Chapter 1 Introduction
1.1 CONTROLLED DRUG DELIVERY

Pharmaceutical industry today is in pursuit of achieving perfection in drug dosage and delivery. One giant leap in this direction is the controlled release concept and technology. Controlled release delivery of drugs is a logical alternative to the other conventional dosage forms due to patient compliance and because it gives prolonged drug levels with less differences in the peak and trough levels, which is desired for best action and minimum side effects. The new dosage forms and drug delivery systems provide excellent improvement in drug therapy by controlled release or drug targeting and are often referred to as Novel drug delivery systems which have been classified by Longer et al, in 1985. The more traditional forms like tablets, capsules, sublingual, give short burst and sometime higher concentration than desired which is deleterious, especially for the drugs, which have narrow therapeutic window. This as well as other factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. A dosage from that release one or more drugs continuously in a predetermined fashion for a fixed period of time either systemically or to a specified target-organ in a controlled drug delivery system. The advent of drug delivery systems brings rate-controlled delivery with fewer side effects, increased efficacy and constant delivery. The primary objective is to ensure safety, patient compliance and improved efficacy of drugs.

1.2 WHAT IS A TRANSDERMAL DRUG DELIVERY DEVICE?

Transdermal drug delivery device, which may be of an active or a passive design, is a device, which provides an alternative route for administering medication. These devices allow for pharmaceuticals to be delivered across the skin barrier. This approach to drug delivery offers many advantages over traditional methods. As a substitute for the oral route, Transdermal drug delivery enables avoidance of gastrointestinal absorption, with its associated pitfalls of enzymatic and pH associated deactivation. This method also allows for reduced pharmacological dosaging due to the shortened metabolism pathway of the Transdermal route versus the gastrointestinal pathway. Transdermal drug delivery system releases its active
ingredient through the patient’s skin providing a uniform blood levels. In addition since the active ingredient moves with the blood stream directly into the targeted organ, the effective dose can be lower than that in the traditional drug type. The Transdermal Delivery System permits constant dosing rather than the peaks and valleys in medication level associated with orally administered medication. Multi-day therapy with a single application, rapid notification of medication in the event of emergency, as well as the capacity to terminate drug effects rapidly via patch removal, are all further advantages of this route. (Taub et al.in 2001)

As a result of pharmaceutical technology research, the Transdermal drug delivery system emerged in pharmaceutical technology in the early 1970s. The Transdermal delivery of drugs has been a subject of research interest since the introduction of the first Transdermal product “Transderm-scop” for the delivery of scopolamine, in 1981. Some Transdermal therapeutic systems have been successfully developed and commercialized to accomplish goals of systemic medication. The therapeutic areas of Angina pectoris, hormone replacement, hypertension, and motion sickness, smoking cessation and pain control have a Transdermal product as part of their armamentarium. Physicians and patients have both accepted Transdermal’s as a logical alternative to other dosage forms. In spite of having all the advantages and being on the top priority of Research and Development divisions of most of the pharmaceutical companies in India, none of the Indian companies have been able to launch a Transdermal delivery system. Reasons being:

The Transdermal technology is very closely guarded and well protected by the patent laws of western countries, where most of the work was carried out.

Only a handful of existing drugs have the intrinsic properties, which allow the formulation into Transdermal system. A major limitation to its wide application is the very low skin permeability of most drugs.

1.2.1 TRANSDERMAL DELIVERY – BENEFITS AND LIMITATIONS

Delivery of pharmaceuticals and biopharmaceuticals via the skin, which envelops the body surface, have been learnt to have the potential advantage of bypassing the hepato-gastrointestinal "first-pass" elimination associated with oral administration.
This nonparenteral route of systemic delivery is non-invasive in nature and can provide both the benefits of direct entry of systemically-active agents into the systemic circulation, like a parenteral route of administration but without its health hazards, as well as maintain a steady, prolonged and therapeutically-effective level, which duplicates a closely monitored intravenous infusion. TDD systems are self-contained, discrete dosage forms which, when applied to intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation.

It has been recognized that the Transdermal rate controlled drug delivery offers one or more of the following potential biomedical benefits. (Chien, 1987)

1. Avoids risks and inconveniences of intravenous therapy.

2. Prevents the variation in the absorption and metabolism associated with oral administration.

3. Permits continuous drug administration and use of drug with short biological half-life.

4. Increases efficacy through the bypass of hepatic first pass elimination.

5. Reduces chance of over or under dosing as a result of prolonged preprogrammed delivery of drug at the required therapeutic rate.

