A Review of Transdermal drug delivery system

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Abstract
Transdermal drug delivery system (TDDS) specialists are continuing to search for new methods that can effectively and painlessly deliver larger molecules in therapeutic quantities to overcome the difficulties associated with oral route,namely poor bioavailability due to first pass metabolism and the tendency to produce rapid blood level spikes(both high and low). Transdermal drug delivery can improve the therapeutic efficacy and safety of drugs by more site specific way but spatial and temporal placement within body is recquired to reduce both the size and number of doses necessary to achieve the objective of systemic medication through topical application to the intact skin surface.This review describes enhancement techniques based on drug/vehicle optimization such as drug selection,prodrugs and ion pairs,supersaturated drug solutions,eutectic systems,complexations, liposomes,vesicles and particles.This review also focuses on the recent innovations in Transdermal drug delivery system (TDDS) which can be a platform for the research and development of pharmaceutical dosage form for transdermal drug delivery.

Keywords: TDDS, first pass metabolism, drug selection
The transdermal route has become one of the most successful and innovative drug delivery system for research in pharmaceutical sciences. Transdermal drug delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively [1]. Transdermal drug delivery is 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. The success of dermatological drug to be used for systemic drug delivery depends on ability of the drug to penetrate through skin in sufficient quantities to achieve the desired therapeutic effect [2]. The first transdermal patch was approved in 1981 for the relief of motion sickness, nausea and vomiting. The transdermal drug delivery market was until recently, solely based on passive patch technology that relied on sample diffusion across the skin. Active patches in which the agent in someway driven through barrier offer a wide array of capabilities allowing delivery compounds over 500 Da and those with challenging physical properties. This has permitted the development of active patches to deliver pain management drugs, proteins and vaccines. Passive patch technology is creating smaller patches with better adhesion [3]. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. Hence transdermal drug delivery is defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation.

Advantages [4]
1. Avoid the risk and inconvenience of intravenous therapy (noninvasive).
2. Avoidance of first pass hepatic metabolism (avoiding the deactivation by digestive and liver enzymes) thus increasing bioavailability and efficacy of drugs.
3. No gastrointestinal degradation (pH, enzymatic activity, drug interaction with food, drink and other orally administered drugs).
4. Substitute for oral administration of medication when that route is unsuitable as with vomiting and diarrhea.
5. Extended therapy avoiding frequent dose administration.
6. Reduce side effect due to optimization of the blood concentration time profile.
7. Greater patient compliance due to elimination of multiple dosing intervals.
8. Enhance therapeutic efficiency.
9. Minimize inter and intra patient variations.
10. Reversibility of drug delivery which would allow the removal of drug source.

Limitations of TDDS [5]
1. Limited skin permeability.
2. Restricted to potent drug.
3. Cannot use for large molecule (>500 Dalton).
4. Significant lag time.
5. Difficulty for adhesion.
6. The drug undergoes degradation in the skin.
7. Variation in absorption efficiency at different sites of skin.

Mechanism of transdermal permeation [6]
For a systemically-active drug to reach a target tissue, it has to possess some physico-chemical properties which facilitate the absorption of the drug through the skin and also the uptake of the drug by the capillary network in the dermal papillary layer (Figure-1).
The rate of permeation, dQ/dt, across various layers of skin tissues can be expressed as:
\[
d\frac{Q}{dt} = P_s(C_d - C_r) \quad \text{(1)}
\]
Where
- $C_d$ = the concentrations of skin penetrate in the donor phase (stratum corneum)
- $C_r$ = receptor phase (systemic circulation)
- $P_s$ = the overall permeability coefficient of the skin

The overall permeability coefficient of the skin is defined by
\[
P_s = \frac{K_s D_{ss}}{h_s} \quad \text{(2)}
\]
- $K_s$ = Partition coefficient of the penetrant
- $D_{ss}$ = Apparent diffusivity of penetrant
- $h_s$ = Thickness of skin

Thus, the permeability coefficient ($P_s$) may be a constant since $K_s$, $D_{ss}$ and $h_s$ terms in equation (2) are constant under the given set of conditions.

A constant rate of drug permeation achieved, if $C_d > C_r$, then the equation (1) may be reduced to
\[
d\frac{Q}{dt} = P_s C_d \quad \text{(3)}
\]
And the rate of skin permeation ($dQ/dt$) becomes a constant, if the $C_d$ value remains fairly constant throughout the course of skin permeation. To maintain the $C_d$ at a constant value, it is critical to make the drug to be released at a rate ($R_r$) which is always greater than the rate of skin uptake ($R_a$), i.e., $R_r >> R_a$ (Figure-2)

By doing so, the drug concentration on the skin surface ($C_d$) is maintained at a level which is always greater than the equilibrium (or saturation) solubility of the drug in the stratum corneum ($C_{es}$), i.e., $C_d >> C_{es}$; and a maximum rate of skin permeation ($dQ/dt)_m$, as expressed by equation (4), is thus reached:
\[
(dQ/dt)_m = P_s C_{es}^c
\]
Apparently, the magnitude of ($dQ/dt)_m$ is determined by the skin permeability coefficient ($P_s$) of the drug and its equilibrium solubility in the stratum corneum ($C_{es}$).
Figure-2: Relationship between the rate of drug release (Rr) from a transdermal drug delivery system (TDDS) and the rate of drug uptake (Ra) by the skin.

Transport through the skin [7]
Skin is structurally complex and thick membrane. Molecules moving from the environment must penetrate the stratum corneum and any material of endogenous or exogenous origin on its surface. They must then penetrate the viable epidermis, the papillary dermis and the capillary walls into the blood stream or lymph channels, whereupon they are removed from the skin by flow of blood or lymph. To move across the skin membrane is obviously a complex phenomenon and challenge in analysis.

