Transdermal Drug Delivery System

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***Abstract*: A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific doseof medication through the skin and into the bloodstream.Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery routeover other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patchprovides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heatmelting thin layers of medication embedded in the adhesive. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over otherdosage forms. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intrapatient variations.**

***Keywords*: Transdermal Patch, Bloodstream, Systemic Circulation.**

1. INTRODUCTION

Transdermal drug delivery is defined as self- contained, discrete dosage forms which, when appliedto the intact skin, deliver the drug, through the skin atcontrolled rate to the systemic circulation. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery system.Transdermal drug delivery systems (TDDS), also known as "patches," are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolismrespectively (1).
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. Thus various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc. emerged. 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 considered. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively (1).

Transdermal delivery not only provides controlled,

Disadvantages of Transdermal Drug Delivery Systems:

1. The drug must have some desirable physicochemical properties for penetration throughstratum corneum and if the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult.
2. Only relatively potent drugs are suitable candidatesfor TDDS because of the natural limits of drug entry imposed by the skin's impermeability.
3. Some patients develop contact dermatitis at the siteof application for one or more of the systemcomponents, necessitating discontinuation.
4. Clinical need is another area that has to be examinedcarefully before a decision is made to develop a transdermal product.
5. The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

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Advantages of Transdermal Drug Delivery Systems:

1. Transdermal medication delivers a steady infusion of a drug over an extended period of time. Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided.
2. Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastrointestinal irritation, low absorption, decomposition due tohepatic "first- pass" effect, formation of metabolites that cause side effects, short half - life necessitating frequent dosing etc.
3. Due to the above advantage, it is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with

a lower daily dose of the drug than is necessary, if, for example, the drug is given orally.
4. The simplified medication regimen leads toimproved patient compliance and reduced inter & intra – patient variability.
5. At times the maintenance of the drug concentrationwithin the diphase is not desired. Application and removal of transdermal patch produce the optimalsequence of pharmacological effect.
6. Self-administration is possible with these systems.

First-generation transdermal delivery systems: The first generation of transdermal delivery systems isresponsible for most of the transdermal patches thathave thus far been in clinical use. Significant advancesin patch technology, and public acceptance, haveenabled therecent surge in first-generationtransdermal patches reaching the market. However,this surge will taper off as drugs with suitableproperties for such systems are depleted.First generation delivery candidates must be low-molecular weight, lipophilic and efficacious at lowdoses. Usually, their transdermal delivery should bemore attractive than oral delivery due to low oralbioavailability, the need or desire for less frequentdosing or steady delivery profiles, or other factors.

Second-generation transdermal delivery systems:-
The second generation of transdermal deliverysystems recognizes that skin permeabilityenhancement is needed to expand the scope oftransdermal drugs. The ideal enhancer should (i) increase skin permeability by reversibly disruptingstratum corneum structure,
(ii) provide an added driving force for transport into theskin and
(iii) Avoid injury to deeper, living tissues.
However, enhancement methods developed in thisgeneration, such as conventional chemical enhancers,iontophoresis and non-avitational ultrasound, have struggled with the balance between achieving increased delivery across stratum corneum, while protecting deeper tissues from damage. As a result, this second generation of delivery systems hasadvanced clinical practice primarily by improving small molecule delivery for localized, dermatological,cosmetic and some systemic applications, but has made little impact on delivery of macromolecules (5).

2. TRANSDERMAL DRUG PERMEATION

Skin as site for transdermal drug administration: The skin of an average adult body covers a surface areaof approximately two square meters and receivesabout one-third of the blood circulating through thebody. The skin is a multilayered organ composed ofmany histological layers. It is generally described interms of three major tissue layers: the epidermis, thedermis, and the hypodermis (Fig. 1). Microscopically,the epidermis is further divided into five anatomicallayers with stratum corneum forming the outer mostlayer of the epidermis, exposing to the externalenvironment. An average human skin surface isknown to contain, on the average, 40-70 hair folliclesand 200-250 sweat ducts on each square centimetre ofskin area. These skin appendages, however, actuallyoccupy, grossly, only 0.1% of the total human skinsurface.