6. Provides a simplified therapeutic regimen leading to a better patient compliance.

7. Presents a rapid termination of medication, if needed by simply removing the Transdermal delivery system from the skin surface.

Limitations of Transdermal Delivery System.

Only a small percentage of drugs can be delivered by the Transdermal route because of these limitations viz.

1. Difficulty of permeation through human skin
2. Only the relatively potent drugs can be administered through this route.

3. Drugs, which irritate the skin and show allergic response, cannot be given.

4. Skin irritation and contact dermatitis of excipients and use of enhancers to increase percutaneous absorption of the drug is another major limitation.

1.3 FACTORS AFFECTING TRANSDERMAL PERMEABILITY

The principal transport mechanism across skin is by the passive diffusion through primarily the trans-epidermal route at steady state or through trans-appendageal route at initial steady state. The factors, which affect the Transdermal permeability, are as follows:

1.3.1 DRUG SELECTION

Feasibility of drug for Transdermal delivery is based on three relevant parameters (Gary, 1987)

- Biological criteria
- Physico-chemical conditions
- Pharmacokinetic behaviour

A. Biological factor

Biological factors, which may affect the feasibility of Transdermal delivery of the drug, are:

a. Transdermal index: The therapeutic agent for the Transdermal administration must be potent as the stratum corneum has excellent barrier properties. In general therefore, Transdermal drug delivery is suitable only for drugs for which the daily dose is of the order of a few milligrams.

b. Drug inactivation: The ability of Transdermal delivery to avoid drug inactivation through hepatic first pass metabolism, is best exemplified by
nitroglycerin which is not only degraded by the liver but also by circulating red blood corpuscles.

c. Biological Half-life: For a drug to be administered by Transdermal route half-life should be short. For drugs with longer half-life attainment of steady state plasma levels of drugs gets delayed considerably as percutaneous absorption is a slow process.

B. Physicochemical properties of the drug

The choice of drugs to be delivered by Transdermal route is difficult due to three basic limitations, inadequate Permeability through skin, inadequate tolerability of drug by skin and clinical need. Currently only a few drugs can be delivered by this route.

a. Partition Coefficient: Drugs, which have partition coefficient of less than -1, have difficulty in distributing from the device into the stratum corneum. The drug with partition coefficient less than two have potential problem in achieving a steady state plasma concentration in a reasonable time span. This is due to drug being held up in the stratum corneum where a reservoir can be established. Ionized materials penetrate the skin poorly. The partition coefficient of a drug molecule may be altered by chemical modification of its functional groups. If it can be done without effecting the pharmacological activity of the drug. Membrane partition increases exponentially as the length of the lipophilic alkyl chain increases. Varying the vehicle pH may also alter the partition coefficient of the drug molecule.

b. pH Conditions: With moderate pH values, the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their Transdermal permeability. Ionized materials penetrate the skin poorly. When pKₐ differs considerably from pH, it may not be possible to administer the drug in unionized form.

c. Molecular weight: Diffusion of drugs in polymers and skin layers is more sensitive to molecular size than transport in liquids. The more the molecular
weight, the less will be the diffusion rate. Drugs having molecular weight of less than 1000 are most suitable for Transdermal delivery.

d. Melting point: A reasonable linear correlation was observed between log (flux) and reciprocal of the melting point of the drug, indicating that the lower the melting point, the better the permeation.

e. Penetrant Concentration: Assuming a membrane limited transport, an increase in the concentration of dissolved drug causes a proportional increase in the flux, when assuming a membrane limited transport. At concentrations higher than the solubility, excess solid drug functions as a reservoir and helps in maintaining a constant drug concentration for a prolonged period of time.

