

TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Transdermal drug delivery has made an important contribution to medical practice, but it has yet to fully achieve its potential as an alternative to the oral delivery and hypodermic injections. An advantage of a transdermal drug delivery route over other types of delivery systems such as oral, topical, intravenous, intramuscular, etc. is that the patch may essentially can provide 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. First-generation transdermal delivery systems have continued their steady increase in clinical use for delivery of small, lipophilic, low-dose drugs. Second-generation delivery systems using chemical enhancers, non-cavitation ultrasound and iontophoresis have also resulted in clinical products; the ability of iontophoresis to control delivery rates in real time provides added functionality. Third-generation delivery systems target their effects to skin's barrier layer of stratum corneum using microneedles, thermal ablation, microdermabrasion, electroporation and cavitation ultrasound. Using these novel second- and third-generation enhancement strategies, transdermal delivery is poised to significantly increase impact on medicine.

Keywords: Transdermal Drug Delivery, Skin Permeation, Membrane moderated systems, Adhesive diffusion controlled system, Microreservoir system.

(TTS). Transdermal delivery may be defined as the delivery of a drug through 'intact' skin so that it reaches the systemic circulation in sufficient quantity, to be beneficial after administration of a therapeutic dose.

Transdermal systems are ideally suited for diseases that demand chronic treatment. Hence, anti-diabetic agents of both therapeutic and prophylactic usage have been subjected to transdermal investigation.

Advantages¹:

- a) Can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administered drug.
- b) Can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhea.
- c) To avoid the first pass effect e.g. Transdermal Nitroglycerin. It is rapidly metabolized by the liver when taken orally.
- d) Noninvasive, avoiding the inconvenience of parenteral therapy.
- e) They provided extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration e.g. Transdermal clonidine 7 day.
- f) The activity of drugs having a short half life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
- g) Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.

TRANSDERMAL DRUG DELIVERY SYSTEM:

Topical formulations containing drugs showing systemic action are called transdermal delivery systems (TDS) or transdermal therapeutic systems

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Disadvantages:

- a) Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation¹.
- b) Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's impermeability.
- c) Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable.
- d) Long time adhere is difficult.

ANATOMY AND PHYSIOLOGY OF SKIN:

The skin has evolved into an extremely efficient barrier, which prevents both excessive water loss from the body and the ingress of xenobiotics. It enables us to withstand a considerable range of environmental challenges. The reasons for this are manifold and may be summarized simply for the purposes of this chapter. The outer layer of the skin, the stratum corneum, forms the rate-controlling barrier for diffusion for almost all compounds. It is composed of dead, flattened, keratin-rich cells, the corneocytes. These dense cells are surrounded by a complex mixture of intercellular lipids. They comprise ceramides, free fatty acids, cholesterol, and cholesterol sulphate. Their most important feature is that they are structured into ordered

bilayer arrays. The predominant diffusional path for a molecule crossing the stratum corneum appears to be intercellular².

The penetration across epithelial borders is a slow process due to the effect of the barrier properties. The skin, in particular the stratum corneum, possesses a barrier to drug penetration due to its high density (1.4 g/cm² in dry state), its low hydration of 15 to 20%. The barrier function is further facilitated by the continuous replacement of stratum corneum, thereby limiting the topical & transdermal bioavailability. Therefore, in recent years, numerous studies have been conducted in the area of penetration enhancement³. Limitations include slow penetration rates, lack of dosage flexibility and a restricted to relatively low dosage drugs⁴.

Human skin comprises of three distinct but mutually dependent tissues:

- a) The stratified, a vascular, cellular epidermis.
- b) Underlying dermis of connective tissues.
- c) Hypodermis.

