth, humans have applied a lot of substances to their skin as cosmetics and therapeutic agents. However, it was the twentieth century when the skin became used as route for long term drug delivery. Today about two third of drugs (available in market) are taken orally, but these are not as effective as required. To improve upon the features the transdermal drug delivery system was emerged. Amongst all techniques which were used for release drugs in a controlled way into the human body, transdermal drug delivery system (TDDS) is widely recognized as one of the most reliable, appealing as well as effective technique. Delivery of drugs through the skin has been an attractive as well as a challenging area for research [1,2,3]. Over the last two decades, transdermal drug delivery had become an appealing and patience acceptance technology as it is minimize and avoids the limitations allied with conventional as well as 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 [4].

Physiology of Skin:

Most of the topical preparations are meant to be applied to the skin. So basic knowledge of the skin and its physiology function are very important for designing topical. The skin of an average adult body covers a surface area approximately $2m^2$ and receives about one third of the blood circulating through the body. An average human skin surface is known to contain, on the average 40-70 hair follicles and 200-300 sweat ducts on every square centimeter of the skin. The pH of the skin varies from 4 to 5.6. Sweat and fatty acid secreted from sebum influence the pH of the skin surface. The skin can be considered to have four distinct layers of tissue:

- Non-viable epidermis.
- Viable epidermis.
- Viable dermis.
- Subcutaneous connective tissue.

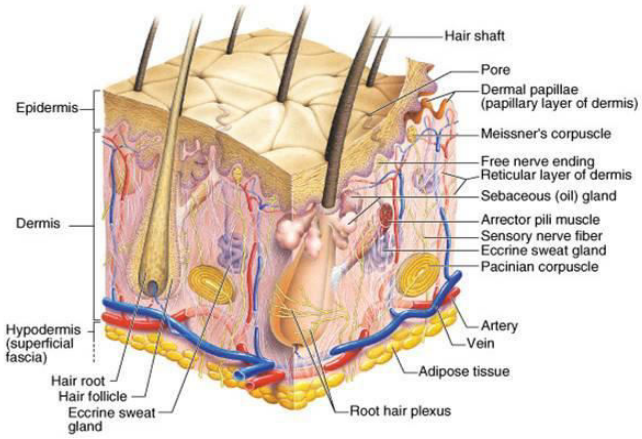

Fig1: Physiology of Skin

1. Non-viable epidermis: Stratum corneum is the outer most layer of skin, which is the actual physical barrier to most substance that comes in contact with the skin. The stratum corneum is 10 to 20 cell layer thick over most of the body. Each cell is a flat, plate like structure - 34-44ìm long, 25-36 ì m wide, 0.5 to 0.20ìm thick - with surface area of 750 to 1200ìm stocked up to each other in brick like fashion. Stratum corneum consists of lipid (5-15%) including phospholipids, glycosphingo lipid, cholesterol sulfate and neutral lipid, protein (75-85%) which is mainly keratin.

2. Viable epidermis: This layer of the skin resides between the stratum corneum and the dermis and has a thickness ranging from 50-100µm. The structures of the cells in the viable epidermis are physicochemical similar to other living tissues. Cells are held together by ton fibrils. The density of this region is not much different than water. The water content is about 90%.

3. Dermis: Just beneath the viable epidermis is the dermis. It is a structural fibrin and very few cells are likeit can be found histological in normal tissue. Dermis thickness ranges from 2000 to 3000µm and consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amphorphus ground substance.

4. Subcutaneous connective tissue: The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue which is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretary pores of the sweat gland and cutaneous nerves. Most investigators consider drug permeating through the skin enter the circulatory

system before reaching the hypodermis, although the fatty tissue could serve as a depot of the drug.

BASIC COMPONENTS OF TDDS:

Drug

Transdermal route of administration cannot be employed for all types of drugs. It depends upon optimal physicochemical properties of the drug, its biological properties. In addition, consideration of the pharmacokinetic and pharmacodynamics properties of drug is necessary. The most important requirement of drug to be delivered transdermal is demonstrated by need for controlled delivery, such as short half-life, adverse effect associated with other route or a complex oral or I.V. dose regimen [5,6].

Polymer

Advances in transdermal drug delivery technology have been rapid because of the sophistication of polymer science that now allows incorporation of polymers in transdermal system (TDS) in adequate quantity. The release rate from TDS can be tailored by varying polymer composition. Selection of polymeric membrane is very important in designing a variety of membrane permeation controlled TDS. The criteria for the polymers

- . The polymer should be chemically non-reactive or it should be an inert drug carrier;
- The polymer must not decompose on storage or during the life span;
- The polymer and its decomposed product should be nontoxic. It should be biocompatible with skin;

Penetration enhancer

An approach commonly researched for promoting permeation through the skin poorly penetrating drug molecules is the incorporation of chemical penetration enhancer to the. Alternatively, physical mechanism such as iontophoresis and phonophoresis can be used for certain cases of drug.