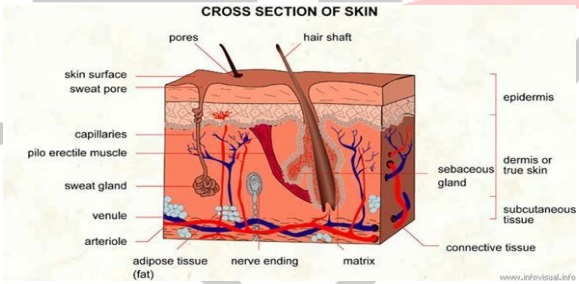

Figure 1: cross-section of hair follicle and skin

Mechanism of transdermal permeation:
For a systemically active drug to reach a target tissue,it has to possess some physico-chemical properties which facilitate the absorption of the drug through theskin and also the uptake of the drug by the capillary network in the dermal papillary layer (7).

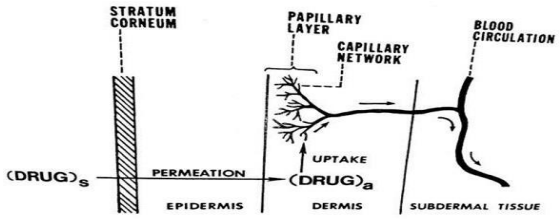

Figure 2: Mechanism of transdermal permeation

Factors affecting transdermal permeation:
1) Physicochemical properties of the penetrantmolecule:
A. Partition coefficient
A lipid/water partition coefficient of 1 or greater is generally required for optimal transdermal permeability. It may be altered by

chemical modification without affecting the pharmacological activity of the drug.

B. pH conditions

Applications of solutions whose pH values are very high or very low can be destructive to the drug.

With moderate pH values, the flux of ionizable drugs can be affected by changes in pH that alter the ratio ofcharged and uncharged species and their transdermal permeability.

C. Penetrant concentration

Assuming membrane related transport, increasing concentration of dissolved drug causes a proportional increase in flux. At concentration higher than the solubility, excess solid drug functions as a reservoir and helps maintain a constant drug constitution for a prolonged period of time.

II) Physicochemical properties of the drug delivery system:

A. Release characteristics

Solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depends on the following factors: Whether the drug moleculesare dissolved or suspended in the delivery systems. The interfacial partition coefficient of the drug from the delivery system to the skin tissue (8).

B. Composition of the drug delivery systems

The composition of the drug delivery systems e.g., boundary layers, thickness, polymers, vehicles notonly affects the rate of drug release, but also thepermeability of the stratum corneum by means ofhydration, making with skin lipids, or other sorption promoting effects e.g., benzocaine permeationdecreases with PEG of low molecular weight

3. BASIC COMPONENTS OF TRANSDERMALDRUG DELIVERY SYSTEMS

The components of transdermal devices include:

1. Polymer matrix or matrices.
2. The drug
3. Permeation enhancers
4. Other excipients

A. Polymer Matrix:

The Polymer controls the release of the drug from thedevice.

Possible useful polymers for transdermal devices are:

a) Natural Polymers:

e.g. Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

b) Synthetic Elastomers:

e.g. Polybutadieine, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc.

c) Synthetic Polymers:

e.g. Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethylmethacrylate, Epoxy etc.

B. Drug

For successfully developing a transdermal drugdelivery system, the drug should be chosen with greatcare. The following are some of the desirableproperties of a drug for transdermal delivery.

Physicochemical properties

1. The drug should have a molecular weight less thanapproximately 1000 daltons.
2. The drug should have affinity for both – lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
3. The drug should have low melting point.

Along with these propertiesthe drug should be potent,having short half life and be non irritating.

C. Permeation Enhancers

These are compounds which promote skin permeability by altering the skin as a barrier to the fluxof a desired penetrant.

These may conveniently be classified under the following main headings:

a) Solvents

These compounds increase penetration possibly byswallowing the polar pathway and/or by fluidizing lipids. Examples include water alcohols – methanol and ethanol; alkyl methyl sulfoxides – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethyl acetamide and dimethyl formamide; pyrrolidones – 2 pyrrolidone, Nmethyl, 2-purrolidone;laurocapram (Azone), miscellaneous solvents – propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

b) Surfactants

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbonchain length.

