

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 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 of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting 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 other dosage 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 inpatient variations.

1.INTRODUCTION

Transdermal drug delivery is defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled 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 metabolism respectively (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.

1.1 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 to hepatic “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 to improved patient compliance and reduced inter & intra – patient variability.
5. At times the maintenance of the drug concentration within the diphasic is not desired. Application and removal of transdermal patch produce the optimal sequence of pharmacological effect.
6. Self administration is possible with these systems.

1.2 Disadvantages of Transdermal Drug Delivery Systems:

1. The drug must have some desirable physicochemical properties for penetration through stratum 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 candidates for TDDS because of the natural limits of drug entry imposed by the skin's impermeability.
3. Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.
4. Clinical need is another area that has to be examined carefully 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.

1.3 First-generation transdermal delivery systems:

The first generation of transdermal delivery systems is responsible for most of the transdermal patches that have thus far been in clinical use. Significant advances in patch technology, and public acceptance, have enabled the recent surge in first-generation transdermal patches reaching the market. However, this surge will taper off as drugs with suitable properties for such systems are depleted. First-generation delivery candidates must be low-molecular weight, lipophilic and efficacious at low doses. Usually, their transdermal delivery should be more attractive than oral delivery due to low oral bioavailability, the need or desire for less frequent dosing or steady delivery profiles, or other factors.

1.4 Second-generation transdermal delivery systems:-

The second generation of transdermal delivery systems recognizes that skin permeability enhancement is needed to expand the scope of transdermal drugs. The ideal enhancer should

- (i) increase skin permeability by reversibly disrupting stratum corneum structure,
- (ii) provide an added driving force for transport into the skin and
- (iii) avoid injury to deeper, living tissues.

However, enhancement methods developed in this generation, such as conventional chemical enhancers, iontophoresis and non-avitalational 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 has advanced 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

2.1 Skin as site for transdermal drug administration:

The skin of an average adult body covers a surface area of approximately two square meters and receives about one-third of the blood circulating through the body. The skin is a multilayered organ composed of many histological layers. It is generally described in terms of three major tissue layers: the epidermis, the dermis, and the hypodermis (Fig. 1). Microscopically, the epidermis is further divided into five anatomical layers with stratum corneum forming the outer most layer of the epidermis, exposing to the external environment. An average human skin surface is known to contain, on the average, 40-70 hair follicles and 200-250 sweat ducts on each square centimetre of skin area. These skin appendages, however, actually occupy, grossly, only 0.1% of the total human skin surface.

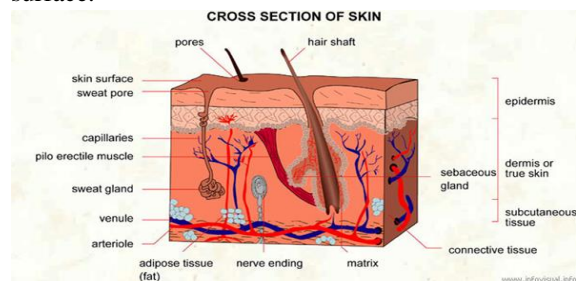


Figure 1: cross-section of hair follicle and skin

2.2 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 the skin and also the uptake of the drug by the capillary network in the dermal papillary layer (7).

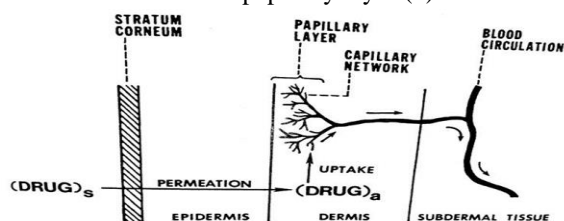


Figure 2: Mechanism of transdermal permeation

2.3 Factors affecting transdermal permeation:

1) Physicochemical properties of the penetrant molecule:

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 of charged 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 molecules are 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 not only affects the rate of drug release, but also the permeability of the stratum corneum by means of hydration, making with skin lipids, or other sorption promoting effects e.g., benzocaine permeation decreases with PEG of low molecular weight

3. BASIC COMPONENTS OF TRANSDERMAL DRUG 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 the device.

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. Polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadiene 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 drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.

Physicochemical properties

1. The drug should have a molecular weight less than approximately 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 properties the 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 flux of a desired penetrant.

These may conveniently be classified under the following main headings:

a) Solvents

These compounds increase penetration possibly by swelling 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-pyrrolidone; 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 hydrocarbon chain length.

- Anionic Surfactants: e.g. Dioctylsulphosuccinate, Sodium lauryl sulphate, Decyldecylmethyl sulphoxide etc.
- Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc.
- Bile Salts: e.g. Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.
- Binary system: These systems apparently open up the heterogeneous multilaminar pathway as well as the continuous pathways. e.g. Propylene glycol-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 their effectiveness sparse. These include eucalyptol, di-o-methyl-β cyclodextrin and soyabean-casein.

D. Other Excipients

a) Adhesives:

The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive which can be positioned on the face of the device or in the back of the device and extending peripherally.

Both adhesive systems should fulfil the following criteria

- Should adhere to the skin aggressively, should be easily removed.
- Should not leave an unwashable residue on the skin.
- Should not irritate or sensitize the skin.

The face adhesive system should also fulfil the following criteria.

- Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.
- Permeation of drug should not be affected.
- 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 the product 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 DRUG DELIVERY SYSTEMS

4.1 Transdermal Patches:

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. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types such as oral, topical, etc is that it provides a controlled release of the medicament into the patient. A disadvantage to development however, stems from the fact that the skin is a very effective barrier. A wide variety of pharmaceuticals can be delivered by transdermal patches.

4.2 Types of Transdermal Patches:

4.2.1. Single layer drug in adhesive

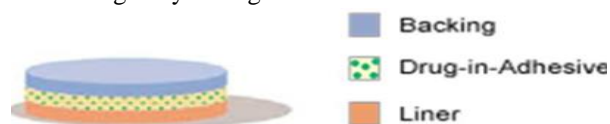


Figure 3: Single layer drug in adhesive

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 surrounded by a temporary liner and a backing

4.2.2. Multi -layer drug in adhesive:

This type is also similar to the single layer but it contains a immediate drug release layer and other layer 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

4.2.3. Drug Reservoir-in-Adhesive

In this system the drug reservoir is embedded between an 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. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug.

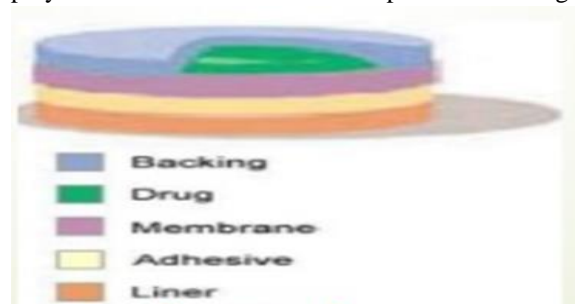


Figure 5: Drug Reservoir-in-Adhesive

4.2.4. Drug Matrix-in-Adhesive

The Matrix 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 (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 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. 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 realistic practical application as the next generation of drug delivery system

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