ABSTRACT

Human skin is a readily surface for drug delivery. over the past three decade, developing controlled drug delivery has become increasingly important I the pharmaceutical industry. transdermal drug delivery is a formulation that is applied to the body surface designed to delivers the active drug across the skin, into the systemic circulation. today about 74%of drug are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged. This article deal with the a brief insight on the introduction, the formulation aspect, permeation enhancers, and the evaluation aspect of transdermal drug delivery system explored to enhance the transdermal drug delivery of drug across the stratum corneum.

KEYWORDS: transdermal drug delivery, permeation enhancers, stratum corneum.

INTRODUCTION

Continuous intravenous infusion is recognized as a superior mode of drug administration not only to bypass hepatic "first-pass" metabolism, but also to maintain a constant and prolonged drug level in the body. A closely monitored intravenous infusion can provide the advantages of both direct entry of drug into the systemic circulation and control of circulating drug levels. However, such mode of drug administration entails certain risks and, therefore, necessitates hospitalization of the patients and close medical supervision of administration.

Recently, it is becoming evident that the benefits of intravenous drug infusion can be closely duplicated, without its hazards, by using the skin as the port of drug administration to provide continuous transdermal drug infusion into the systemic circulation.
To provide continuous drug infusion through an intact skin, several transdermal therapeutic systems have been developed for topical application onto the intact skin surface to control the delivery of drug and its subsequent permeation through the skin tissue. It is exemplified by the development and marketing of scopolamine-releasing transdermal therapeutic system for 72-hr prophylaxis or treatment of motion-induced nausea, of nitroglycerin and isosorbide denigrate-releasing trans-dermal therapeutic systems for once-a-day medication of angina pectoris and of clonidine-releasing transdermal therapeutic system for weekly treatment of hypertension. The intensity of interests in the potential biomedical applications of transdermal controlled drug administration is demonstrated in the increasing research activities in a number of health care institutions in the development of various types of transdermal therapeutic systems for long term continuous infusion of therapeutic agents, including antihypertensive, anti-anginal, anti-histamine, anti-inflammatory, analgesic, anti-arthritic, steroidal, and contraceptive drugs.

This chapter intends to review fundamentals of skin permeation, approaches for transdermal controlled drug administration, *in vitro* and *in vivo* kinetic evaluations of transdermal therapeutic systems and their correlations, as well as formulation design and optimization.

**Skin and drug permeation**

For understanding the concept of transdermal drug delivery systems, it is important to review the structural and biochemical features of human skin and those characteristics which contribute to the barrier function and the rate of drug access into the body via skin. The structure of human skin is shown in Figure 1.

**The Skin**: The skin is one the most extensive organs of the human body covering an area of about 2m² in an average human adult. The skin separates the underlying blood circulation network from the
Figure No. 1: Structure of human skin outside environment, serves as a barrier against physical, chemical and microbial attacks, acts as a thermostat in maintaining body temperature, protects against harmful ultraviolet rays of the sun and plays a role in the regulation of blood pressure. Anatomically, the skin has many histologic layers but in general, it is described in terms of three major tissue layers: the epidermis, the dermis and the hypodermis. The structure of epidermis is shown in Figure 2.

Figure No. 2: Structure of epidermis

The epidermis results from an active epithelial basal cell population and is approximately 150 micrometers thick. It is the outermost layer of the skin and the process of differentiation results in migration of cells from the basal layer towards the skin surface. The end result of
this process is the formation of a thin, stratified, and extremely resilient layer at the skin surface. Below this layer are the other layers of the epidermis - the stratum lucidum, stratum granulosum, and stratum spinosum and stratum germinativum. Together, these other layers constitute the viable epidermis.

The stratum corneum or the horny layer is the rate-limiting barrier that restricts the inward and outward movement of chemical substances. The interior of the cells is crisscrossed with densely packed bundles of keratin fibers. Due to this, the dry composition of the horny layer is 75-85% protein, most of which is the intracellular keratin and a part being associated with a network of cell membranes. The bulk of the remainder of the substance of the stratum corneum is a complicated mixture of lipids which lies between regions, the mass of intracellular protein and the intercellular lipoidal medium.

