Review Article

Transdermals as Novel Drug Delivery System: An Review

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ABSTRACT

Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range of drugs for which topical and transdermal delivery is a better therapeutic response. Transdermal drug delivery systems (TDDS) are dosage forms involves drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. Skin of an average adult body covers a surface of approximately 2 m^2 and receives about one-third of the blood circulating through the body. Skin is an effective medium for absorption of the drug takes place and enters the circulatory system. The adhesive of the transdermal drug delivery system is critical to the safety, efficacy and quality of the product. Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. Enhancement via modification of the stratum corneum by hydration, chemical enhancers acting on the structure of the stratum corneum lipids and keratin, partitioning and solubility effects are also discussed. Thus the aim of this review work is to focus on the recent innovations in Transdermal Drug Delivery Systems which can be a platform for the research and development of pharmaceutical drug dosage form for Transdermal Drug Delivery. The main disadvantage to transdermal delivery systems stems from the fact that the skin is a very effective barrier as a result, only medications those molecules are small enough to penetrate the skin can be delivered in this method.

Keywords: Applications, evaluation, penetration enhancer, skin, trans dermal delivery, TDDS.

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INTRODUCTION

The new idea several trans dermal drug delivery systems have recently been developed, aiming to achieve the objectives of systemic medications through topical applications to the intact skin surface[1]. Trnsdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism espectively[2]. FDA approved the first Tran dermal system Transderm-SCOP in 1979. FDA approved this for the prevention of nausea and vomiting associated with ravel, particularly by sea[3]. Recently, the trans dermal route has most succeseeeful innovative research area in drug delivary .The worldwide transdermal patch market approaches £ 2 billion, based on only some drugs including scopolamine, nitroglycerine, clonidine, estrogen, testosterone, fentanyl, and nicotine, with a lidocaine patch soon to be marketed[4]. A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Transdermal formulation maintain drug concentration within the therapeutic window for prolong period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration.

ADVANTAGES

- Avoid the risk and inconvenience of intravenous therapy.

- Which upon application on a suitable skin surface will be able to deliver the drug into the systemic circulation at sufficient concentration to ensure therapeutic efficacy?
- Maintains constant blood levels for longer period of time.
- Self administration is possible with these systems.
- Reduction of dosing frequency an enhancement of patient compliance.
- Decrease the dose to be administered
- Substitute for oral administration of medication when that route is unsuitable as with vomiting and diarrohea
- Allows continued drug administration permitting the use of a drug with short biological half-life.

DISADVANTAGES

- Drugs have large molecular size makes absorption difficulty. So drug molecule should ideally be below 800-1000 daltons.
- Transdermal drug delivery system cannot achieve high drug levels in blood/plasma.
- The barrier function of the skin changes from one site to another on the same person, from person to person and with age.
- Drugs with very low or high partition coefficient fail to reach blood circulation.
- TDDS cannot develop if drug or formulation causes irritation to skin.
- The possibility of local irritation may develop at the site of application.
- Many problems like Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation.

STRUCTURE OF SKIN

The skin can be considered to have four distinct layers of tissue [5]. Shown in (**Fig.1**)

- Non-viable epidermis (stratum corneum)
- Viable epidermis
- Viable dermis
- Subcutaneous connective tissue
- Non-viable epidermis (stratum corneum):

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.

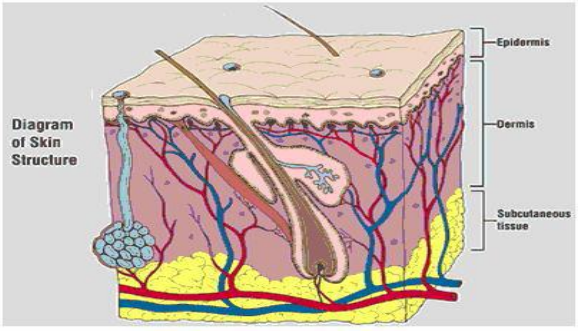

Fig.1: Skin

Each cell is a flat, plate-like structure - 34-44 µm long, 25- 36 µm wide, 0.5 to 0.20 µm thick - with a surface area of 750 to 1200 µm2 stocked up to each other in brick like fashion. Stratum corneum consist of lipid (5-15%) including phospholipids, glycosphingolipid, cholesterol sulfate and neutral lipid, protein (75-85%) which is mainly keratin.

- **Viable epidermis:**

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

- **Dermis:**

Just beneath the viable epidermis is the dermis. It is a structural fibrin and very few cells are like it can be found histologically in normal tissue. Dermis thickness range from 2000 to 3000 µm and consists of a matrix of loose connective tissue composed of fibrous tissue.

- **Subcutaneous connective tissue**

The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretory 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.

TRANSPORT THROUGH THE SKIN

Skin is structurally complex and thick membrane. Molecules moving from the environment must penetrate the stratum corneum and any material of endogenous or exogenous origin on its surface. They must then penetrate the viable epidermis, the papillary dermis and the capillary walls into the blood stream or lymph channels, where upon they are removed from the skin by flow of blood or lymph. To move across the skin membrane is obviously a complex phenomenon and challenge in analysis [6][7]. The potential pathway to the viable tissue through hair follicle with associated sebaceous gland via sweat ducts or across continuous stratum corneum between these appendages.

