

Percutaneous Absorption Drug Delivery System: A Review

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Abstract

The conventional oral dosage forms have some drawbacks like poor bioavailability, first pass effect, frequent dosing which may be inconvenient to patients. Transdermal drug delivery systems (TDDS) are polymeric patches containing dissolved or dispersed drug that deliver therapeutic agent at a constant rate through skin. Transdermal delivery has made an important contribution to medical practice but has yet to fully achieve its potential as an alternative to oral delivery and hypodermic injections. The principle of TDDS is that they could provide sustained drug delivery (and hence constant drug concentration in plasma) over a prolonged period of time. TDDS can be designed to input drug at appropriate rate to maintain plasma drug levels for therapeutic efficacy. Ultimately the success of all the transdermal system depends on the ability of the drug to permeate skin in sufficient quantities to achieve its desired therapeutic effect. This review article provides a detailed study of transdermal that is advantage, disadvantages, mechanism, factors affecting skin permeation and types. This article also focuses on the application and future approaches of transdermal drug delivery system

Keywords: TDDS, skin, first pass metabolism, pain management

Introduction

Transdermal drug delivery Transdermal drug delivery systems (TDDS) are defined as self contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation(Finnin B C 1999;88). The Transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs. In comparison to conventional pharmaceutical dosage forms (Allen L V, 2005).

TDDS offer many advantages, such as elimination of first pass metabolism, sustained drug delivery, reduced frequency of administration, reduced side effects and improved patient compliance.

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. 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 (Barry B ,2002). The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy the common ingredients which are used for the preparation of TDDS are as follows.

Limitations for a drug substance to be incorporated into a Transdermal delivery system are: -

- Heavy drugs molecules (>500 Da) usually difficult to penetrate the stratum cornea.
- Drugs with very low or high partition coefficient fail to reach blood circulation.
- Drugs that are highly melting can be given by this route due to their low solubility both in water and fat.

- Many approaches have been attempted to deliver medicament across skin barrier and enhance the efficacy (Cleary G W ,1988)

BASIC COMPONENTS OF TDDS: Basic components of TDDS includes the following

- Polymer matrix / Drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminates
- Release liner
- Other excipients like plasticizers and solvents

Polymer matrix: Polymer is an integral and foremost important component of transdermal drug delivery systems. Different classes of polymeric materials have been used to achieve rate controlled drug delivery. The mechanism of drug release depends upon the physicochemical properties of the drug and polymer used in the manufacture of the device. The following criteria should be satisfied for a polymer to be used in a transdermal system (Dipen MP,2011).

- Molecular weight, glass transition temperature, chemical functionality or polymer must allow diffusion and release of the specific drug.
- The polymer should permit the incorporation of a large amount of drug.
- The polymer should not react, physically or chemically with the drug
- The polymer should be easily manufactured and fabricated into the desired product and in expensive.
- The polymer must be stable and must not decompose in the presence of drug and other excipients used in the formulation, at high humidity conditions, or at body temperature.
- Polymers and its degradation products must be non toxic.
- No single material may have all these attributes; e.g., cosolvents such as ethanol, propylene glycol, PEG 400 could be added to increase drug solubility.

Various techniques which are employed to modify the polymer properties and thus drug release rates:

Techniques of matrix

- **Cross linked polymers:** The higher the degree of cross linking, the more dense the polymer and slower the diffusion of drug molecules through the matrix.
- **Polymer blends:** Polymers have been blended on varying ratios to combine the advantages of the individual polymers. Advantages of polymer blends include easy fabrication of devices, manipulation of drug loading and other devices properties such as hydration, degradation rate and mechanical strength.
- **Plasticizers:** Plasticizers have been known to reduce the stiffness of the polymer backbone, thereby increasing the diffusion characteristics of the drug. Commonly used plasticizers are polyethylene glycol, propylene glycol, glycerol, dibutyl phthalate.