A. Route of drug penetration through human skin
When a molecule reaches intact skin, it contacts cellular debris, microorganisms, sebum and other materials. The diffusant then has three potential entry routes to the viable tissue, through the hair follicles with their associated sebaceous glands, via the sweat ducts or across the continuous stratum corneum between these appendages.

These figures illustrate three potential routes for drug permeation.

1. Intra cellular /trans cellular : across the cells
2. Intercellular/paracellular:between the cells
3. Transfollicular:through hairshaft opening

Electron photo-microscopic examination shows that intracellular region in stratum corneum is filled with lipid reach amorphous material. During cornification the lipid composition shifts from polar to neutral constituents. In the dry stratum corneum intracellular diffusion volume may be as high as 5% and least 1% of the fully hydrated stratum corneum. This intracellular volume is at least an order magnitude larger than that (approximate 0-2%) estimated for the intra-appendageal pathway, thus, intracellular diffusion could be significant. Both the structured lipid environment between the cells and the hydrated protein, within a corneocytes plays major role in skin permeability, cell membranes are probably of only minor consequences (Figure-3 and 4). The intracellular pathway avoids the cell contents ,but the aqueous pathway is more tortuous.The major pathway for penetration of small polar molecules is likely to be transcellular and through stratum corneum. The intercellular route is considered an unlikely avenue because of its
volume and long pathlength. The transfollicular pathway in which the drug travels through cells and across them is the shortest way the most likely provides relatively large area for diffusion of a molecule. The transfollicular pathway involves passage or diffusion of drug molecule through the hair shaft openings which presumably are filled with sebum.

Figure-3: Simplified diagram of stratum corneum and its routes of drug penetration.

Figure-4: Pathways through human skin

**Basic components of TDDS [8-10]**

- Polymer matrix/Drug reservoir
- Drug
- Permeation Enhancers
- Pressure sensitive adhesives
- Backing Laminate
- Release Liner
- Other excipients

**Polymers**

Polymers are the backbone of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers and PSAs.
Additionally they should provide consistent and effective delivery of a drug throughout the product’s intended shelf life and should be of safe status. Companies involved in the field of transdermal delivery concentrate on a few selective polymeric systems. For example, Alza Corporation mainly concentrates on ethylene vinyl acetate (EVA) copolymers or microporous polypropylene and Searle Pharmacia concentrates on silicon rubber. Similarly Colorcon, UK uses HPMC for matrix preparation for propranolol transdermal delivery and Sigma uses ethyl cellulose for isosorbide dinitrate matrix. The polymers utilized for TDDS can be classified as,

**Natural Polymers**: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.

**Synthetic Elastomers**: e.g. polybutadiene, hydrid rubber, polyisobutylene, silicon rubber, nitrile, acrylnitrile, neoprene, butylrubber etc.

**Synthetic Polymers**: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polystyrene, polyvinylpyrrolidone, polymethylmethacrylate etc.

The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxypropylmethylcellulose are used as matrix formers for TDDS. Other polymers like EVA, silicon rubber and polyurethane are used as rate controlling membrane.

**Drug**

The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non-compliance due to frequent dosing. The foremost requirement of TDDS is that the drug possesses the right mix of physicochemical and biological properties for transdermal drug delivery. It is generally accepted that the best drug candidates for passive adhesive transdermal patches must be non ionic, of low molecular weight (less than 500 Daltons), have adequate solubility in oil and water (log P in the range of 1-3), a low melting point (less than 200°C) and are potent (dose in mg per day).

**Ideal properties drug for TDDS.**

<table>
<thead>
<tr>
<th>Property</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half life</td>
<td>&lt;10hrs</td>
</tr>
<tr>
<td>Therapeutic index</td>
<td>low</td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>low</td>
</tr>
<tr>
<td>pH</td>
<td>between 5-9</td>
</tr>
<tr>
<td>Skin permeability</td>
<td>0.5x10^-3</td>
</tr>
</tbody>
</table>

Drug solution in direct contact with release liner. For successfully developing transdermal delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.

**(a) Physicochemical Properties**

1. The drug should have are molecular weight less than approximately 500 Daltons.
2. The drug should have affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conductive to successful drug delivery via the skin.
3. The drug should have a low melting point.

**(b) Biological Properties**

1. The drug should be potent with a daily dose of the order of a few mg per day.
2. The half life (t1/2) of the drug should be short.
3. The drug must not induce a cutaneous or allergic response.
4. Drug which degrade in the G.I tract or inactivated by hepatic first pass effect are suitable candidates for transdermal delivery.
5. Tolerance to the drug must not develop under the near zero order release profile of transdermal delivery.
6. Drugs which have to be administered for a long period of time or which cause adverse
effects to non-target tissues can also be formulated for transdermal delivery.

**Permeation Enhancers**

Three pathways are suggested for drug penetration through the skin: polar, non-polar, and polar/non-polar. The enhancers act by altering one of these pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The key to altering the nonpolar pathway is to alter the rigidity of the lipid structure and fluidize the crystalline pathway (this substantially increases diffusion). The fatty acid enhancers increase the fluidity of the lipid portion of the Stratum Corneum. Some enhancers (binary vehicles) act on both polar and nonpolar pathways by altering the multilaminate pathway for penetrants. Enhancers can increase the drug diffusivity in the Stratum Corneum (SC) by dissolving the skin lipids or by denaturing skin proteins. The type of enhancer employed has a significant impact on the design and development of the product. The success of dermatological drug products that are intended for systemic drug delivery, such as the transdermal, depends on the ability of the drug to penetrate through the skin in sufficient quantities to achieve its desired therapeutic effect. The methods employed for modifying the barrier properties of the SC to enhance the drug penetration (and absorption) through the skin can be categorized as (1) Chemical and (2) physical methods of enhancement.

**Chemical Enhancers**

Chemicals that promote the penetration of topically applied drugs are commonly referred to as accelerants, absorption promoters, or penetration enhancers. These agents act by increasing the drug permeability through the skin by causing reversible damage to the SC or by increasing (and optimizing) thermodynamic activity of the drug when functioning as co solvent or by increasing the partition coefficient of the drug to promote its release from the vehicle into the skin or by conditioning the SC to promote drug diffusion. Promoting penetration and establish drug reservoir in the SC.