Method to Enhance Drug Penetration & Absorption [7]

- Chemical enhancement.
- Physical enhancement.
- Biochemical enhancement.
- Super saturation enhancement.

Properties of penetration enhancers [8,9,10]:

- They should be non-allergenic, non-irritating & non-toxic.
- They would ideally work rapidly &the activity & duration of effect should be both predictable and reproducible.
- They should have no pharmacological activity within the body i.e. should not bind to receptor sites.
- They should work unidirectional i.e. avoiding the loss of endogenous material from the bodywhereas should allow therapeutic agents into the body.
- They should be appropriate for formulation into diverse topical preparations, thus should be compatible with both Excipients and drugs.
- They should be cosmetically acceptable with an appropriate skin 'feel'.

Mechanism of penetration enhancers [11-14]:

Penetration enhancers may act by one or more of three main mechanisms:

- Disruption of the highly ordered structure of stratum corneum lipid.
- Interaction with intercellular protein.
- Improved partition of the drug, co enhancer or solvent into the stratum corneum.

The enhancers act by altering one of three pathways. By protein conformational change or solvent swelling the polar pathway is altered. The fluidity of the lipid protein portion of the stratum corneum is increased by fatty acid enhancers. By altering the multi laminate pathway for penetration some enhancers act on both polar and non-polar pathway. Drug diffusivity through skin proteins is increase by enhancer. On the design and development of the product significant effect is employed by type of enhancer.

Adhesive layer

The adhesive must posses' sufficient property so as to firmly secure the system to the skin surface and to maintain it in position for as long as desired, even in the presence of water. Any traces of adhesive left behind must be capable of being washed with soap and water after removal of transdermal patch, to achieve contact between the transdermal patch and the skin pressure sensitive patch to be used.

Backing layer

The backing layer must be impermeable to drug and permeation enhancers. The main purpose of backing membrane to holding the entire system together and at the same time protects the drug reservoir from exposure to the atmosphere, which could result in the breakage or loss of the drug by volatilization.

Release liner

When the drug that has migrated into the adhesive layer. The peel strip prevents the loss of drug during storage and protects the finished device against contamination. Polyesters foils and other metalized laminates are typical materials which are commonly used.

Other Excipients:

Plasticizers: Plasticizers have been also used in many formulation ranging from 5-20 %(w/w, dry basis) along with ductility and brittleness of the film,

it is also responsible for adhesiveness of the film with other surface membranes and improvement in strength of film some of its example are glycerol and sorbitol, at 15% w/w (dry basis) phosphate, phthalate ester, fatty acids ester and glycol derivative such as PEG 200 and PEG 400.

TYPES OF TRANSDERMAL PATCH:

Single-layer Drug-in-Adhesive

The Single-layer Drug-in-Adhesive system is characterized by the inclusion of the drug directly within the skin- contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the Excipients under a single backing film. The rate of release of drug from this type of system is dependent on the diffusion across the skin.

Multi-layer Drug-in-Adhesive

The Multi-layer Drug-in-Adhesive 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 drugs-in- adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film.

Drug Reservoir-in-Adhesive

The transdermal reservoir system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the semi-permeable membrane and adhesive by a release liner. 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.

Drug Matrix-in-Adhesive

The Matrix-in-adhesive system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix.

ADVANTAGES

- ❖ It is convenient method and requires only once weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy.
- ❖ Those patients who cannot tolerate oral dosage forms. Transdermal drug delivery can be used as an alternative route of administration.
- ❖ It is of great application in patients who are nauseated or unconscious.
- ❖ Drugs that cause gastrointestinal upset can be good candidates for transdermal delivery because this method avoids direct effects on the stomach and intestine.
- ❖ Drugs that are degraded by the enzymes and acids in the gastrointestinal system may also be good targets.
- ❖ An additional limitation to oral drug delivery, First pass metabolism can be avoided with transdermal administration.
- ❖ Drugs that require relatively consistent plasma levels are very

DISADVANTAGES

- ❖ At the site of application, Possibility of local irritation.
- ❖ Erythema, itching, and local edema can be caused by the drug, the adhesive or other excipient in the patch formulation.
- ❖ Allergic reactions may be possible.
- ❖ A molecular weight less than 500 Dalton is essential.