Drug substance : Drug is in direct contact with release liner.

Ex: Nicotine, Methotrexate and Estrogen.

Penetration enhancers

- These are the compounds, which promote skin permeability by altering the as a barrier to the flux of a desired penetrant and are considered as an integral part of most transdermal formulations. To achieve and maintain therapeutic concentration of drug in the blood, the resistance of skin to diffusion of drugs has to be reduced in order to allow drug molecules to cross skin and to maintain therapeutic levels in blood. They can modify the skin's barrier to penetration either by interacting with the formulation that applied or with the skin itself .
- The penetration enhancer should be pharmacologically inert, non toxic, non allergenic, non-irritating and ability to act specifically, reversibly and for predictable duration. It should not cause loss of body fluids, electrolytes or other endogeneous materials.

Ex: Terpenes, Terpenoids, Pyrrolidones.

Solvents like alcohol, Ethanol, Methanol.

Surfactants like Sodium Lauryl sulfate, Pluronic F127, Pluronic F68.

Drug reservoir components

- It must be compatible with the drug and must allow for drug transport at the desired rate. If an ointment is used, the drug reservoir must possess the desired viscosity attributes to ensure reliable manufacturing process. It must possess the desired adhesive and cohesive properties to hold the system together. Materials used are: mineral oils, polyisobutylene, and colloidal silica, HPC.

Backing laminates

- The primary function of the backing laminate is to provide support. They should be able to prevent drug from leaving the dosage form through top. They must be impermeable to drugs and permeation enhancers. They should have a low moisture vapor transmission rate. They must have optimal elasticity, flexibility, and tensile strength. They must be chemically compatible with the drug, enhancer, adhesive and other excipients. They must be relatively inexpensive and must allow printing and adhesive lamination. Typical backing membranes are composed of a pigmented layer, an aluminium vapor coated layer, a plastic film (polyethylene, polyvinyl chloride, polyester) and a heat seal layer.

Rate controlling membrane

- Rate controlling membranes in transdermal devices govern drug release from the dosage form. Membranes made from natural polymeric material such as chitosan show great promise for use as rate controlling membranes. Recently composite poly-2-hydroxyethyl methacrylate (PHEMA) membranes have been evaluated as rate controlling barriers for transdermal application.

Adhesive layer

The fastening of all transdermal devices to the skin using a pressure sensitive adhesive that can be positioned on the face or in the back of device is necessary. It should not cause irritation, sensitization or imbalance in the normal skin flora during its contact with the skin. It should

adhere to the skin aggressively. The three major classes of polymers evaluated for potential medical applications in TDDS include:

- Polyisobutylene type pressure sensitive adhesives
- Acrylic type pressure sensitive adhesives
- Silicone type pressure sensitive adhesives

Release liners

The release liner has to be removed before the application of transdermal system, and it prevents the loss of the drug that has migrated into the adhesive layer during storage. It also helps to prevent contamination. It is composed of a base layer, which may be nonocclusive or occlusive, and a release coating layer made of silicon or Teflon. Other materials include polyesters, foil, Mylar and metalized laminate

TYPES OF TRANSDERMAL PATCHES:

a) 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.

b) Multi -layer drug in adhesive:

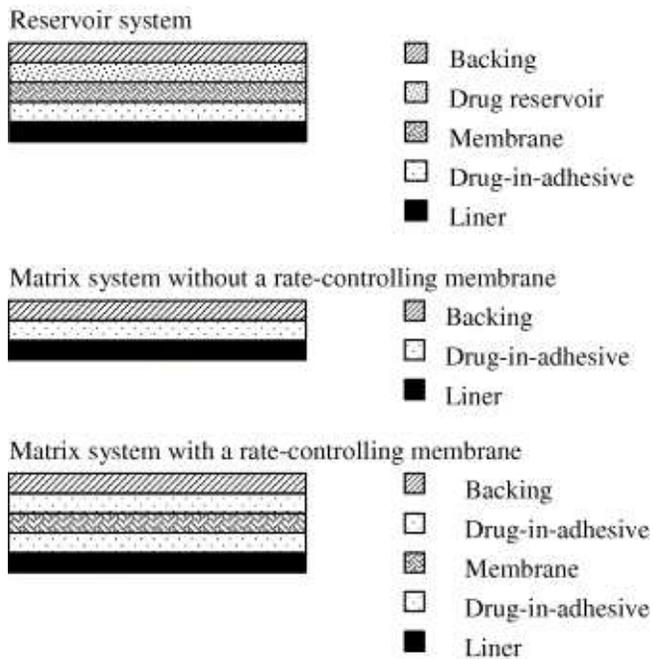
This type is also similar to the single layer but it contains a immediate drug release layer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.

c) Vapour patch:

In this type of patch the role of adhesive layer not only serves to adhere the various layers together but also serves as release vapour. The vapour patches are new to the market, commonly used for releasing of essential oils in decongestion. Various other types of vapor patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

d) Reservoir system:

In this system the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the ratecontrolling 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.



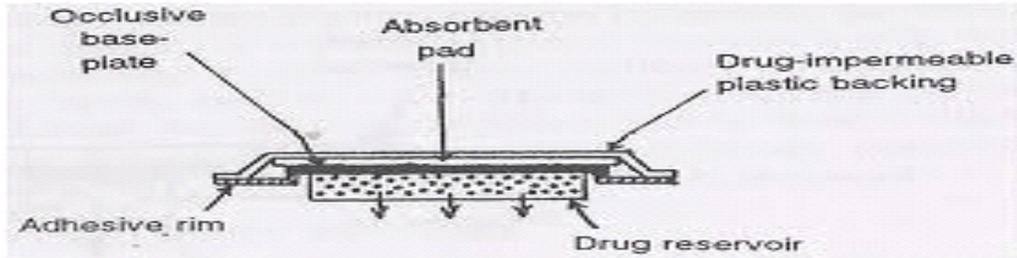


Fig4: Matrix diffusion controlled transdermal drug delivery system

e) Matrix system:

i. Drug-in-adhesive system:

In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting (in the case of hot-melt adhesives) on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

ii. Matrix-dispersion system:

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.

f) Micro reservoir system:

In this type the drug delivery system is a combination of reservoir and matrix-dispersion system. The drug reservoir is formed by first suspending the drug in an aqueous solution of water soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents.

General clinical considerations in the use of TDDS

The patient should be advised of the following general guidelines. The patient should be advised of the importance of using the recommended site and rotating locations within the site. Rotating locations is important to allow the skin to regain its normal permeability and to prevent skin irritation.

1. TDDSs should be applied to clean, dry skin relatively free of hair and not oily, inflamed, irritated, broken, or callused. Wet or moist skin can accelerate drug permeation beyond ondansetron time. Oily skin can impair the adhesion of patch. If hair is present at the site, it should be carefully cut, not wet shaved, nor should a depilatory agent be used, since later can remove stratum corneum and affect the rate and extent of drug permeation.
2. Use of skin lotion should be avoided at the application site, because lotions affect the hydration of skin and can alter partition coefficient of drug.
3. Cutting should not physically alter TDDSs, since this destroys integrity of the system.
4. The protecting backing should be removed with care not to touch fingertips. The TDDS should be pressed firmly against skin site with the heel of hand for about 10 seconds (www.drugbank.com).

Conclusion

Transdermal drug delivery systems represent a beneficial innovation for drug delivery, particularly in patients who cannot swallow or remember to take their medications. Clinicians and other allied health professionals should understand the appropriate administration techniques for transdermal systems to ensure optimal patient outcomes and to ensure the safety of all who encounter patients who use TDDS. Future developments of TDDSs will likely focus on the increased control of therapeutic regimens and the continuing expansion of drugs available for use. Transdermal dosage forms may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care.

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