**Sulphoxides**

Dimethyl sulphoxides (DMSO) is one of the earliest and most widely studied penetration enhancers. It is a powerful aprotic solvent which hydrogen bonds with itself rather than with water. It is colourless, odourless and is hydroscopic and is often used in many areas of pharmaceutical sciences as a “universal solvent”. DMSO alone has been applied topically to treat systemic inflammation. DMSO works rapidly as a penetration enhancer - spillage of the material onto the skin can be tasted in the mouth within a second. Although DMSO is an excellent accelerant, it does create problems. The effect of the enhancer is concentration-dependent and generally cosolvents containing > 60% DMSO are needed for optimum enhancement efficacy. However, at these relative high concentrations, DMSO can cause erythema and wheal of the stratum corneum. Denaturing of some skin proteins results in erythema, scaling, contact urticaria, stinging and burning sensation.

**Azone**

Azone (1-dodecylazacycloheptan-2-one or laurocapran) was the first molecule specifically designed as a skin penetration enhancer. Azone is a colourless, odourless liquid with a melting point of -7 °C and it possesses a smooth, oily but yet non-greasy feel. Azone is a highly lipophilic material with a log p octanol / water of around 6.2 and it is soluble in and compatible with most organic solvents including alcohol and propylene glycol. Azone enhances the skin transport of a wide variety of drugs including steroids, antibiotics and antiviral agents. Azone is most effective at low concentrations, being employed typically
between 0.1-5% but more often between 1-3%. Azone partitions into a bilayer lipid to disrupt their packing arrangement but integration into the lipid is unlikely to be homogeneous. Azone molecules may exist dispersed within the barrier lipid or separate domains within the bilayer.

**Pyrrolidones**

Pyrrolidones have been used as permeation enhancers for numerous molecules including hydrophilic (e.g. mannitol and 5-flourouracil) and lipophilic (progesterone and hydrocortisone) permeants. N-methyl-2-pyrolidone was employed with limited success as a penetration enhancer for captopril when formulated in a matrix-type transdermal patch. The pyrrolidones partition well into human stratum corneum within the tissue and they may act by altering the solvent nature of the membrane. Pyrrolidones have been used to generate reservoirs within the skin membrane. Such a reservoir effect offers a potential for sustained release of a permeant from the stratum corneum over extended time periods.

**Fatty acids**

Percutaneous drug absorption has been increased by a wide variety of long-chain fatty acids, the most popular of which is oleic acid. It is of interest to note that many penetration enhancers such as azone contain saturated or unsaturated hydrocarbon chains and some structure-activity relationships have been drawn from the extensive studies of Aungst who employed a range of fatty acids, acids, alcohols, sulphoxides, surfactants and amides as enhancers for naloxone. Shin et al studied various penetration enhancers like glycols (diethylene glycol and tetraethylene glycol), fatty acids (lauric acid, myristic acid and capric acid) and nonic surfactant (polyoxyethylene-2-oleyl ether, polyoxyethylene-2-stearly ether) on the release of triprolidone. Lauric acid in Propylene glycol enhanced the delivery of highly lipophilic antiestrogen. Oleic acid greatly increased the flux of many drugs such as increasing the flux of salicylic acid 28-fold and 5-flourouracil flux 56-fold through human skin membrane in vitro. The enhancer interacts with and modifies the lipid domains of the stratum corneum as would be expected for a longchain fatty acid with cis-configuration.

**Essential oil, terpenes and terpenoids**

Terpenes are found in essential oils, and are compounds comprising of only carbon, hydrogen and oxygen atoms, but which are not aromatic. Numerous terpenes have long been used as medicines as well as flavoring and fragrance agents. The essential oils of eucalyptus, chenopodium and ylang-ylang have been found to be effective penetration enhancers for 5-flourouracil transversing human skin in vivo. Cornwell et al investigated the effect of 12 sesquiterpenes on the permeation of 5-flourouracil in human skin. Pretreatment of epidermal membranes with sesquiterpene oil or using solidsesquiterpenes saturated in dimethyl isosorbide increased the absorption of 5-flourouracil. L-menthol has been used to facilitate in vitro permeation of morphine hydrochloride through hairless rat skin as well as diffusion of imipramine hydrochloride across rat skin and hydrocortisone through hairless mouse skin. One mechanism by which this agent operates is to modify the solvent nature of the stratum corneum, thus improving drug partitioning into the tissue. Many terpenes permeate human skin well and large amounts of terpene have been found in the epidermis after application from a matrix-type patch. Terpenes may also modify drug diffusivity through the membrane. During steady state permeation experiments using terpenes as penetration enhancers, the lag time for permeation was usually reduced, indicating some increase in drug diffusivity.
through the membrane following terpene treatment.

**Oxazolidinones**

Oxazolidinones are a new class of chemical agents which have the potential for use in many cosmetic and personal care product formulations. This is due to their ability to localize co-administered drug in skin layers, resulting in low systemic permeation. The structural features of these permeation enhancers are closely related to sphingosine and ceramide lipids which are naturally found in the upper skin layers. Oxazolidinones such as 4-decyloxazolidin-2-one has been reported to localize the delivery of many active ingredients such as retinoic acid and diclofenac sodium in skin layers. This compound has a higher molecular weight and lipophilicity than other solvent-type enhancers, physical characteristics that may be beneficial in terms of a reduction in local toxicity because of the lack of effective absorption of these enhancers into the lower skin layers where irritation is likely to be occur.

**Urea**

Urea promotes transdermal permeation by facilitating hydration of the stratum corneum and by the formation of hydrophilic diffusion channels within the barrier. Cyclic urea permeation enhancers are biodegradable and non-toxic molecules consisting of a polar parent moiety and a long chain alkyl ester group. As a result, enhancement mechanism may be a consequence of both hydrophilic activity and lipid disruption mechanism.