The epidermis rests on the much thicker dermis. The dermis essentially consists of about 80% of protein in a matrix of muco-polysaccharide "ground substance". A rich bed of capillaries is encountered 20 ㎛ or so into the dermal field. Also contained within the dermis are lymphatics nerves and the epidermal appendages such as hair follicles, sebaceous glands and sweat glands. Excepting the soles of the feet, the palms of the hand, the red portion of the lips and associated with one or more sebaceous glands which are outgrowths of epithelial cells. The sweat gland is divided into the eccrine and apocrine types and is widely distributed over the surfaces of the body. The sweat glands serve to control body heat by secretion of a dilute salt solution.

**Percutaneous Absorption**

Percutaneous absorption involves passive diffusion of substances through the skin. The mechanism of permeation can involve passage through the epidermis itself or diffusion through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands, which is shown in **Figure 3**.
Figure No. 3: - Mechanism of drug permeation through skin

**Trans epidermal absorption**

The trans-epidermal pathway is principally responsible for diffusion across the skin. The main resistance encountered along this pathway arises in the stratum corneum. Permeation by the trans-epidermal route first involves partitioning into the stratum corneum. Diffusion then takes place across this tissue. The current popular belief is that most substances diffuse across the stratum corneum via the intercellular lipoidal route. However, there appears to be another microscopic path through the stratum corneum for extremely polar compounds and ions. When a permeating drug exits at the stratum corneum, it enters the wet cell mass of the epidermis and since the epidermis has no direct blood supply, the drug is forced to diffuse across it to reach the vasculature immediately beneath. It is a permeable field that functions as a viscid watery regime to most penetrate. It appears that only ions and polar non-electrolytes found at the hydrophilic extreme and lipophilic non-electrolytes at the hydrophobic extreme have any real difficulty in passing through the viable field. The epidermal cell membranes are tightly joined and there is little to no intercellular space for ions and polar non-electrolyte molecules to diffusively squeeze through.

Passage through the dermal region represents a final hurdle to systemic entry. Permeation through the dermis is through the interlocking channels of the ground substance. Since the viable epidermis and dermis lack major physicochemical distinction, they are generally considered as a single field of diffusion, except when penetrate of extreme polarity are involved, as the epidermis offers measurable resistance to such species.
Transfollicular (shunt pathway) absorption
The skin's appendages offer only secondary avenues for permeations. Sebaceous and eccrine glands are the only appendages which are seriously considered as shunts bypassing the stratum corneum since these are distributed over the entire body. Though eccrine glands are numerous, their orifices are tiny and add up to a miniscule fraction of the body's surface. Moreover, they are either evacuated or so profusely active that molecules cannot diffuse inwardly against the gland's output. For these reasons, they are not considered as a serious route for percutaneous absorption. However, the follicular route remains an important avenue for percutaneous absorption since the opening of the follicular pore, where the hair shaft exits the skin, is relatively large and sebum aids in diffusion of penetrate. Partitioning into sebum, followed by diffusion through the sebum to the depths of the epidermis, is the envisioned mechanism of permeation by this route. Vasculature subserving the hair follicle located in the dermis is the likely point of systemic entry.

Clearance by local circulation
The earliest possible point of entry of drugs and chemicals into the systemic circulation is within the papillary plexus in the upper dermis. The process of percutaneous absorption is general, regarded as ending at this point. However, some molecules bypass the circulation and diffuse deeper in the dermis.

KINETICS OF TRANSDERMAL PERMEATION:
Trans-dermal permeation of a drug involves the following steps
1. Absorption by stratum corneum
2. Penetration of drug through viable epidermis
3. Uptake of the drug by the capillary network in the dermal papillary layer.
The rate of permeation across the skin is given by
\[
\frac{dQ}{dt} = P_s (C_d - C_r)
\]  
(1) Where \(C_d\) and \(C_r\) are the concentrations of skin penetrate in the donor compartment and in the receptor compartment. \(P_s\) is the overall permeability coefficient of the skin tissues to the penetrate. This permeability coefficient is given by the relationship:
\[
P_s = \frac{K_s D_{s5}}{h_s}
\]  
(2)
(2) where \( K_s \) is the partition coefficient for the interfacial partitioning of the penetrate 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 penetrate 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 penetrate can be considered to be constant.

From equation (1) it is clear that a constant rate of drug permeation can be obtained only when \( C_d >> C_r \), 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 (\( C_r \)). Then the equation (1) becomes:

\[
\frac{dQ}{dt} = P_s C_d
\]  

(3) and the rate of skin permeation (\( dQ/dt \)) 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 (\( R_d \)) that is either constant or greater than the rate of skin uptake (\( R_a \)).