PRINCIPLES OF TRANSDERMAL PERMEATION:

Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration. Skin is the most

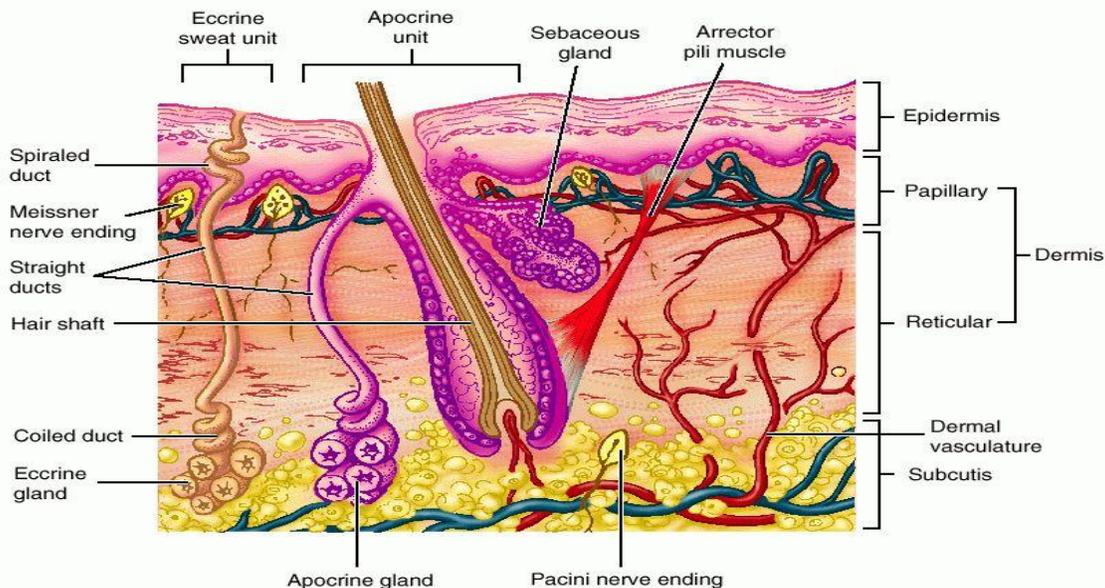


Figure 1: Anatomy of Skin

intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows⁵:

1. Diffusion of drug from drug reservoir to the rate controlling membrane.
2. Diffusion of drug from rate limiting membrane to stratum corneum.
3. Sorption by stratum corneum and penetration through viable epidermis.
4. Uptake of drug by capillary network in the dermal papillary layer.
5. Effect on target organ.

KINETICS OF TRANSDERMAL PERMEATION⁶:

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:

$$dQ/dt = Ps (Cd - Cr)$$

Where Cd and Cr 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. Ps is the overall permeability coefficient the skin tissue to the penetrant. This permeability coefficient is given by the relationship:

$$Ps = D_{ss} K_s / h_s$$

Where Ks 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 Ps for a skin penetrant can be considered to be constant. From above equation it is clear that a constant rate of drug permeation can be obtained only when Cd >> Cr i.e. the drug concentration at the surface of the stratum corneum Cd is consistently and substantially greater than the drug concentration in the body Cr. The equation becomes:

$$dQ/dt = Ps Cd$$

The rate of skin permeation is constant provided the magnitude of Cd remains fairly constant throughout the course of skin permeation. For keeping Cd 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 >> R_a. Since R_r >> R_a, the drug concentration on the skin surface Cd is maintained at a level equal to or greater than the equilibrium solubility of the drug in the stratum corneum C_s i.e. Cd >> C_s. Therefore a maximum rate of skin permeation is obtained and is given by the equation:

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

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

BIOPHARMACEUTICAL PARAMETERS IN DRUG SELECTION FOR TRANSDERMAL PATCH⁷:

- Dose should be low i.e. <20mg/day.
- Half life should be 10 h or less.
- Molecular weight should be <400.
- Partition coefficient should be Log P (octanol-water) between 1.0 and 4.
- Skin permeability coefficient should be <0.5 X 10⁻³cm/h.
- Drug should be non-irritating and non-sensitizing to the skin.
- Oral bioavailability should be low.
- Therapeutic index should be low.