**Physical enhancers**

The iontophoresis and ultra sound (also known as phonophoresis or sonophoresis) techniques are examples of physical means of enhancement that have been used for enhancing percutaneous penetration (and absorption) of various therapeutic agents.

**Pressure sensitive adhesives**

A PSA is a material that helps in maintaining an intimate contact between transdermal system and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy, and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue. Polyacrylates, polyisobutylene and silicon based adhesives are widely used in TDDSs. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. For matrix systems with a peripheral adhesive, an incidental contact between the adhesive and the drug and penetration enhancer should not cause instability of the drug, penetration enhancer or the adhesive. In case of reservoir systems that include a face adhesive, the diffusing drug must not affect the adhesive. In case of drug-in-adhesive matrix systems, the selection will be based on the rate at which the drug and the penetration enhancer will diffuse through the adhesive. Ideally, PSA should be physic chemically and biologically compatible and should not alter drug release.

**Backing Laminate**

While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipients compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer. However, an overemphasis on the chemical resistance may lead to stiffness and high occlusive to moisture vapor and air, causing patches to lift and possibly irritate the skin during long wear. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high...
moisture vapor transmission rate. Examples of some backing materials are vinyl, polyethylene and polyester films.

Release Liner

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water. Typically, release liner is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metallized laminates.

Other excipients

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylphthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

APPRAOCHES TO DEVELOPMENT TRANSDERMAL THERAPEUTIC SYSTEMS [8-11]

Several technologies have been successfully developed to provide a rate control over the release and the transdermal permeation of drugs. These technologies can be classified into two major categories as follows:

A. Rate-programmed transdermal DDS

B. Physical stimuli-activated transdermal DDS

A. Rate-programmed transdermal DDS

1. Membrane permeation – controlled systems

2. Adhesive dispersion – type systems.


4. Micro reservoir type or micro sealed dissolution controlled systems

B. Physical stimuli-activated transdermal DDS

i. Structure based
   - microneedles
   - macroflux
   - MDTS

ii. Electrically based
   - Iontophoresis
   - Ultrasound
   - Photochemical waves
   - Electroporation
   - Electroosmosis

iii. Velocity based
   - Powder jet
   - Needle free injection

iv. Others
   - Transferosomes
   - Medicated tattoos
   - Skin abrasion
   - Heat
   - Laser radiation
   - Magnetophoresis

Membrane permeation – controlled systems

In this type of system, drug reservoir is encapsulated in a shallow compartment moulded from a drug-impermeable metallic plastic laminate and a rate controlling polymeric membrane which may be micro porous or non-porous. The drug molecules are permitted to release only through the rate – controlling polymeric membrane. In the drug reservoir compartment, the drug solids are either dispersed homogenously in a solid polymer matrix (e.g. Polyisobutylene adhesive) or suspended in an unbleachable, viscous liquid medium (e.g. Silicon fluids) to form a paste like suspension.
The rate of drug release from this type of 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 system. However, a rare risk also exists when an accidental breakage of the rate controlling membrane can result in dose dumping or rapid release of entire drug content. Examples of this system are

**Transderm – Nitro**
Nitroglycerin – releasing transdermal system for once a day medication in angina pectoris.

**Transderm – Scop**
Scopolamine – releasing transdermal system for 72 hrs. Prophylaxis of motion sickness.

**Catapres**
Clonidine-releasing transdermal system for 7 day therapy of hypertension.

**Estraderm**
Estradiol – releasing transdermal system for treatment of menopausal syndrome for 3 – 4 days.

The membrane permeation-controlled technology has also been used for controlled percutaneous absorption of prostaglandin-derivatives.

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 skin. The intrinsic rate of drug release from this type of drug delivery system is defined by

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

Where \(C_r\) is the drug concentration in the reservoir compartment and \(P_m\) and \(P_a\) 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.

\[
P_m = K_m/r \cdot D_m/h_m
\]
\[
P_a = K_a/m \cdot D_a/h_a
\]

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.

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 film. The rate of drug release in this system is defined by,
\[ \frac{dQ}{dt} = \frac{K_a r}{D_a} \frac{C_r}{h_a} \]
Where \( K_a r \) is the partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer.

**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 e.g. Poly (isobutylene) or poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent casting or hot melt, on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. On the 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.

**Frandol tape**
Releases Isosorbide dinitrate for once-a-day medication of angina pectoris.

**Deponit**
Delivers nitroglycerine for the treatment of angina pectoris.

![Figure-6: adhesive diffusion-controlled Transdermal drug delivery system.](image)

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 membrane.

The rate of drug release from this drug reservoir gradient controlled system is given by,
\[ \frac{dQ}{dt} = \frac{K_a r}{D_a} \frac{A(h_a)}{h_a(t)} \]
In the above equation, the thickness of the adhesive layer for drug molecules to diffuse through increases with time \( h_a(t) \). 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 \( A(h_a) \). In the above equation, the thickness of the adhesive layer for drug molecules to diffuse through increases with time \( h_a(t) \). 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 \( A(h_a) \).

**Matrix diffusion controlled systems**
In this approach the drug reservoir is formed by homogenously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then molded into amedicated disc with a defined surface area and controlled
thickness. The dispersion of drug particles in the polymer matrix can be accomplished by either homogenously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross linking of polymer chains or homogenously blending drug solids with a rubbery polymer at an elevated temperature. The drug reservoir can be formed by dissolving the drug and the polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or vacuum. This drug reservoir containing polymer disc is then pasted onto an occlusive base plate in a compartment fabricated from a drug impermeable plastic backing membrane. The polymer is spread along the circumference of the patch to form an adhesive rim around the medicated disc e.g. Nitro-Dur; Delivers nitroglycerin for the treatment of angina pectoris.

