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TRANSDERMAL DRUG DELIVERY SYSTEM: REVIEW

Virendra Yadav

Department of Pharmaceutics , Manav Bharti University, Solan, Himachal Pradesh, India

ABSTRACT

Keywords:

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Correspondence to Author:

Virendra yadav

Department of Pharmaceutics, Manav
Bharti University, Solan, Himachal
Pradesh, India

Transdermal drug delivery system (TDDS) are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. It works very simply in which drug is applied inside the patch and it is worn on skin for long period of time. By this constant concentration of drug remain in blood for long time. Polymer matrix, drug, permeation enhancers are the main components of TDDS; polymers includes Zein, Shellac (as a natural) to synthetic ones (Polybutadiene, Polysiloxane, Polyvinyl chloride, Polyvinyl alcohol etc.). TDDS are of many types varying from single layer drug in adhesive to multi layer drug in adhesive and others are reservoir and the matrix systems. The market value of TDDS products are increasing with rapid rate, more than 35 products have now been approved for sale in US, and approximately 16 active ingredients are approved globally for use as a TDDS. Transdermal drug delivery is a recent technology which promises a great future it has a potential to limit the use of needles for administering wide variety of drugs but cost factor is a important thing to consider since developing nations like INDIA have second highest population, but due to higher cost TDDS are the hidden part of therapy used in general population.

INTRODUCTION: Transdermal drug delivery systems are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate ¹.

A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow for pharmaceuticals to be delivered across the skin barrier ⁵.

In theory, transdermal patches work very simply. A drug is applied in a relatively high dosage to the inside

of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin.

Since, there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow ³.

Advantages of this route ⁶: This approach to drug delivery offers many advantages over traditional methods;

- As a substitute for the oral route,

- Transdermal drug delivery enables the avoidance of gastrointestinal absorption, with its associated pitfalls of enzymatic and pH associated deactivation.
- This method also allows for reduced pharmacological dosaging due to the shortened metabolism pathway of the transdermal route versus the gastrointestinal pathway.
- The patch also permits constant dosing rather than the peaks and valleys in medication level associated with orally administered medications. Multi-day therapy with a single application,
- Rapid notification of medication in the event of emergency, as well as the capacity to terminate drug effects rapidly via patch removal.

Disadvantages of TDD:

- The drug that requires high blood levels cannot be administered and may even cause irritation or sensitization of the skin.
- The adhesives may not adhere well to all types of skin and may be uncomfortable to wear.
- High cost of the product is also a major drawback for the wide acceptance of this product⁵.

Properties that influence Transdermal Delivery

- Release of the medicament from the vehicle.
- Penetration through the skin barrier.
- Activation of the pharmacological response⁷.

Kinetics of Transdermal Permeation: Knowledge of skin permeation kinetics is vital to the successful development of transdermal therapeutic systems. Transdermal permeation of a drug involves the following steps:

1. Sorption by stratum corneum.
2. Penetration of drug through epidermis.
3. Uptake of the drug by the capillary network in the dermal papillary layer.

This permeation can be possible only if the drug possesses certain physiochemical properties. The rate of permeation across the skin is given by-

$$\frac{dQ}{dt} = P_s (C_d - C_r)$$

Where C_d and C_r are the concentration of the skin penetrant in the donor compartment i.e. on the surface of stratum corneum and in the receptor compartment i.e. body respectively. P_s is the overall permeability coefficient of the skin tissue to the penetrant. This permeability coefficient is given by the relationship:

$$P_s = \frac{D_{ss} K_s}{h_s}$$

Where K_s is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system on to the stratum corneum, D_{ss} is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues and h_s is the overall thickness of skin tissues. As K_s , D_{ss} and h_s are constant under given conditions the permeability coefficient P_s for a skin penetrant can be considered to be constant. From equation (1) it is clear that a constant rate of drug permeation can be obtained only when $C_d \gg C_r$ i.e. the drug concentration at the surface of the stratum corneum C_d is consistently and substantially greater than the drug concentration in the body C_r . The equation becomes:

$$\frac{dQ}{dt} = P_s C_d$$

The rate of skin permeation is constant provided the magnitude of C_d remains fairly constant throughout the course of skin permeation. For keeping C_d constant the drug should be released from the device at a rate R_r i.e. either constant or greater than the rate of skin uptake R_a i.e. $R_r \gg R_a$. Since $R_r \gg R_a$, the drug concentration on the skin surface C_d is maintained at a level equal to or greater than the equilibrium solubility of the drug in the stratum corneum C_s i.e. $C_d \gg C_s$. Therefore a maximum rate of skin permeation is obtained and is given by the equation:

$$(dQ/dt)_m = P_s C_s$$

From the above equation it can be seen that the maximum rate of skin permeation depends upon the skin permeability coefficient P_s and is equilibrium solubility in the stratum corneum C_s . Thus skin permeation appears to be stratum corneum limited⁸.