C. Pharmacokinetic behaviour

The kinetic parameters associated with release of drug from Transdermal patch can be summarized as

a. F (K) describes the input kinetic from the Transdermal device.

b. $K_a$ shows that there will be competition between the patch and the stratum corneum for the drug. Smaller value of $K_a$ indicates about better design of Transdermal system.

c. $K_1$ and $K_2$ are the first order rate constants. $K_1$ describes drug transport across the stratum corneum and $K_2$ across the viable tissue. Therefore $K_1$ and $K_2$ are proportional to the corresponding diffusion coefficients through these layers of skin.

d. $K_3$ describes the affinity of drug for stratum corneum in comparison to viable epidermis and allows for greater interaction between drug and stratum corneum. The ratio of $K_1/K_2$ for a drug may be viewed as an effective partition coefficient between the stratum corneum and viable epidermis and has been shown to be linearly correlated with the Octanol-Water partition coefficient ($K$) of that drug.
1.3.2 PHYSICOCHEMICAL PROPERTIES OF DRUG DELIVERY SYSTEM

For the availability of drug for systemic circulation from TDD systems, events taking place can be summarized as:

a. Drug transport within the delivery systems to device skin interface.

b. Partitioning of drug from the delivery system into stratum corneum.

c. Diffusion of drugs the stratum corneum

d. Drug partitioning between stratum corneum and the viable epidermis.

e. Transport of drug into the viable tissues. Drug uptake by the cutaneous microcapillary network and subsequent systemic distribution.

Diffusion: The transport characteristics of a drug are determined primarily by its size and level of interaction with delivery systems, stratum corneum and viable epidermis.

Partitioning: For better penetration of drug, the molecule must favor the stratum corneum over the device. Moreover, partitioning of drug molecule from stratum corneum to viable tissue must be reasonably balanced to ensure adequate penetration of drug into systemic circulation. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.

The predominant events involved in the delivery of drug from the Transdermal device are partition and diffusion.

In case of membrane-moderated device, first the drug will partition from the reservoir into the polymer matrix that comprises the rate limiting membrane, then the diffusion will occur by concentration gradient at a rate which will be controlled by the diffusion coefficient of the drug in the polymer. Diffusion coefficient will be a function of nature of polymer and the molecular size of the drug.
1.3.3 RELEASE CHARACTERISTICS

The solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depends on the following factors:

a. Whether the drug molecules are dissolved or suspended in the delivery system.

b. The interfacial partition coefficient of drug from the delivery system to the skin tissue.

c. pH of the vehicle.

1.3.4 COMPOSITION OF THE DRUG DELIVERY SYSTEM

Composition of the drug delivery system not only affects the rate of drug release, but also the permeability of stratum corneum by means of hydration, mixing with skin lipids or other sorption promoting effects.

1.4 TYPES OF TRANSDERMAL DRUG DELIVERY SYSTEM/DEVICES

Several technologies have been successfully developed to provide a rate-controlled release and skin permeation of drugs. To be more precise, there are two concepts in the design of Transdermal delivery namely, the reservoir type and the membrane type. The others are the extensions of these two concepts. These technologies can be classified as: (Sharad, 1989)

1.4.1 RESERVOIR TYPE DEVICES

Several TDDS have been formulated from this technology e.g. Transderm - Scop (Ciba/Alza), Transderm-Nitro (Ciba/Alza), Estraderm (Ciba-Geigy), Nicoderm (Alza), Catapres) TTS (Boehringer/Ingelheim).

The drug is stored in a reservoir from which it diffuses through a rate limiting membrane to the site of absorption. In this 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. The drug molecules are permitted to release only through the rate controlling polymeric membrane. In the drug reservoir, the drug solids are either dispersed in a solid polymeric matrix or
suspended in a unleachable, viscous liquid medium, e.g., a silicone fluid to form a paste like suspension. The rate limiting membrane can be a micro porous or a non-porous polymeric membrane e.g. ethylene vinyl acetate copolymer, with a defined drug permeability property. On the external face of the polymeric membrane, a thin layer of drug compatible, hypoallergenic adhesive polymer, e.g. silicone or poly acrylate adhesive, may be applied to achieve an intimate contact of the Transdermal system with the skin surface (Figure 1.1). The rate of the drug release from this type of Transdermal system can be tailored by varying the polymer composition, permeability co-efficient and/or thickness of the rate limiting membrane and adhesive. In concept, this type of system is good when the stratum corneum is not the principal rate-limiting barrier for the diffusion of drugs and the rate control from the device is desired.

The intrinsic rate of drug release from membrane controlled Transdermal delivery devices can be expressed as follows

\[
\frac{dQ}{dt} = \frac{C_r}{\frac{1}{P_{rm}} + \frac{1}{P_a}}
\]

where,

- \( P_{rm} \) is the permeability coefficient of the rate controlling membrane
- \( P_a \) is the permeability coefficient of the adhesive
- \( C_r \) is the concentration of the drug in the reservoir.