Since \( R_d \) is greater than \( R_a \), 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 (\( C_s \)). Therefore, a maximum rate of skin permeation is obtained and is given by the equation:

\[
(dQ/dt)_m = P_s C_s
\]  

(4)

from the above equation, it can be seen that the maximum rate of skin permeation depends on the skin permeability coefficient (\( P_s \)) and its equilibrium solubility in the stratum corneum (\( C_s \)).

**STAGES IN DRUG DELIVERY IN A TRANSDERMAL PATCH:**

1. Release of medicament from the vehicle
2. Penetration through the skin barriers;
3. Activation of the pharmacological response.

Effective therapy optimizes these steps as they are affected by three components, the drug, the vehicle and the skin.
Which represents the movement of drug molecules arising from, for example, a trans-dermal drug delivery system with a rate-controlling membrane, illustrates the complexity of percutaneous absorption. Any drug particles must first dissolve so that molecules may diffuse towards the membrane within the patch. The penetrants partitions into the membrane diffuse across the polymer and partitions into the skin adhesive. The molecules diffuse towards the vehicle/stratum corneum interface. They then partition into the stratum corneum and diffuse through it. Some drug may bind at a depot site; the remainder permeates further, meets a second interface, and partitions into the viable epidermis. For a lipophilic species this partition coefficient may be unfavorable, i.e., less than 1. Within the epidermis, enzymes may metabolize the drug or it may interact at a receptor site.

After passing into the dermis, additional depot regions and metabolic sites may intervene as the drug moves to capillary, partitions into its wall and out into the blood for systemic removal. A fraction of the diffusant may partition into the subcutaneous fat to form a further depot. A portion of the drug can reach deep muscle layers, as illustrated by, for example, the efficacy of non-steroidal anti-inflammatory drugs.

However, there are further complications. The following factors may be important: the non-homogeneity of the tissues; the presence of lymphatics; interstitial fluid; hair follicles and sweat glands; cell division; cell transport to and through the stratum corneum; and cell surface loss. The disease, the healing process, the drug and vehicle components may progressively modify the skin barrier. As vehicle ingredients diffuse into the skin, cellular debris, sweat, sebum and surface contaminants pass into the dermis, changing its physicochemical characteristics. Emulsions may invert or crack when rubbed in, and volatile solvents may evaporate.

**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

The general structure of transdermal patch is shown in **Figure 4**.
1. POLYMER MATRIX

The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in a transdermal system (Kydoineus & Berner, 1987):

1. Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
2. The polymer should be stable, non-reactive with the drug, easily manufactured and fabricated into the desired product; and inexpensive.
3. The polymer and its degradation products must be non-toxic or non-antagonistic to the host.

Possible useful polymer for trans-dermal devices is:

**Natural polymers**

Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, starch etc.

**Synthetic elastomers**

Polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrene butadiene rubber, Neoprene etc.

**Synthetic polymers**

Polyvinyl alcohol, Poly vinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinyl pyrrolidone, Polymethylmethacrylate, etc.
2. DRUG
For successfully developing a trans-dermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for trans-dermal 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 portioning characteristics are not conducive to successful drug delivery via the skin.

**Biological properties**
1. The drug should be potent with a daily dose of the order of a few mg/day.
2. The half life ($t_{1/2}$) of the drug should be short.
3. The drug must not induce a cutaneous irritant or allergic response.
4. Drugs which degrade in the GI tract or are inactivated by hepatic first pass effect are suitable candidates for trans-dermal delivery.
5. Tolerance to the drug must not develop under the near zero-order release profile of trans-dermal delivery.

3. PERMEATION ENHANCERS
These are compounds which promote skin permeability by altering the skin as a barrier to the flux of desired penetrants
Enhancement of flux across membranes reduces to considerations of:
- Thermodynamics (lattice energies, distribution coefficients)
- Molecular size and shape
- Reducing the energy required to make a molecular hole in the membrane
These may conveniently be classified under the following main headings:

**Solvents**
These compounds increase penetration possibly by swelling the polar pathway. Examples include water alcohols – methanol and ethanol; alkyl methyl sulfoxides – alkyl homolog’s of methyl sulfoxide, dimethyl acetamide and dimethyl form amide; pyrrolidone – 2 pyrrolidone, N-methyl, 2-pyrrolidone; laurocapram (Azone) miscellaneous solvents – propylene glycol, glycerol, silicone fluids,
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. These compounds are, however, skin irritants, therefore, a balance between penetration enhancement and irritation have to be considered. Anionic surfactants can penetrate and interact strongly with the skin. Cationic surfactants are reportedly more irritant than the anionic surfactants; the nonionic’s having long been recognized as those with the least potential for irritation and has been widely studied. Examples of commonly used surfactants are:

Anionic surfactants
Diocetyl sulphosuccinate, Sodium lauryl sulphate, Decodecylmethylsulphoxide etc.