Basic Components of Transdermal Drug Delivery Systems-

1. Polymer matrix or matrices.
 2. The drug
 3. Permeation enhancers
 4. Other excipients
1. **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, Polyvinyl pyrrolidone, Polymethylmethacrylate, Epoxy etc.
 2. **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:

- The drug should have a molecular weight less than approximately 1000 Daltons.
- The drug should have affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
- The drug should have low melting point.
- Along with these properties the drug should be potent, having short half life and be non-irritating.

3. **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, N-methyl, 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. Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decylmethyl 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 soybean casein⁸.

4. **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 and in the back of the device and extending peripherally. Both adhesive systems should fulfill 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 fulfill 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) etc⁹.

Desirable features for transdermal patches

- Composition relatively invariant in use.
- System size reasonable.
- Defined site for application.
- Application technique highly reproducible.
- Delivery is (typically) zero order.
- Delivery is efficient¹⁰.

Types of Transdermal Patches: There are four Major Transdermal Systems:

1. Single-layer Drug-in-Adhesive



FIG. 1: 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 skin¹¹. The intrinsic rate of drug release from this type of drug delivery system is defined by

$$\frac{dQ}{dT} = \frac{C_r}{1/P_m + 1/P_a}$$

Where C_r is the drug concentration in the reservoir compartment and P_a and P_m are the permeability coefficients of the adhesive layer and the rate controlling membrane, P_m is the sum of permeability coefficients simultaneous penetrations across the pores and the polymeric material. P_m and P_a , respectively, are defined as follows.

$$P_m = \frac{K_{m/r} \cdot D_m}{h_m}$$

$$P_a = \frac{K_{a/m} \cdot D_a}{h_a}$$

where $K_{m/r}$ and $K_{a/m}$ are the partition coefficients for the interfacial partitioning of drug from the reservoir to the membrane and from the membrane to adhesive respectively; D_m and D_a are the diffusion coefficients in the rate controlling membrane and adhesive layer, respectively; and h_m and h_a are the thicknesses of the rate controlling membrane and adhesive layer, respectively. (8, 9)

2. Multi-layer Drug-in-Adhesive:

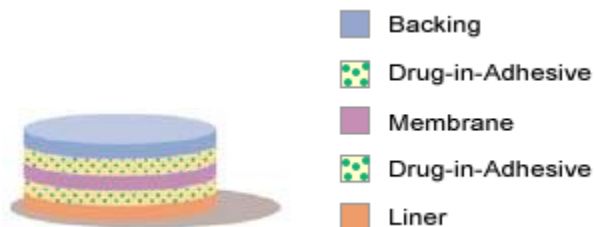


FIG. 2: MULTI-LAYER DRUG-IN-ADHESIVE

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 drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film¹¹.

The rate of drug release in this system is defined by:

$$\frac{dQ}{dt} = \frac{K_{a/r} \cdot D_a}{ha} C_r$$

Where $K_{a/r}$ is the partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer^{1,9}.

3. Drug Reservoir-in-Adhesive:

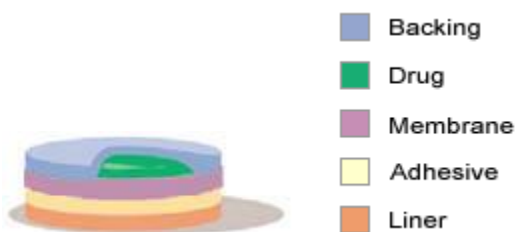


FIG. 3: DRUG RESERVOIR-IN-ADHESIVE

The Reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. 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 membrane¹¹.