![Figure-7: Matrix dispersion-type transdermal drug delivery system](image)

The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix. The rate of drug release from this type of system is defined as,

\[
\frac{dQ}{dt} = \sqrt{\frac{A C_p D_p}{2t}}
\]

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.

**Micro reservoir type or Micro sealed Dissolution**

The micro reservoir type drug delivery system can be considered a combination of the reservoir and matrix diffusion type drug delivery systems. In this approach, the drug reservoir is formed by first suspending the drug solids in the aqueous solution of water soluble liquid polymer (e.g. Polyethylene glycol) and then dispersing the drug suspension homogenously in lipophilic polymer viz. silicone elastomers by high energy dispersion technique to form several discrete, unleachable micro spheres of drug reservoirs. This thermodynamically unstable dispersion is quickly stabilized by immediately cross-linking the polymer chains in situ, which produces a medicated polymer disc with a constant surface area and a fixed thickness. A transdermal therapeutic system is then produced by positioning the medicated disc at the centre and surrounding it with an adhesive rim. E.g. Nitroglycerin: Releasing transdermal therapeutic system for once – a day treatment of angina pectoris
The microreservoir system has been claimed to follow the zero order release of drugs without the danger of dose dumping. The rate of release of drugs from the microreservoir system is given by
\[
\frac{dQ}{dt} = D_p D_d m K_p D_{phd} + D_d h_p m K_p (n S_p D_I (1-n)/h_1 (1/k_1 + 1/k_m)
\]
Where
\[m = a/b\]
a is the ratio of the drug concentration in the bulk elution medium over drug solubility in the same medium
b is the ratio of the drug concentration at the outer edge of the polymer coating over the drug solubility in the same polymer composition
n = the ratio of drug concentration at the inner edge of the interfacial barrier over drug solubility in the polymer matrix
\[D_I, D_p\] and \[D_d\] are respectively the drug diffusivities in the liquid layer surrounding the drug particles, polymer coating member surrounding the polymer matrix and the hydrodynamic diffusion layer surrounding the polymer coating with respective thickness of \[h_1, h_p\] and \[h_d\]
\[K_1\] = the partition coefficient for the interfacial partitioning of the drug from the liquid compartment to the polymer matrix
\[K_m\] = the partition coefficient for the interfacial partitioning of the drug from the polymer matrix to the polymer coating membrane
\[K_p\] = the partition coefficient for the interfacial partitioning of the drug from the polymer coating membrane to the elution solution (or skin)
\[S_1\] = the solubility of the drug in the liquid compartment
\[S_p\] = the solubility of the drug in the polymer matrix

**Structure-Based Enhancement Techniques**

**Microfabricated Microneedles**

Microfabricated microneedles are devices which are hybrids of the hypodermic needle and transdermal patch through the use of microscopic needles that can deliver the drug effectively (like a hypodermic needle). Their small size offers the potential advantages of delivering large molecules across the stratum corneum without extreme pain to the patients. The first microneedles systems consisted of a drug reservoir and a plurality of projections (microneedles) extending from the reservoir, which penetrate the stratum corneum and epidermis to deliver the drug. The microneedle concept employs an array of micron-scale needles that can deliver drug into the epidermis and dermis, which ultimately leads to uptake by the capillaries for systemic delivery but not so far that
microneedles hit the nerves. This is the reason for the device being less painful to patients. The most common material used for microfabrication of needles is silicon. These microneedles have extremely sharp tips (radius of curvature, <1 μm) that facilitate easy piercing of the skin. Individual silicon needles measuring approximately 150 μm in length and with 80 μm base diameter are fabricated onto arrays of approximately 400 microneedles (approx. 3 × 3 mm). Needles with hollow centers have also been produced, each containing a bore of 5-70 μm (depending on the required design) through which drug can be administered. A broad range of compounds such as calcein (623 Da), insulin (6000 Da), BSA (66000 Da) and polymeric nanoparticles are delivered at significant rates through skin permeabilized by microfabricated microneedles.

**Macroflux**

Macroflux® technology is another novel transdermal drug delivery system that ALZA Corporation has developed to deliver biopharmaceutical drugs in a controlled reproducible manner that optimizes bioavailability and efficacy without significant discomfort for the patient. The system incorporates a titanium microprojection array that creates superficial pathway through the skin barrier layer to allow transportation of therapeutic proteins and vaccines or access to the interstitial fluids for sampling. Macroflux® has an area of up to 8 cm² and contains as many as 300 microprojection per cm² with individual microprojection length being < 200 μm. The maximal adhesive patch size is 10 cm². A coating process is used to apply drug to the tip of each microprojection in the array. When the patch is applied to the skin, the drug-coated microprojections penetrate through the skin barrier layer into the epidermis. The microcapillaries for systemic distribution absorb the drug. The rate of absorption is promoted by the high local drug concentration around the microprojections and the large surface area provided by the patch array.

Three types of Macroflux® have been designed and tested in preclinical studies. They include,

- Dry-Coated Macroflux® system for short duration administration that consist of a drug coated microprojection array adhered to a flexible polymeric adhesive backing.
- D-TRANS® Macroflux® system for short duration administration that consist of a microprojection array coupled with a drug reservoir.
- E-TRANS® Macroflux® system for pulsatile or on demand delivery that include a microprojection array coupled with an electrotransport system.