APPROACHES USED IN DEVELOPMENT OF TRANSDERMAL PATCH⁵:

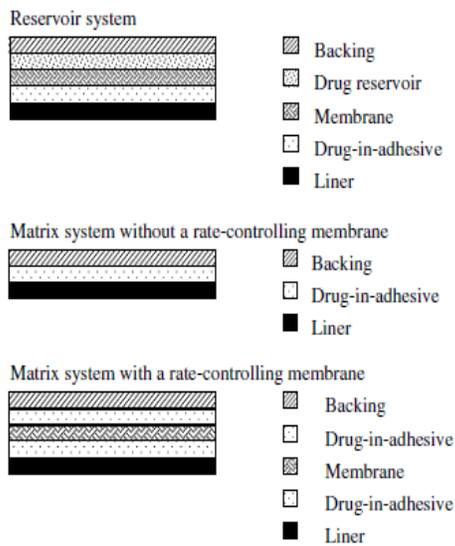


Figure 2: Types of TDDS.

A. Membrane moderated systems:

In this, the drug reservoir is totally encapsulated in a shallow compartment molded from a drug impermeable metallic plastic laminate and a rate controlling polymeric membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid polymer matrix or suspended in an unleachable, viscous liquid medium e.g. silicon fluid. The rate controlling membrane can be micro

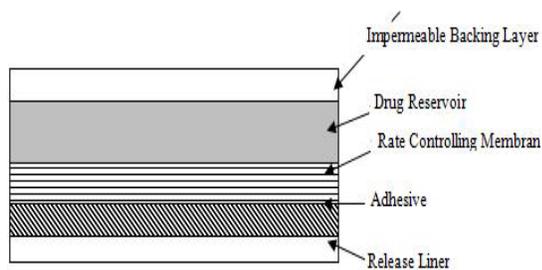


Figure 3: Representation of Membrane moderated systems

porous or nonporous polymeric membrane e.g. ethylene vinyl acetate co-polymer on the external surface of the polymeric membrane, a skin layer of drug, compatible hypo allergic adhesive polymer may be applied to achieve an intimate contact of TDDS with skin surface. Marketed systems: Transderm-Nitro system for once a day; Transderm-Scop system- 3 days medication; Catapres- TTS – for weekly treatment

B. Adhesive diffusion controlled system:

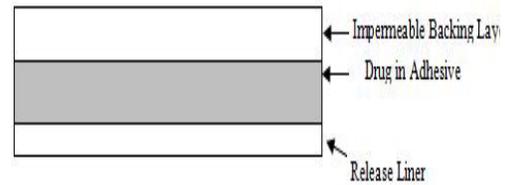


Figure 4: Representation of Adhesive diffusion controlled system

It is the simplest version of the membrane moderated drug delivery systems. In this system the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting onto a flat sheet of drug impermeable metallic plastic backing to form thin drug reservoir layer. On the top of the reservoir layer, layers of non-medicated rate controlling adhesive polymer of constant thickness are applied. Drug -in -adhesive patch may be single layer or multi layer. The multi layer system is different from single layer in that it adds another layer of drug-in-adhesive, usually separated by a membrane. Characteristics of drug in adhesive patch may account for improved patient compliance due to ease of remembering once weekly patch application, improved cosmetic acceptance and better adhesion. Marketed devices: Climara®; Nicotrol; Deponit®

C. Matrix dispersion:

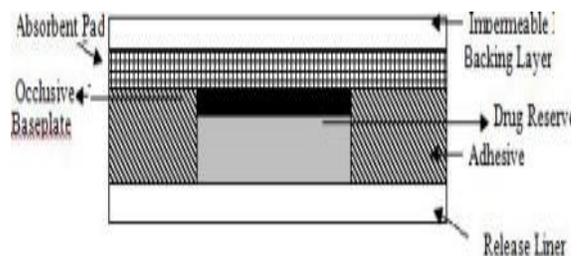


Figure 5: Representation of Matrix dispersion

Here the drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix and medicated polymer is then molded into disc with defined area and thickness. This is glued onto an occlusive base plate on the surface of the disc, the adhesive polymer is spread along the circumference to form a stripe of adhesive rim around the disc.