A. Multi-reservoir Rate-limiting Devices

A characteristic feature of this system is that an enhancer is stored in the compartment separate from a drug reservoir. (Figure 1.2). The system has a conventional impermeable backing of materials followed by a reservoir of a vehicle or an enhancer, a rate limiting membrane and a drug reservoir in the adhesive. This reservoir may also contain stabilizer, diluents and other inert materials such as a gelling agent.
A similar type of system containing a peripheral ring adhesive may also be prepared (Figure 1.3). This may be preferred when the drug and the enhancer have lower than desired permeation rates through the adhesive layer.

B. Reservoir-type Devices without Rate-limiting Membrane

Devices with rate limiting adhesive layer: The adhesive diffusion controlled reservoir type of device (Figure 1.4) differ in that a dispersion of drug in adhesive polymer (reservoir) is spread as a thin layer on the impermeable backing. Layers of rate limiting adhesive polymers without any drug are then spread on the top of the reservoir layer. This concept has been utilized by Pharma-Schwarts (Germany) in the development of their transdermal Nitroglycerin delivery system, Deponit. The release rate from such a system may be described as follows.

\[
\frac{dQ}{dt} = \frac{KDC}{h}
\]

where,

\[K = \text{Partition coefficient of the drug between reservoir and adhesive layer,}\]

\[D = \text{Diffusion coefficient of adhesive,}\]

\[h = \text{Thickness of adhesive and}\]

\[C = \text{Concentration of drug in reservoir.}\]

C. Microencapsulated Drug Reservoir Type Devices:

When the drug is dispersed as microcapsules all throughout the contact adhesive, the rate-limiting step in the delivery is the diffusion of the drug through the walls of the microcapsules. The permeation rate of drug across the microcapsule is a function of the porosity, thickness and diffusion coefficients of the membrane and also of the solubility of the drug in the membrane. Obviously, the most important component in such a system is the micro encapsulation agent.
The microcapsules are then dispersed into pressure sensitive adhesives and a thin layer of the dispersion is cast on the backing material (Figure 1.5). The thickness of the adhesive layer varies with the amount of drug required for loading.

D. Reservoir Devices with solubility Membrane:

Two rate-controlling steps characterize this type of system. First step is the polymer matrix material that dissolves the drug and controls the rate of passage of drug in the solubility membrane, then diffusion of the drug through the solubility membranes.

In this type of system the drug is dispersed in a polymer matrix as reservoir, which is sandwiched, between an impermeable backing and solubility membrane. This type of drug delivery system could be described as a simplified version of the membrane-moderated drug delivery system. In this system the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive, by solvent casting, onto a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. On the top of the drug reservoir layer, layers of non-medicated, rate controlling adhesive polymer of constant thickness are applied to produce an adhesive diffusion-controlled drug delivery system (Figure 1.6). Examples are Deponit (Pharma-Schwartz), Frandol tape (Toaeiyo).

1.4.2 MATRIX-TYPE TRANSDERMAL DEVICES

The drug in the matrix type system is uniformly dispersed throughout a hydrophilic or lipophilic polymer matrix, which is then cured into a polymer disk of predetermined thickness and surface area. The matrix is then glued to aluminum foil, which is sealed to drug-impermeable backing through an absorbent pad. Most such systems do not give an adhesive overlay but instead possess a peripheral adhesive ring.

A. Polymer Matrix- Type Transdermal Devices

This device is exemplified by Nitro-Dur (Figure 1.7) (Key pharmaceuticals). The critical components in the design fall into four categories. (a) Aluminum foil package (b) absorbent pad (c) adhesion components and (d) Polymer- GTN (Glyceryl trinitrate) matrix).
The aluminum foil package has an aluminum foil release liner (cover strip) and an aluminum foil base plate. The GTN matrix is completely surrounded by these two components during its shelf life. At the time of application, the aluminum foil cover strip is peeled off, exposing the matrix. The foil base plate stays behind the matrix for the duration of the application and thus serves as a barrier for GTN and other liquid components of the matrix.

This system has a micro porous adhesive tape just above and around the base plate and a non-occlusive absorbent pad just underneath the backing. The micro porous adhesive tape allows the permeation of excessive moisture and maintenance of good adhesion during wear.