Factors Affecting Topical Absorption of Drug [4]

Physiological Factors

1. Skin thickness – It varies from epidermis to subcutaneous layer. Epidermis has high thickness about 100-150µm. Skin on the sole & palm has a high rate of diffusion.
2. Lipid content - It is an effective water barrier, when lipid weight in stratum corneum is low percutaneous penetration increases.
3. Density of hair follicles – hair follicle infundibulum has a large storage capacity approximately 10 times more than the stratum corneum.
4. Density of sweat glands
5. Skin pH –The pH of the skin surface is influence by sweat and fatty acid secreted from sebum.
6. Hydration of skin –It can improve permeation of drug.
7. Inflammation of skin – that disrupts the continuity of stratum corneum increases permeability.
8. Skin temperature – When temperature is increase the rate of skin permeation is also increase.
9. Blood flow

Physiochemical Factors

1. Partition coefficient – more the value of log p more effortlessly will be the percutaneous absorption of the drug.
2. Molecular weight (< 400 Dalton)

3. Degree of ionization – only unionized drug molecules get absorbed well.

Factors to be considered when choosing a Topical Preparation [5,6]

1. Effect of the vehicle e.g. Penetration of the active ingredient & efficacy is improve by occlusive vehicle. The vehicle itself may have a cooling, drying, emollient or protective action.
2. Match the type of preparation with the type of lesions. For example, for acute weepy dermatitis avoid greasy ointments.
3. Match the type of preparation with the site (e.g., gel or lotion for hairy parts)
4. Irritation or sensitization potential. Generally, gels are more irritating than ointments and water-in-oil creams. Ointments do not contain preservatives or emulsifiers if allergy to these agents is a concern.

EVALUATION PARAMETERS FOR THE FORMULATION:

Thickness of the Patch:

The thickness of the drug loaded transdermal patch is measured in different points by using a digital micrometer and the standard deviation and average thickness 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 [15, 16].

Weight Uniformity:

Before testing at 60°c the prepared patches are dried for 4hrs. 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 [16].

Folding Endurance:

Cut the specific area of the patch 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 [17].

Percentage Moisture Content:

The prepared individually weighed film that to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. The films are to be reweighed and determine the percentage moisture content after 24 hrs. From the below mentioned formula [15, 18].

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

Content uniformity test:

10 patches are selected randomly and content is determined each an 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 [15,16].

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 [16,17].

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

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 contain with the suitable method (UV and HPLC technique). Each value represents average of three different samples [16,18].

Shear Adhesion Test

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. Which 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 take to pull the tape off the plate the longer the time take for removal, grater is the shear strength [19].

Flatness:

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the center and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness [20].

$$\% \text{ constriction} = \frac{(L_1 - L_2)}{L_1} \times 100$$

L_2 = Final length of each strip

L_1 = Initial length of each strip

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.

'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 [21,22].

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.

Skin Irritation Study:

Skin sensitization testing can be performed on healthy rabbit average weight almost (1.2-1.5kg). The prepared formulation are applied on the surface of rabbit skin after clean and remove hair from the dorsal surface by shaving and clean the surface by using rectified spirits then after 24 hrs. Patch can remove from the skin and observed on the basic of the severity of skin injury [23,24].

***In-Vitro* Drug Release Studies:**

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. With adhesive dry films of known thickness were cut into definite shape, weighed, and fixed over a glass plate. The glass plate was then placed in a 500 ml of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32 ± 0.5°C. 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 (5 ml aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment was performed in triplicate and the mean value calculated [21].

***In- Vitro* Skin Permeation Studies:**

An in vitro permeation study can be carried out by using diffusion cell on thick abdominal skin of male Westar rats weighing 200 to 250 g. Using electric clipper hair from the abdominal region is removed carefully; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment, and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusion. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece was mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume was removed from the receptor compartment at regular intervals, and an equal volume of fresh medium was replaced. Samples were filtered through filtering medium and analyzed spectrophotometrically or using HPLC. Flux was determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm^2) versus time in hours, and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm^2) [22,23].

CONCLUSION:

The transdermal drug delivery is the most promising route of drug administration which is used for treatment against highly metabolites drug such as nitroglycerin patch for angina, clonidine for hypertension, scopolamine for motion sickness and estradiol for estrogen deficiency. Nicotine patch had revolutionized smoking cessation, all through used by over a million patients per year. Transdermal drug delivery of a drug product which is currently approved as oral dosage form allow for the avoidance of first pass metabolism. Dermal patch are most common form of transdermal delivery of drug. Through this patch researcher trying to overcome the hurdle associated from oral route like poor bioavailability and GI irritation.

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