Therapeutic peptides, proteins and vaccines such as desmopressin, human growth hormone (HGH), TH 9507 (a human growth hormone releasing factor analog), ovalbumin (45000 Da protein) are in the developmental stage for transdermal delivery by Macroflux®

**Metered-Dose Transdermal Spray (MDTS)**

Metered-dose transdermal spray (MDTSTM), originally developed at the Victorian College of Pharmacy [Monash University (Parkville Campus), Parkville, Victoria, Australia] and currently being commercialized by Acrux Limited [Melbourne, Victoria, Australia] has the potential to expand the growth of TDD systems by broadening patient acceptance and pharmaceutical applications for enhanced TDD. MDTS relies on the combination of a newly identified GRAS (generally recognized as safe) chemical penetration enhancer (AcrossTM) and the accurate and precise topical dosing of a volatile: nonvolatile vehicle. This MDTS can be classified, as an enhanced, passive TDD system. It is a topical solution made up
of a volatile cum nonvolatile vehicle containing the drug dissolved as a single-phase solution. A finite metered-dose application of the formulation to intact skin results in subsequent evaporation of the volatile component of the vehicle, leaving the remaining nonvolatile penetration enhancer and drug to rapidly partition into the stratum corneum during the first minute after application, resulting in a stratum corneum reservoir of drug and enhancer. Following a once daily application of the MDTS, a sustained and enhanced penetration of the drug across the skin can be achieved from the stratum corneum reservoir. Different types of penetration enhancers, such as ethanol and azone, are commonly used. Clinical experience with estradiol-MDTS to post-menopausal women have shown increased higher plasma level of estradiol than the baseline value measured by radioimmunoassay.

The MDTS has the following potential advantages:
1. Enhanced passive tdds with little or no skin irritation primarily as a result of its nonocclusive nature.
2. Improved cosmetic acceptability
3. Dose flexibility
4. Simplicity of manufacture.

**Electrically-Based Enhancement Techniques**

**Iontophoresis:**
Iontophoresis may be defined as the facilitation of ionizable drug permeation across the skin by an applied electrical potential, the driving force of which may be simply visualized as electrostatic repulsion. A typical iontophoresis device consists of a battery, microprocessor controller, drug reservoir and electrodes. The technique involves the application of a small electric current (usually 0.5 mA/cm²) to a drug reservoir on the skin, with the similarly charged electrodes (on the surface of the skin) placed together in the drug reservoir producing a repulsion effect that effectively drives the solute molecules away from the electrode and into the skin.

There are three explanations of how iontophoresis increases transdermal drug delivery. The first, proposes that the drugs are forced across the skin by simple electronic repulsion of similar charges. Anionic drugs can cross the skin by using a negatively charged electrode. Similarly cationic drugs enter the skin more successfully when a positively charged electrode is used. The second, explanation suggests that the electric current enhances permeation by inhibiting the skin’s ability to perform its protective barrier function. The third, states that iontophoresis causes water, a very effective penetration enhancer, to enter the stratum corneum by electro-osmosis. Dissolved drugs can be carried across the skin along with the penetrating water during iontophoresis. At physiological pH, human skin has slight negative charge; therefore, certain cationic drugs can more easily cross the skin during iontophoresis due to reduced resistance. Several studies have addressed the application of iontophoresis to the delivery of low molecular weight solutes (< 500 Da). For delivery of macromolecules, proteins and peptides such as calcitonin, corticotrophin-releasing hormone, δ-sleep-inducing peptide, dextrin sulphate, inulin, insulin, gonadotropin releasing hormone, growth hormone releasing factor, neutral thyrotrophin releasing hormone, parathyroid hormone and vasopressin iontophoresis may also be utilized. To date, clinical studies have been limited to smaller molecules such as lidocaine, ketorolac dexamethasone, etofenamate, naproxen, vincristine, cortisone and fentanyl.
**Ultrasound**

Ultrasound (sonophoresis, phonophoresis and ultraphonophoresis) is a technique for increasing the skin permeation of drugs using ultrasound (20 KHZ to 16 MHZ) as a physical force. It is a combination of ultrasound therapy with topical drug therapy to achieve therapeutic drug concentrations at selected sites in the skin. In this technique, the drug is mixed with a coupling agent usually a gel but sometimes a cream or ointment is used which transfers ultrasonic energy from the device to the skin through this coupling agent. Application of low – frequency ultrasound (20 -100 KHZ) enhances skin permeability more effectively than high – frequency ultrasound (1 -16 MHZ). The mechanism of transdermal skin permeation involves disruption of the stratum corneum lipids, thus allowing the drug to pass through the skin. A corresponding reduction in skin resistance was observed due to cavitation, microstreaming and heat generation. Reverse ultrasound technology may also be used for the extraction of interstitial fluid samples for analysis.

**Photomechanical Waves**

Photomechanical waves (PW’s) are the pressure pulses produced by ablation of a material target (polystyrene) by Q-switched or mode-locked lasers. Photomechanical waves are able to render the stratum corneum more permeable to macromolecules via a possible transient permeabilisation effect due to the formation of transient channels. The largest molecule that has been reported to be delivered through the rat skin to date has a molecular weight of 40,000Da. Suggestions have been made that many clinically important proteins such as insulin (6000 Da) and hematoprotien (48000 Da) are within or close to the delivery capability range of PW’s. However, this relatively new technique does not yet seem to have produced any human clinical data.

**Electroporation**

This method involves the application of high voltage pulses to the skin, which has been suggested to induce formation of transient pores. High voltages in the form of direct current [DC (100 volts)] caused by electrical pulses with short treatment durations (milliseconds) are most frequently employed. Other parameters that affect delivery include pulse properties such as wave form, rate and number. The mechanism of penetration is the formation of transient pores due to electric pulses that subsequently allow the passage of macromolecules from the outside of the cell to the intracellular space via a combination of possible processes such as diffusion and local electrophoresis. The electrical resistance of the skin is reported to drop as much as three orders of magnitude within microseconds of administration of an electric pulse. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e., small molecules, proteins, peptides and oligonucleotides) including biopharmaceuticals with molecular weights greater than 7KDa. Increase in transdermal penetration of up to 104 fold have been reported in vitro for various sizes of molecules such as metoprolol, lidocaine, tetracaine, vitamin C, timolol and fentanyl dyes, including calcein and methylene blue, and macromolecules up to 40 KDa including cyclosporine A, heparin, leutenising hormone releasing hormone, insulin, oligonucleotides and dextrans (MW 4.4 – 39 KDa).
**Electro-Osmosis**

If a charged porous membrane is subjected to a voltage difference, a bulk fluid or volume flow, called electro osmosis occurs without concentration gradients, suggesting that this flow is not diffusion. This bulk fluid flow by electro osmosis was found to be of the order of micro liters per hour per square centimeter of hairless mouse skin. The electro–osmotic flow occurs from anode to cathode, thus enhancing the flux of positively charged (cationic) drugs and making it possible to deliver neutral drugs.