- Anionic Surfactants: e.g. Dioctylsulphosuccinate,Sodium lauryl sulphate, Decodecylmethyl sulphoxide etc.
- Nonionic Surfactants: e.g. Pluronic F127,Pluronic F68, etc.
- Bile Salts: e.g. Sodium staurocholate, Sodiumdeoxycholate, Sodium tauroglycocholate.
- Binary system: These systems apparently open up the heterogeneous multilaminate pathway as well as the continuous

pathways. e.g. Propyleneglycol-oleic acid and 1, 4-butane diol-linoleic acid.

c) Miscellaneous chemicals

These include urea, a hydrating and keratolytic agent;N, N-dimethyl-m-toluamide; calcium thioglycolate;anticholinergic agents. Some potential permeation enhancers have recently been described but the available data on theireffectiveness sparse. These include eucalyptol, di-o- methyl-ß cyclodextrin and soyabean-casein.

D. Other Excipients

a) Adhesives:

The fastening of all transdermal devices to the skin hasso far been done by using a pressure sensitive adhesivewhich can be positioned on the face of the device or inthe back of the device and extending peripherally.

Both adhesive systems should fulfil the followingcriteria

(i) Should adhere to the skin aggressively, should beeasily removed.

(ii) Should not leave an unwashable residue on theskin.

(iii) Should not irritate or sensitize the skin.

The face adhesive system should also fulfil thefollowing criteria.

(i) Physical and chemical compatibility with the drug,excipients and enhancers of the device of which it is apart.

(ii) Permeation of drug should not be affected.

(iii) The delivery of simple or blended permeation enhancers should not be affected.

b) Backing membrane:

Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is impermeable substance that protects theproduct during use on the skin e.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminium foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc) etc

4. TYPES OF TRANSDERMAL DRUGDELIVERY SYSTEMS

Transdermal Patches:

A transdermal patch or skin patch is a medicatedadhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types suchas oral, topical, etc is that it provides a controlled release of the medicament into the patient. Adisadvantage to development however, stems from thefact that the skin is a very effective barrier. A wide variety of pharmaceuticals can be delivered by transdermal patches.

Types of Transdermal Patches:

Single layer drug in adhesive

Figure 3: Single layer drug in adhesive

In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and also responsible for the releasing the drug to the skin. The adhesive layer is surroundedby a temporary liner and a backing

Multi -layer drug in adhesive:

This type is also similar to the single layer but it contains a immediate drug release layer and otherlayer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.

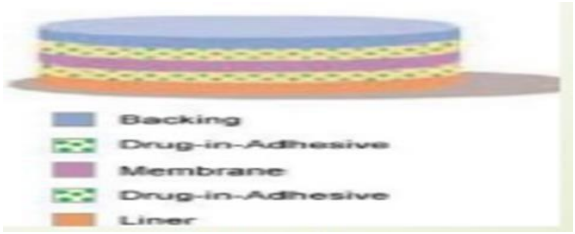

Figure 4: Multi -layer drug in adhesive

Drug Reservoir-in-Adhesive

In this system the drug reservoir is embedded betweenan impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenicadhesive polymer can be applied as outer surfacepolymeric membrane which is compatible with drug.

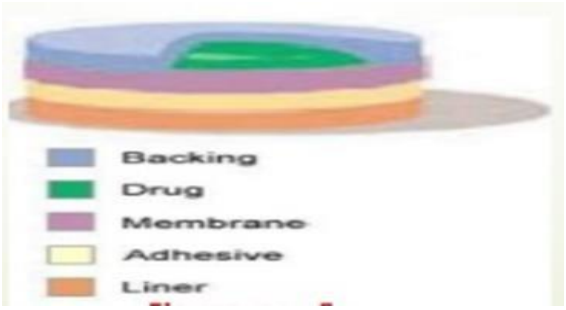

Figure 5: Drug Reservoir-in-Adhesive

Drug Matrix-in-Adhesive

The Matrix system design is characterized by theinclusion of a semisolid matrix containing a drugsolution 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 (13,14,15,16).

Figure 6: Drug Matrix-in-Adhesive**5.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 siteof 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 varietyof drugs in the future. TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. Tooptimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS realistic practical application as the next generation of drug delivery system

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