Advantages of matrix patches include absence of dose dumping, direct exposure of polymeric matrix to the skin and no interference of adhesive.

Marketed System : Nitro-Dur®

D. Microreservoir system:

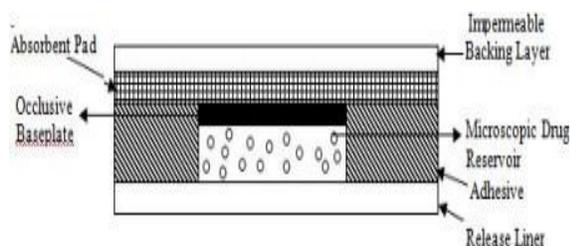


Figure 6: Representation of Microreservoir system

These are considered as combination of reservoir and matrix dispersion type. In this the drug reservoir is formed by first suspending the drug solids in an aqueous solution of water soluble polymer and then dispersing the drug suspension homogenously in lipophilic polymer, by high shear mechanical force to form unleachable microscopic spheres of drug reservoir. This dispersion is stabilized immediately by cross-linking the polymer chains which produces a medicated disc with constant surface area and thickness. Marketed system: Nitrodisc®

RECENT ADVANCES IN THE FIELD OF TRANSDERMAL PATCHES:

Many research works have been and are few are going on in this field. Few of the latest research done in the field of transdermal patches are stated below:

➤ **Patch technology for protein delivery:** Transdermal delivery of large proteins is a novel and exciting delivery method. There is no commercial technology currently available that incorporates proteins into transdermal patches. TransPharma uses its unique printed patch technology for transdermal delivery of proteins thereby complementing its ViaDerm delivery technology. Such printed patches contain accurate doses of proteins in dry state. It is postulated that the highly water soluble proteins are dissolved by the interstitial fluid that is secreted from the skin through the RF-MicroChannels, forming a highly concentrated protein solution in situ. The delivery of the dissolved molecules is then carried out, via the RF-Micro Channels, into the

viable tissues of the skin, diffusing across a steep concentration gradient⁸.

- **Pain-free diabetic monitoring using transdermal patches:** The first prototype patch measures about 1cm and is made using polymers and thin metallic films. The 5×5 sampling array can be clearly seen, as well as their metallic interconnections. When the seal is compromised, the interstitial fluid, and the biomolecules contained therein, becomes accessible on the skin surface. Utilizing micro-heating elements integrated into the structural layer of the patch closest to the skin surface, a high-temperature heat pulse can be applied locally, breaching the stratum corneum. During this ablation process, the skin surface experiences temperatures of 130°C for 30ms duration. The temperature diminishes rapidly from the skin surface and neither the living tissue nor the nerve endings are affected. This painless and bloodless process results in disruption of a 40–50µm diameter region of the dead skin layer, approximately the size of a hair follicle, allowing the interstitial fluid to interact with the patch's electrode sites⁹.
- **Testosterone transdermal patch system in young women with spontaneous premature ovarian failure:** In premenopausal women, the daily testosterone production is approximately 300 µg, of which approximately half is derived from the ovaries and half from the adrenal glands. Young women with spontaneous premature ovarian failure (sPOF) may have lower androgen levels, compared with normal ovulatory women. Testosterone transdermal patch (TTP) was designed to deliver the normal ovarian production rate of testosterone. The addition of TTP to cyclic E2/MPA therapy in women with sPOF produced mean free testosterone levels that approximate the upper limit of normal¹⁰.
- **Transdermal patch of oxybutynin used in overactive bladder:** The product is a transdermal patch containing Oxybutynin HCl and is approved in US under the brand name of Oxytrol and in Europe under the brand name of Kentera. OXYTROL is a thin, flexible and clear patch that is applied to the abdomen, hip or buttock twice weekly and provides continuous and consistent delivery of oxybutynin over a three to four day interval. OXYTROL offers OAB

patient's continuous effective bladder control with some of the side effects, such as dry mouth and constipation encountered with and oral formulation. In most patients these side effects however are not a troublesome⁹.