The rate of drug release from this drug reservoir gradient controlled system is given by:

$$\frac{dQ}{dt} = \frac{K_{a/r} \cdot Da}{ha(t)} A(ha)$$

In the above equation, the thickness of the adhesive layer for drug molecule to diffuse through increases with time $ha(t)$. To compensate for this time dependent increase in the diffusional path due to the depletion of drug dose by release, the drug loading level is also increased with the thickness of diffusional path $A(ha)$ ^{7,8}.

4. Drug Matrix-in-Adhesive:



FIG. 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 matrix¹¹.

The rate of drug release from this type of system is defined as:

$$\frac{dQ}{dt} = \frac{AC_p D_p}{2t}^{\frac{1}{2}}$$

Where A is the initial drug loading dose dispersed in the polymer matrix and C_p and D_p are the solubility and diffusivity of the drug in the polymer respectively. Since, only the drug species dissolved in the polymer can release, C_p is essentially equal to C_R , where C_R is the drug concentration in the reservoir compartment^{8,9}.

Transdermal Market: The market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future. An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world.

More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally ¹². **Table 1** gives detail information of the

different drugs which are administered by this route and the common names by which they are marketed; it also gives the conditions for which the individual system is used ¹³.

Transdermal Drug Delivery: Past, Present, Future:

TABLE 1: CHARACTERISTICS OF SEVERAL DRUGS DELIVERED TRANSDERMALLY

Active Ingredient	Mol. Wt. (Daltons)	Trade Name(s)	Daily Dose	Frequency of Application	Type of System
Clonidine	230	Catapres-TTS [®]	0.1–0.3 mg	Weekly	Reservoir
Estradiol	272	Esclim [®] Vivelle [®] Vivelle-Dot [®] Climara [®]	0.025–0.1 mg	Weekly	Drug-in-adhesive
Ethinyl Estradiol	296	Ortho-Evra [®]	0.15 mg	Weekly	Drug-in-adhesive
Norelgestromin	328		0.02		
Fentanyl	337	Duragesic [®] Transdermal System [®]	0.6 mg	Once every three days	Reservoir
Lidocaine	234	Lidoderm [®]	Not stated	Daily	Drug-in-adhesive
Nicotine	162	Nicoderm CQ [®] Nicotrol [®]	7–21 mg	Daily	*
Nitroglycerine	227	Nitro-Dur [®] Nitrodisc [®]	1.4–11.2 mg	Daily	Drug-in-adhesive Reservoir
Scopolamine	303	Transderm-Scop [®]	0.33 mg	Once every three days	Reservoir
Testosterone	288	Androderm [®]	2.5–5 mg	Daily	Re

Advance Development in TDDS:

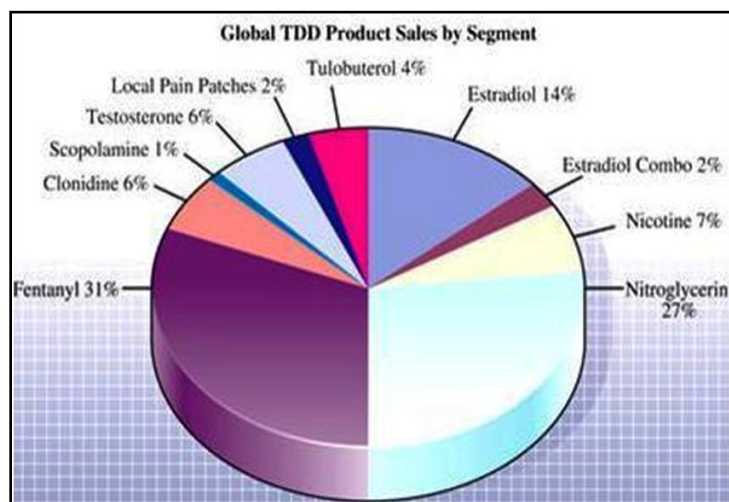


FIG. 5: ADVANCE DEVELOPMENT IN TDDS

Drug in adhesive technology has become the preferred system for passive transdermal delivery; two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-

size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch ¹².

A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier (primarily the stratum corneum) or increasing the energy of the drug molecules. These so-called "active" transdermal technologies include iontophoresis (which uses low voltage electrical current to drive charged drugs through the skin), electroporation (which uses short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (which uses low frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (which uses heat to make the skin more permeable and to increase the energy of drug molecules). Even magnetic energy, coined magnetophoresis, has been investigated as a means to increase drug flux across the skin ¹².

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.

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