Nonionic surfactants
Pluronic F127, Pluronic F68, etc

Bile salts
propylene glycol-oleic acid and 1, 4-butane diol-linoleic acid

Miscellaneous chemicals
; N, N-dimethyl-m-tolumide; calcium thioglycolate; anti-cholinergic agents.

4. OTHER EXCIPIENTS
Adhesives
The fastening of all trans-dermal devices to the skin has so far been done by using a pressure sensitive adhesive. The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally. Both adhesive systems should fulfill the following criteria

1. Should not irritate or sensitize the skin or cause an imbalance in the normal skin flora during its contact time with the skin.
2. Should adhere to the skin aggressively during the dosing interval without its position being disturbed by activities such as bathing, exercise etc.

The face adhesive system should also fulfill the following criteria.
1. Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.
2. The delivery of simple or blended permeation enhancers should not be affected.

**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. e.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate, adhesive foam pad with occlusive base plate etc.

**APPROACHES USED IN DEVELOPMENT OF TRANSDERMAL DRUG DELIVERY SYSTEMS**

Four different approaches have been utilized to obtain trans-dermal drug delivery systems:

**1. MEMBRANE PERMEATION – CONTROLLED SYSTEMS**

**Membrane-moderated trans-dermal drug delivery system**

In this type of system, the drug reservoir is totally encapsulated in a shallow compartment molded from a drug-impermeable metallic plastic laminate and a rate controlling polymeric membrane which may be micro-porous or non-porous e.g., ethylene vinyl acetate (EVA) copolymer, with a defined drug permeability property. A cross-sectional view of this system is shown in Figure 5. The drug molecules are permitted to release only through the rate-controlling 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 such as silicone fluid to form a paste like suspension. A thin layer of drug compatible, hypoallergenic adhesive polymer e.g. silicone or Polyacrylate adhesive may be applied to the external surface of the rate controlling membrane to achieve an intimate contact of the trans-dermal system and the skin surface the rate of drug release from this type of trans-dermal drug delivery system can be tailored by varying the polymer composition, permeability coefficient and thickness of the rate limiting membrane and adhesive. The constant release rate of the drug is the major advantage of membrane permeation controlled trans-dermal system. However, a rare risk also exists when an accidental breakage of the rate controlling membrane can result in dose dumping or a rapid release of the entire drug content. Examples of this system are:

- Nitroglycerin-releasing trans-dermal system for once a day medicating in angina pectoris.
- Scopolamine-releasing trans-dermal system prophylaxis of motion sickness
- Estradiol-releasing trans-dermal system for treatment of menopausal syndrome for 3-4 days
The intrinsic rate of drug release from this type of drug delivery system is defined by

$$\frac{dQ}{dt} = \frac{C_R}{\frac{1}{P_m} + \frac{1}{P_a}}$$  \hspace{1cm} (5)

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, respectively. For a micro-porous membrane, $P_m$ is the sum of permeability coefficients for simulations penetration across the pores and the polymeric material $P_m$ and $P_a$ respectively, are defined as follows:

$$P_m = \frac{K_{m/f} \cdot D_m}{h_m}$$  \hspace{1cm} (6)

$$P_a = \frac{K_{a/m} \cdot D_a}{h_a}$$  \hspace{1cm} (7)

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 the 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 membrane, the porosity and tortuosity of the membrane should be taken into the calculation of the $D_m$ and $h_m$ values. Substituting equations for $P_m$ and $P_a$

$$\frac{dQ}{dt} = \frac{K_{m/f} \cdot K_{a/m} \cdot D_m \cdot D_a}{K_{m/f} \cdot D_m \cdot h_a + K_{a/m} \cdot D_a \cdot h_m} C_R$$

Which defines the intrinsic rate of drug release from a membrane moderated drug delivery system.

Figure No. 5:- Membrane permeation type TDDS
2. ADHESIVE DISPERSION TYPE SYSTEMS

This is a simplified form of the membrane permeation controlled system. As represented in Figure 6 the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer eg. Poly (isobutylene) or poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent casting or hot melt, on to the flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer.