- **Nanotechnology gaining hold:** Another enhancer that is gaining advancement is microneedles. This technology combines the advantage of a needle and the transdermal patch. The devices are dime-sized pieces of polymer with hundreds of hollow microneedles between 100 and 1,000 micrometers long. These small needles penetrate the top layers of skin and allow the drug to pass through with ease. This technology can be combined with an electronically controlled micropump that delivers the drug at specific times or upon demand. Once approved by the FDA, these devices would allow the patient or physician to control the time and dose of the drug being delivered. These devices have the potential to place drugs precisely into the area where special immune cells reside, making these drugs capable of modulating the immune system, with relative ease. Alza is using a slightly different variation on the use of needles. The company has developed the patented Macroflux transdermal technology that uses microprojections to create superficial pathways through the dead skin barrier. The tips of the projections contain active drug — a quick bolus¹¹.
- **Pain relief:** Pain relief routinely benefits from transdermal patch technology. Most of the readers are aware of the Duragesic patch. There are several others now on the market. One is Lidoderm, a lidocaine 5 percent patch, which is used for post herpetic neuralgia. Other exciting advancements in pain control include the E-Trans fentanyl HCl patch. This credit card-size patch is an active delivery device that has a self-contained battery that delivers pulses of fentanyl HCl, a strong narcotic. This mimics the use of intravenous self-controlled analgesic systems that are very expensive, cumbersome, and require considerable nursing care¹¹.
- **Molecular absorption enhancement technology:** Considerable research has been done on absorption enhancers, compounds that promote the passage of drugs through the stratum corneum. Terpene derivatives as well as

certain phenols seem to improve transdermal absorption. For example, linalool, alpha terpineol, and carvacrol were studied in conjunction with haloperidol (a commonly prescribed neuroleptic drug). All three enhanced haloperidol absorption, but only linalool increased it to a therapeutic level. Limonene, menthone, and eugenol were found to enhance transdermal absorption of tamoxifen. Phloretin, a polyphenol, enhanced the absorption of lignocaine. In general, absorption enhancement research has been done with excised animal skin (pig or rabbit) or human skin obtained from cadavers or plastic surgery procedures¹².

- **Future technologies and approaches:** Thermal Poration is the formation of aqueous pathways across stratum corneum by the application of pulsed heat, this approach has been used to deliver conventional drugs and to extract intestinal fluid glucose from human subjects^{8,13}.
- ✓ Jet injectors are receiving increased attention now days, which is opening doors for improved device design for controlled, needle free injection of drug solutions across the skin and into deeper tissue.
- ✓ Small needle is inserted a few millimeters into skin and drug solution is flowed through the needle into the skin at controlled rates using a micro-infusion pump that is contained within a large patch affixed to skin, morphine has been delivered to humans using this approach.
- ✓ During the past decade several theories have been put forward in addressing the combinations of chemicals and iontophoresis; chemicals and electroporation; chemicals and ultrasound; iontophoresis and ultrasound; electroporation and iontophoresis; and electroporation and ultrasound.
- ✓ TransPharma is focused on products for which our technology will provide clear benefits over existing therapies. Such benefits could include improving safety and compliance through the use of a drug patch or enhancing efficacy with the use of sustained release patch formulations, among others.
- ✓ The ViaDerm system may be applied to the delivery of local medications for topical applications in the fields of dermatology and cosmetics. The ViaDerm system may also allow enhanced immunisations, providing a

nonpainful, safe and effective alternative to current intramuscular or subcutaneous vaccination methods.

- ✓ Altea Therapeutics is currently in clinical development of a transdermal patch designed to address a major unmet need by preventing 'off' periods and provide an improved therapeutic option for managing Parkinson's disease.

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