**Velocity Based Enhancement Techniques**

**Needle-Free Injections**

The highest value, least developed and most technically challenging group of needle-free technologies is prefilled, disposable injectors. The development of such technologies is primarily driven by the demand for a convenient, non-invasive alternative to the conventional needle and syringe injection. The earliest needle-free injectors became available as early as 1866, when the French company H.Galante manufactured an “Apparatus for aqua puncture”. Some of the needle-free injectors under development are:

(a) **Intragel®**: One of the prefilled disposable injectors, intragel, under development, is designed to use the nitrogen propelled device which has a blank drug capsule. The patient snaps off the tip, tears off the safety end and plunges the nozzle against the skin pressurized gas, and then pushes the liquid formulation through a narrow orifice into the skin.

(b) **Implajet®**: Implajet first pushes a tiny, potential “Pioneer tip” thorough the skin ahead of the drug. The tip pierces the tissue, creating a channel through which the therapeutic agent follows immediately.

(c) **Jet Syringe®**: The jet syringe, which can deliver up to 0.5 ml; can be configured with an adjustable dose fillable ampoule or proprietary prefilled glass ampoule for fixed dose applications. It is suitable for short-term infrequent injection therapies.

(d) **Iject®**: The design of Iject is based on Biojector 2000. It is a light weight, hand-held liquid NFI [Needle-free injectors]. It can deliver 0.1 to 1.0 ml subcutaneously and intramuscularly.

(e) **Mini-ject®**: The Mini-ject system utilizes a glass drug cartridge to accommodate for longer term drug storage and stability; a polycarbonate syringe, to accommodate for a wide range of pressure profiles; and a proprietary multiphase energy system that can deliver a specific pressure profile to ensure that the entire drug is delivered comfortably. It can target specific tissue layers including the dermal, subcutaneous and intramuscular layers.

(f) **Crossjet®**: It comprises three modules. The gas generator contains the chemical energy source and is triggered by the impact of a syringe, the drug container and the third module, nozzle, of polycarbonate with one or more orifices depending on the quantity of the formulation. The outer layers of the skin using a suitable energy source, usually a compact gas source, is used to propel a pre-measured quantity of liquid medicine through the skin and into the underlying subcutaneous tissue, without the use of a needle. The needle-free devices have been developed for the delivery of drugs such as insulin, sumatriptan and human growth hormone.

**Powderjet Device**

The core technology involves the high velocity injection of particle formulated drugs and vaccines into any physically accessible tissue. These may be for therapy or prevention of disease and may be small molecules, peptides, proteins and genes. The Powderjet system involves the propulsion of solid drug particles into the skin by means of high-speed gas flow. This needle-free method is painless and causes no bleeding.
and damage to the skin. The use of compressed gas to force solid drug particle through a convergent divergent nozzle was reported by Bellhouse et al. using compressed helium. Drug particle velocities of up to 800 m/s were obtained at the nozzle exit. Adjusting the momentum density of the particles within the gas flow optimizes the depth of penetration of the drug particles. Particle velocity is controlled within the device by three parameters namely nozzle geometry, membrane burst strength and gas pressure. Powderject system consists of a gas canister that allows helium gas at high pressure to enter a chamber at the end of which drug cassette containing powdered drug between two polycarbonate membranes. At the release, virtually instantaneous rupture of both membranes causes the gas to expand rapidly, forming a strong shock wave that travels down the nozzle at speed of 600–900 m/s. Powderject device has been reported to successfully deliver testosterone, lidocaine hydrochloride, and macromolecules such as calcitonin and insulin.

**Other Enhancement Techniques**

**Transfersomes**

To date, the most promising transdermal drug carrier is the recently developed and patented Transfersome® which penetrates the skin barrier along the transepidermal moisture gradient. This leads the carriers through the “virtual “pores between the cells in the organ without affecting its biological and general barrier properties. Lipid – based suspensions, such as liposomes and niosomes, have been proposed as low-risk drug carriers. Transfersome carriers can create a highly concentrated drug depot in the systemic circulation. Liposomes are microscopic bilayer vesicles, which are usually made of phospholipids (mainly phosphatidylcholine) and cholesterol, contain both hydrophilic and lipophilic portions and can serve as carriers for polar and non polar drugs. Niosomes have a similar morphology, but are made of nonionic surfactants, typically alkyl poloxyethylene ethers, mixed with cholesterol. Transfersomes contain at least one component that controllably destabilizes the lipid bilayers and thus makes the vesicles very deformable. Additives useful for this purpose are bile salts, polysorbates, glycolipids, alkyl or acyl – poly ethoxylenes etc. Transfersome carriers loaded with various agents of different molecular size and lipophilicity (lidocaine, tetracaine, cyclosporine, diclofenac, tamoxifen, etc.) have been shown to cross the skin barrier. In addition, polypeptides such as calcitonin, insulin, α- and γ-interferon, and, Cu – Zn super oxide dismutase, serum albumin, and dextrose have been successfully delivered across the skin with transfersome carriers.