The pressure-sensitive adhesive is behind the release liner at the periphery of the matrix to provide adhesion of the unit to the skin. The release from the adhesive type devices show a square route of time dependence.

\[ \frac{dQ}{dt} = \frac{LC_mD_m^{1/2}}{2T} \]

where, \( L \) is the loading dose in the matrix, \( C_m \) is the concentration of the drug in the matrix, \( D_m \) is the diffusion coefficient of the drug in the polymer and \( T \) is the time. At steady state the release may be expressed as follows:

\[ \frac{Q}{L^{1/2}} = \left(2L - C_m \right)^{1/2} \]

B. Micro porous matrix type devices

The micro porous matrix is impregnated with a diffusive medium in which the drug can dissolve and which also determines the drug release rate. By varying composition, pore size, effective thickness, of the micro porous rate controlling material, viscosity of formulation and impregnating solvent, the delivery rate can be controlled and varied. The micro porous matrix containing the drug rests on pressure sensitive adhesive layer. The patented micro porous rate controlling device consists of a backing material and a drug containing micro porous matrix, which rests on the
pressure sensitive adhesive layer. The drug passes through the rate controlling micro porous material, which continuously monitors the flow of the drug through the skin by monitoring the viscous or diffusive transfer mechanisms.

C. Hydrophilic matrix devices

The device consists of semisolid state polymeric matrix acting as a reservoir as well as hydrophilic bridge to the skin, which facilitate the drug permeation into and through the skin by wetting the skin. The hydrophobic matrix consists of polysaccharides such as polyvinyl sulphonates, PVA, PVP, polyacrylates and polyacrylamides. The matrix also contains hydrogen-bonding liquids such as water, glycerol, propylene glycol and polyethylene glycol. The formulation may also include an aqueous emulsion of adhesive to improve the tack of the patch. A gel is formed at room temperature; however heating may also be used to facilitate gelling. The hydrogen bonding rearrangement results in a properly cross-linked gel that is stable and swell in high humidity conditions. The system is self-adhering and can be removed and reapplied. The Transdermal delivery rate from such a system is a function of the reservoir (matrix) formulation, the hydrophilic bridges formed between the system and the skin and the drug concentration within the aqueous phase of the skin.

D. Adhesive matrix devices

In this type of system the adhesive matrix also acts as a reservoir of drug and represents a new concept in Transdermal delivery. This type of system is exemplified by Nitro Dur II (Figure 1.8) (Key pharmaceuticals). In Nitro Dur II nitroglycerin is dispersed in an acrylic adhesive. This acts as an adhesive matrix, which is coated onto an adhesive type of backing material with clear polypropylene type of release liner. The rate of drug release from this type of Transdermal drug delivery (TDD) systems can be expressed as

\[
\frac{dQ}{dt} = \left(\frac{K_{a/r} - D_{a}}{r}\right) \frac{C_{a}}{h_{a}}
\]
where, \( K_{av} \) is Partition coefficient for interfacial partitioning of drug from reservoir to adhesive layer, \( h_a \) is Thickness of the adhesive layer and \( D_a \) being Diffusion coefficient of the adhesive layer.

1.4.3 MICRO SEALED DELIVERY DEVICES

This type of drug delivery system can be considered as a combination of the reservoir type and matrix dispersion type of drug delivery system (Figure 1.9). The drug reservoir is formed by first suspending the drug solids in an aqueous solution of water soluble polymer and then dispersing homogenously the drug, suspension in a lipophilic polymer by high shear mechanical force, to form thousands of unleachable, microscopic 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 thickness. The medicated disc is positioned at the center and surrounded by an adhesive film.

This hybridization of the reservoir and matrix types of system is represented by Nitro-Disc (G.D. Searle Pharmaceuticals, Chicago)
Figure 1.1 Reservoir type devices with rate limiting membrane

Figure 1.2 Multireservoir Rate-limiting device

Figure 1.3 Multireservoir Rate-limiting device with a peripheral ring adhesive

FIGURE 1: TRANSDERMAL DRUG DELIVERY DEVICES
Figure 1.4 Adhesive diffusion controlled reservoir type devices

Figure 1.5 Microencapsulated Drug Reservoir type Devices

Figure 1.6 Reservoir Devices with Solubility Membrane

FIGURE 1: TRANSDERMAL DRUG DELIVERY DEVICES
Figure 1.7 Polymer matrix Type Devices

Figure 1.8 Adhesive matrix type devices

Figure 1.9 Microsealed Delivery Devices

FIGURE 1: TRANSDERMAL DRUG DELIVERY DEVICES
1.5 ANATOMY AND FUNCTION OF HUMAN SKIN

Human skin provides an excellent barrier between the external environment and the body. It is self-repairing composite membrane which protects against physical, chemical, microbial, and radiological attack and performs a homeostatic role by controlling moisture and heat loss from the body. It also serves as a food reserve and a sensory organ transmitting external environmental information. Human skin may be subdivided into three mutually dependent layers.