BASIC COMPONENTS OF TDDS:

- The drug
- Polymer matrix
- Permeation enhancers
- Adhesive
- Backing layer.

DRUG

Some of the desirable properties of a drug for transdermal delivery [25].

- The drug molecule should possess an adequate solubility in oil and water.
- The drug should have a molecular weight less than approximately 1000 daltons.
- The drug should have low melting point
- The drug molecule would require a balancedmpartition coefficient to penetrate the stratum corneum.

POLYMER MATRIX

These polymers control the release of the drug from the drug reservoir.

- Natural polymers: shellac, gelatin, waxes, gums, starch etc.
- Synthetic polymers: polyvinyl alcohol, polyamide, polyethylene, polypropylene, Polyurea, polymethylmethacrylate etc.

PERMEATION ENHANCERS

These include water, pyrolidones, fatty acids and alcohols, azone and its derivatives, alcohols and glycols, essential oils, terpenes and derivatives, sulfoxides like dimethyl sulfoximide and their derivatives, urea and surfactants. Lipid action, the enhancer interacts with the organized intracellular lipid structure of the stratum corneum so as to disrupt it and make it more permeable to drug molecules. Very many enhancers operate in this way. Some solvents act by extracting the lipid Components and thus make the horny layer more permeable. Protein modification, Ionic surface active molecules in particular tend to interact well with the keratin in the corneocytes, to open up the dense keratin structure and make it more permeable. The intracellular route is not usually prominent in drug permeation, although drastic reductions to this routes resistance could open up an alternative path for drug penetration. Partitioning promotion, many solvents can enter the stratum corneum, change its solvent properties and thus increase the partitioning of a second molecule into the horny layer.

ADHESIVE

Serves to adhere the patch to the skin for systemic delivery of drug.
Ex: Silicones, Polyisobutylene.

BACKING LAYER

Backing layer protects patch from outer environment. Ex: Cellulose derivatives, Polypropylene silicon rubber.

MANUFACTURING OF TDDS

Large scale production of TDDS products requires manufacturing technologies that are new to or modified form,the traditional pharmaceutical industry [8].

1. Membrane permeation-controlled system

The drug is a processed into the physical/chemical form required for incorporation into the product. Then the drug, adhesive component and excipients are mixed with solvents to achieve uniform solution or dispersion. These adhesive compositions are deposited as thin films on moving substrates which are subsequently dried to remove solvent. The next step consist of lamination of the dried adhesive film and other layer to form five layer product consisting of release linear, contact adhesive, control membrane, drug reservoir, and backing substrate. The laminate is then printed and die cut into the final dosage form.

2. Adhesive dispersion type system

The manufacturing process of this system can be subdivided into [9].

- Preperation of individual matrix solutions

- Coating the individual matrix layer
- Building the multi layer laminate
- Seperating units of the multi layer laminate
- Packaging

3. Matrix diffusion controlled system

4. Microsealed dissolution controlled system

EVALUATION OF TDDS

1. Evaluation of Adhesive [10-20,25,26]

A. Peel Adhesion test

In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. 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. Peel adhesion is the force required to remove an adhesive coating from a test substrate. Peel adhesion properties are affected by the molecular weight of the adhesive polymer, the type and amount of additives, and polymer composition. It is tested by measuring the force required to pull a single coated tape, applied to a substrate, at a 180^0 angle.

B. Thumb tack test

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 shown in (**Fig. 2**)

Fig.2: Thumb tack test

C. 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 shown in (**Fig. 3**).

D. Peel-tack test

In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min.

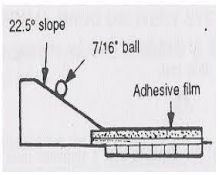

Fig.3: Rolling ball tack test

The peel force required to break the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width. Shown in (**Fig. 4**).

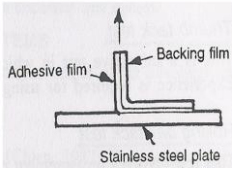

Fig.4: Peel-tack test

E. 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 shown in (**Fig. 5**).

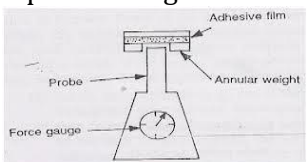

Fig.5: Probe Tack test

2. In-vitro drug release Evaluation

The paddle over disc method can be employed for assessment 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 upto 24hrs and analysed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

A. In-vitro skin permeation studies

An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats weighing 200-250 gm. Hair from the abdominal region is to be removed carefully by using a electric clipper, 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 diffusant. The temperature of the cell was maintained at 32+0.50c using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectro photo metrically or HPLC. Flux can be determined directly as the slope of the curve between the steady state values of the amount of drug permeated vs. time in hrs and permeability coefficients were deduced by dividing the flux by the initial drug load.

3. In vivo evaluation

In vivo evaluation study is 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

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. The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmaco dynamic 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.

4. Stability studies [21,24]

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.

APPLICATION OF TDDS [22,23]

- Transdermal patch of nicotine, which releases nicotine in controlled doses to help with cessation of tobacco smoking.
- Clonidine, the antihypertensive drug and ketoprofen, the non-steroidal anti-inflamatory drug are also available in the form of transdermal patches.
- Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis. Other transdermal patches for hormone delivery include the contraceptive patch .
- Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD).
- Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl and Buprenorphine

CONCLUSION

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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