**Medicated Tattoos**

Med-Tats is a novel means of delivering compounds transdermally and is produced by Lipper–Man Ltd [Morristown, N.J.]. Medicated Tattoo (Med-Tat) is a modification of temporary tattoo which contains an active drug substance for transdermal delivery. Med–Tats are applied to clean, dry skin in the same manner as traditional temporary tattoos and, according to Lipper –Man Ltd, are not unsightly but rather are attractive and fun to wear. There is no predetermined duration of therapy for Med–Tats; instead, the manufacturer provides a color chart that can be compared to the color of the patient’s tattoo to determine when the tattoo should be removed. This visual comparison, which relies on the dyes incorporated into the patch, introduces a significant amount of interpatient variability. Drugs and other compounds used in Med-Tats prototypes include acetaminophen and vitamin C. The main advantage of medicated tattoos is the
delivery of drugs to children who cannot tolerate more traditional dosage forms.

**Skin Abrasion**

The abrasion technique involves the direct removal or disruption of the upper layers of the skin to facilitate the permeation of topically applied medicaments. Some of these devices are based on techniques employed by dermatologists for superficial skin resurfacing (e.g., microdermabrasion) which are used in the treatment of acne, scars, hyperpigmentation and other skin blemishes. Microciscissuing is a process which creates microchannels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules. Carlisle Scientific [Carlisle, MA] is currently in the process of developing a pen-like handheld device called the microscissioner. In addition, Med Pharm Ltd. [Charlbury, United Kingdom] had recently developed a novel dermal abrasion device (D3S) for the delivery of difficult to formulate therapeutics ranging from hydrophilic low molecular weight compounds to biopharmaceuticals. In vitro data have shown that the application of the device can increase the penetration of angiotensin into the skin 100-fold compared to untreated human skin.

**Controlled Heat Aided Drug Delivery (CHADD) System**

Heat increases skin temperature that leads to increase in microcirculation and blood vessel permeability, thus facilitating drug transfer to the systemic circulation. Drug solubility, both in the patch formulation and within the skin increase with a rise in temperature. Zars, Inc [Salt Lake City, UT, USA] has developed a technology that takes advantage of heat’s ability to increase transdermal permeation. This technology is known as Controlled Heat-aided Drug Delivery (CHADD) system. CHADD system is a small heating unit that can be placed on top of a traditional patch. An oxidation reaction within the unit provides heat at a limited intensity and duration. The disadvantage of this technology is that heat can slightly compromise the barrier function of the skin.

**Laser Radiation**

This method involves direct and controlled exposure of a laser beam to the skin which results in the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs. In 1991, Nelson et al. reported that mid-infrared laser (1 J/cm²) ablation of pig stratum corneum enhanced the permeation of both hydrocortisone and interferon. A handheld portable laser device has been developed by Norwood Abbey Ltd. (Victoria, Australia) that has been approved by the U.S. and Australian regulatory bodies for the administration of a topically applied anaesthetic. However, the structural changes caused by this technique still need to be assessed for safety and reversibility, particularly at the higher intensities that may be needed to enhance the penetration of large molecular weight solutes where evidence of deeper level ablation effects exist.

**Magnetophoresis**

Magnetophoresis is a novel approach in enhancing drug delivery across biological barriers. Benzoic acid, a diamagnetic substance, was selected as a drug candidate. The influence of magnetic field strength on diffusion flux was determined and was found to increase with increasing applied strength.
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<th>MANUFACTURER</th>
<th>INDICATION</th>
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<td>Thera tech/Protocol and Gamble</td>
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<td>Testosterone</td>
<td>Alza</td>
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**Table-1: TRANDERMAL PATCHES AVAILABLE IN MARKET [11]**

**EVALUATION PARAMETERS [12-15]**

1. Interaction studies:
Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation.
development. Interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc.

2. **Thickness of the patch:**
The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

3. **Weight uniformity:**
The prepared patches are to be dried at 60°C for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

4. **Folding endurance:**
A strip of specific area is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

5. **Percentage Moisture content:**
The prepared films are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

\[
\text{Percentage moisture content} = \left(\frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}}\right) \times 100.
\]

6. **Percentage Moisture uptake:**
The weighed films are to be kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.

\[
\text{Percentage moisture uptake} = \left(\frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}}\right) \times 100.
\]

7. **Water vapour permeability (WVP) evaluation:**
Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula

\[
\text{WVP} = \frac{W}{A}
\]

Where, WVP is expressed in gm/m2 per 24hrs, W is the amount of vapour permeated through the patch expressed in gm/24hrs and A is the surface area of the exposure samples expressed in m2.

8. **Drug content:**
A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples.

9. **Uniformity of dosage unit test:**
An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2m membrane filter and analysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated.

10. **Polariscope examination:**
This test is to be performed to examine the drug crystals from patch by polariscope. A specific surface area of the piece is to be kept on the object slide and observe for the drugs crystals to distinguish whether the
drug is present as crystalline form or amorphous form in the patch.

11. Shear Adhesion test:
This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of crosslinking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time taken for removal, greater is the shear strength.

12. Peel Adhesion test:
In this test, the force required to remove an adhesive coating from a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180° angle, and the force required for tape removed is measured.

13. Thumb tack test:
It is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected.

14. Flatness test:
Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

15. Percentage Elongation break test:
The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula.

\[ \text{Elongation percentage} = \frac{L_1 - L_2}{L_2} \times 100 \]

Where, \( L_1 \) is the final length of each strip and \( L_2 \) is the initial length of each strip.

16. Rolling ball tack test:
This test measures the softness of a polymer that relates to tack. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

17. Quick Stick (peel-tack) test:
In this test, the tape is pulled away from the substrate at 90°C at a speed of 12 inches/min. The peel force required to break the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

18. Probe Tack test:
In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams.

19. In vitro drug release studies:
The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus
was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5-mL aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

20. **In vitro skin permeation studies:**
An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using an electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm-2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm-2).

21. **Skin Irritation study:**
Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

22. **Stability studies:**
Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°C and 75±5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content.

**CONCLUSION:**
The TDDS review articles provide valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who is involved in TDDS. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS a realistic practical application as the next generation of drug delivery system.

**REFERENCES:**
3. Tanner T, Marks R. Delivering Drugs by the Transdermal Route: review and comment. Skin Research and Technology .2008;14:249-260