On top of the drug reservoir layer, thin layers of non-medicated, rate controlling adhesive polymer of a specific permeability and constant thickness are applied to produce an adhesive diffusion-controlled delivery system. An example of this type of system is isosorbide dinitrate releasing trans-dermal therapeutic system for once a day medication of angina pectoris. This adhesive diffusion controlled drug delivery system is also applicable to the trans-dermal controlled administration of verapamil.

The rate of drug release in this system is defined by

\[
\frac{dQ}{dt} = \frac{K_{af} \cdot D_a}{h_a} \cdot C_R
\]

Where \(K_{af}\) is the partition coefficient for the interfacial portioning of the drug from the reservoir layer to adhesive layer.

Figure No. 6:- Adhesive dispersion type TDDS

3. MATRIX DIFFUSION CONTROLLED SYSTEMS

In this approach, the drug reservoir is prepared by homogeneously dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then
molded into a medicated disc with a defined surface area and controlled thickness. The dispersion of drug particles in the polymer matrix can be accomplished by either homogeneously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross linking of the polymer chains or homogeneously blending drug solids with a rubbery polymer at an elevated temperature. The drug reservoir can also be formed by dissolving the drug and polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or under vacuum. This drug reservoir containing polymer disc is then pasted on to an occlusive polymer is then spread along the circumference to form a strip of adhesive rim around the medicated disc as shown in Figure 7.

![Diagram of a matrix diffusion controlled type TDDS](image)

**Figure No. 7:- Matrix diffusion controlled type TDDS**

This type of trans-dermal system is exemplified by the nitroglycerin releasing trans-dermal therapeutic systems. These are designed to be applied to the intact skin to provide a continuous trans-dermal infusion of nitroglycerin at a daily dose of 0.5 mg/cm² for therapy of angina pectoris. It is a modified version of Nitro Dur in which the drug is dispersed in an acrylic based polymer adhesive with a resinous cross linking agent which results in a much thinner and more elegant patch. Patent disclosures have also been filed for applying this drug delivery system for trans-dermal controlled administration of estradiol discetyate and verapamil.

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

\[
\frac{dQ}{dt} = \left( \frac{AC_p D_p}{2t} \right)^{1/2}
\]
3. MICRO-RESERVOIR TYPE OR MICRO-SEALED DISSOLUTION CONTROLLED SYSTEMS.

This can be considered a combination of the reservoir and matrix diffusion type drug delivery systems. Here the drug reservoir is formed by first suspending the drug solids in an aqueous solution of a water soluble liquid polymer and then dispersing the drug suspension homogeneously in a lipophilic polymer viz. silicone elastomers by high energy dispersion technique to form several discrete, unleachable microscopic spheres of drug reservoirs. The quick stabilization of this thermodynamically unstable dispersion is accomplished by immediately cross linking the polymer chains in situ which produces a medicated polymer disc with a constant surface area and a fixed thickness. Depending upon the physiochemical property of the drug and the desired rate of drug release, the device can be further coated with a layer of biocompatible polymer to modify the mechanism and rate of drug release. A transdermal therapeutic system is produced by positioning the medicated disc at the centre and surrounding it with an adhesive rim, as shown in Figure 8.

![Figure No.8: Micro reservoir type of TDDS](image)

The rate of release of drugs from the micro-reservoir system is defined by

$$\frac{dQ}{dt} = \frac{D_p D_d m K_p}{D_p h_d + D_d h_p m K_p} \left[ n S_p \frac{D_l - S_l (1-n)}{h_l} \left( \frac{1}{K_l} + \frac{1}{K_m} \right) \right]$$

Where $m = a/b$, $a$ is the ratio of the drug concentration in the bulk of the elution medium over drug solubility in the same medium and $b$ is the ratio of drug concentration at the outer edge of the polymer coating over the drug solubility into the same polymer composition; $n$ is the ratio of drug concentration at the inner edge of the interfacial barrier over drug solubility in the polymer matrix; $D_l$ and $D_p$ and $D_d$ are respectively the drug diffusivities in the liquid layer surrounding the drug particles, polymer coating membrane surrounding the polymer matrix and the hydrodynamic diffusion layer surrounding the polymer coating with respective thickness of $h_l$, $h_p$ and $h_d$; $K_l$ $K_m$ and $K_p$ are the partition coefficients for the interfacial
partitioning of the drug from the liquid compartment to the polymer matrix, from the polymer matrix to the polymer coating membrane and from the polymer coating membrane to the elution solution (or skin) respectively. \( S_l \) and \( S_p \) are the solubilities of the drug in the liquid compartment and in the polymer matrix respectively

**EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEMS**

**A. Peel adhesion properties**

Peel adhesion is the force required to remove all adhesive coating from test substrate, its important in transdermal devices because the adhesive should provide adequate contact of device with the skin of the adhesive polymer, the type and amount of adhesive, and polymer composition. Its tested by measuring the force required to pull a single coated tape, applied to substrate, at a 180\(^\circ\) angle

No residue on the substrate indicates adhesive failure which is desirable for transdermal devices, remnants on substrate indicates cohesive failure. Signifying a deficit of cohesive strength in the coating as shown in **Figure 9**.

![Figure No.9:- Peel adhesion test](image)

**B. Tack properties**

Tack is the ability of a polymer to adhere to substrate with little contact pressure. It is important in transdermal devices which are applied with finger pressure. Tack is dependent on the molecular weight and composition of polymer as well as use tackifying resins in the polymer. Test for tack include:

1) **Thumb tack test**

This is subjective test in which evaluation is done by pressing the thumb briefly into the adhesive experience is required for using test.
2) Rolling ball tack test
This test involves measurement of distance travelled by a stainless steel along the upward face of adhesive. The diameter of ball is 7/16 inches and it released on inclined track having angle 22.5°. More the distance travelled, less the tacky polymer. Distance travelled by ball is measured in inches which determine the tackiness of polymer. It determines the softness of adhesive polymer. as shown in Figure 10

![Figure No 10:- Bolling ball tack tes](image)

3) Quick-stick (or peel-tack) test
The peel force required to break the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90° at a speed of 12 inch/min.

The force is recorded as the tack value and expressed in ounces (or grams) per inch width with higher values indicating increasing tack. as shown in Figure 11

![Figure No 11:- Peel tack or quick stick test](image)
4) **Probe tack test**

In this, the tip of probe with defined surface roughness brought in to contact with adhesive and when the bond is formed between the adhesive an probe, removal of probe at a fixed rate away from the adhesive which break the bond. The force required to break the bond is recorded as tack and it is expressed in grams as shown in **Figure 12**.

![Figure No 12:- Probe tack test](image)

**C. shear strength properties**

The cohesive strength of an adhesive polymer is determined by this test. The value of strength can be affected by the degree of cross linking, the molecular weight, the composition of polymer and the amount of tackifiers added. An adhesive coated patch is stacked on plate made of stainless steel and specified weight hung from the patch parallel to this plate. The time taken to pull off the patch from the plate determines the cohesive strength. More the time taken, greater is the shear strength as shown in **Figure 13**.

![Figure No 13:- shear strength test](image)

**2. In vitro drug release evaluation**

The design and development of transdermal drug delivery system is greatly aided by in vitro studies. *In vitro* studies can help investigating mechanisms of skin permeation of the drug.
before it can be developed into a transdermal therapeutic system. Information such as the
time needed to attain steady-state permeation and the permeation flux at steady state can be
obtained from in vitro studies of the developed transdermal drug delivery system and used to
optimize the formulation before more expensive in vivo studies are performed. Studies on
skin metabolism can also be performed. The advantages of in vitro studies include ease of
methodology, ease of analytical assay since there are no complications arising from the
disposition of the drug in the body and better control over experimental conditions than is
possible \textit{in vivo}.

In \textit{in vitro} studies, excised skin is mounted on skin permeation cells. It is generally considered
valid to use excised skin in \textit{in vitro} studies because the stratum corneum which is
physiologically inactive tissue, is the principal barrier to the permeation of a drug and
diffusion through the stratum corneum is a passive process. Then an availability of human
cadaver skin. Which is the most logical choice for in vitro studies, has led to investigation of
other animal skin hairless mouse skin is generally favoured because no potentially
detrimental hair removing procedure is required, the species is easily available and skin
specimens can be excised just prior to the permeation study. Good correlations between
permeation data across hairless mouse skin and human cadaver skin are obtained. Various
skin permeation systems have been designed and used in \textit{in vitro} studies.

3. Effect of skin uptake and metabolism

It has been shown that skin possesses some ability to metabolize drug the contribution of skin
metabolism to the elimination of a drug from the body may be relatively small as compared
to that. In the liver when a drug is administered systemically. Never the less, skin could
become an important organ for metabolism when a drug is applied directly to the skin
surface, since by this route, every molecule that becomes systemically available must
penetrate through the metabolic activity rich region in the epidermis depending on the
pharmacological activity of the metabolite formed, the metabolic reaction occurring in skin
could affect the therapeutic activity of a drug applied to the skin. Alternatively, we may also
take advantage of this metabolic conversion in the skin to improve the transdermal
bioavailability of a poorly permeated drug by applying its prodrug or derivative. Once the
prodrug has travelled down to the epidermis region, it will be metabolized and the active drug
will be formed and delivered into the systemic circulation. the pro drug approach has been the
focus of research in the design and development of transdermally active drug.
4. **In vivo evaluation**

In vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using animal models human volunteers.

In vivo evaluation of transdermal drug delivery systems can be carried out using:

A. Animal models
B. Human volunteers
C. Biophysical models

**a) Animal models**

Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted leads to a conclusion that hairless animals are preferred over hairy animals in both in vitro and in vivo experiments. Rhesus monkey is one of the most reliable models for in vivo evaluation of transdermal drug delivery in man.

**b) Human models**

The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug.

**c) Biophysical Models**

Models based on steady-state mass balance equation, solution of Fick’s second law of diffusion for the device, stratum corneum and viable epidermis, as well as linear kinetics have been described in the literature. It can be concluded that many techniques for in-vivo
evaluation of transdermal systems have been put forward there is scope for further refinement. Some of the unresolved issues include the barrier function of the skin with age, skin metabolism, *in vivo* functioning of penetration enhancers etc.

## EXAMPLES OF TDDS PRODUCTS

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>TDDS</th>
<th>Design/contents</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>Habitrol (Novartis Consumer)</td>
<td>Multi-layered round patch: (1) an aluminized backing film; (2) a pressure-sensitive acrylate adhesive; (3) Methacrylic acid copolymer solution of nicotine dispersed in a pad of nonwoven viscose and cotton; (4) an acrylate adhesive layer; and (5) a protective aluminized release liner that overlays the adhesive layer and is removed prior to use.</td>
<td>Transdermal therapeutic systems providing continuous release and systemic delivery of nicotine as an aid in smoking cessation programs. The patches listed vary somewhat in nicotine content and dosing schedules.</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Deponit (Schwarz Pharma)</td>
<td>A three-layer system: (1) covering foil; (2) Nitroglycerin matrix with polysobutylene adhesive, plasticizer and release membrane; and (3) Protective foil removed before use.</td>
<td>TDDSs designed to provide the controlled release of nitroglycerin for treatment of angina. Daily application to chest, upper arm or shoulder.</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>TrnsdermScop (Novartis Consumer)</td>
<td>Four-layered patch: (1) Backing layer of aluminized polyester film; (2) Drug reservoir of scopolamine, mineral oil, and polyisobutylene; (3) A microporous polypropylene membrane for rate delivery of scopolamine; and (4) Adhesive of polyisobutylene, mineral oil, and scopolamine</td>
<td>TDDS for continuous release of scopolamine over a 3-day period as required for the prevention of nausea and vomiting associated with motion sickness. The patch is placed behind the ear. When repeated administration is desired, the first patch is removed and the second patch placed behind the other ear. Also FDA-approved for prevention of nausea associated with certain anesthetics and analgesics used in surgery.</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Testoderm (Alza)</td>
<td>Three-layer patch: Backing layer of polyethylene terephthalate</td>
<td>The patch is placed on the scrotum in the treatment of testosterone deficiency.</td>
</tr>
</tbody>
</table>
CONCLUSION
Transdermal drug delivery system 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. The search for the ideal skin penetration enhancer has been the focus of considerable research effort over a number of decades. Although many potent enhancers have been discovered, in most cases their enhancement effects are associated with toxicity, therefore limiting their clinical application. In recent years the use of a number of biophysical techniques has aided in our understanding of the nature of the stratum corneum barrier and the way in which chemicals interact with and influence this structure. A better understanding of the interaction of enhancers with the stratum corneum and the development of structure activity relationships for enhancers will aid in the design of enhancers with optimal characteristics and minimal toxicity. The transdermal drug delivery system could be one day one of the best novel drug delivery system.

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REFERENCE