The subcutaneous fatty layer (hyper dermis)

The overlaying dermis, and

The epidermis i.e. the outermost stratum Corneum of the skin.

<table>
<thead>
<tr>
<th>Layer</th>
<th>Thickness (mm)</th>
<th>Structure</th>
<th>Principle function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermis</td>
<td>0.2 (0.1-0.8)</td>
<td>Cells</td>
<td>Mechanical strength</td>
</tr>
<tr>
<td>Dermis</td>
<td>1-4</td>
<td>Fibers in matrix</td>
<td>Mechanical strength</td>
</tr>
<tr>
<td>Hypodermis</td>
<td>0-several mm</td>
<td>Fat</td>
<td>Insulation, Shock absorber</td>
</tr>
</tbody>
</table>

Constituents:

75-80% Proteins, 5-15% lipids and 5-10%, unidentified material on a day mid weight basis. The protein fraction predominantly comprises α-keratin (approximately 70%)
with some β-keratin (10%) and the cell envelope (5%). The lipid constituents vary with body site; the abdomen comprises neutral lipids (75%), sphingolipids (18%), polar lipids (5%) and cholesterol sulfate (2%). Phospholipids are largely absent, a unique feature for a mammalian membrane. The lipid composition of the intercellular domain of the stratum corneum has been well researched. The architecture of the horny layer may be modeled as a brick and mortar structure. In this model, the keratinized corneocytes function as protein "bricks" embedded in a lipid "mortar". The lipids construct multiple bilayers, despite the minimal charged phospholipid content, and it has been proposed that there is sufficient amphiphilic material in the lipid fraction, such as polar free fatty acids and cholesterol sulfate, to maintain a bilayer form. The precise molecular arrangement of intercellular lipid bilayers in the horny layer is still being investigated. Lipids covalently bound to the surface of corneocytes may play a part in determining the barrier function of the membrane. Additionally protein molecules may be intrinsically or extrinsically incorporated into the lipid bilayers.

- Permeation pathways through human skin
- Transport across the skin is by passive diffusion only.
- The horny layer provides the rate-determining barrier and the diffusants are rapidly cleared from the dermal side.
- The stratum corneum is uniform in character, although it is not homogenous
- The drug dissolves in the stratum corneum. Transport through Human Skin transport through human Stratum Corneum.
FIGURE 2: SIMPLIFIED STRUCTURE OF HUMAN SKIN
Figure 2.1: The "Brick and Mortar Model" of Stratum Corneum
Along the course of skin permeation, a drug molecule will encounter a number of diffusional resistances, which counteracts its penetration through various skin tissue layers.

<table>
<thead>
<tr>
<th>Route</th>
<th>Relative Surface Area (%)</th>
<th>Diffusional Pathway (µm)</th>
<th>Relative Vol. of Stratum Corneum (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcellular</td>
<td>99</td>
<td>25</td>
<td>90-99</td>
</tr>
<tr>
<td>Intercellular</td>
<td>0.7</td>
<td>350</td>
<td>1-10</td>
</tr>
<tr>
<td>Transfollicular</td>
<td>1.7</td>
<td>200</td>
<td>0.1</td>
</tr>
</tbody>
</table>

The total diffusional resistance ($R_s$) that a drug molecule has to overcome during the course of permeation across the skin tissues and the subsequent uptake by the capillary network for transport to the general circulation, is described\(^{14}\) mathematically by

$$R_s = R_{sc} + R_e + R_{pd} + R_t$$

$$= \frac{H_{sc}}{D_{sc}} + \frac{H_e}{D_e K_e} + \frac{H_{pd}}{K_{pd} D_{pd}} + \frac{1}{F_{cn} H_s}$$

Where,
\[ R = \text{diffusional resistance} \]

\[ H = \text{thickness} \]

\[ D = \text{diffusivity} \]

\[ K = \text{partition coefficient} \]

\[ K_{\text{sc}} = \text{Stratum corneum / vehicle or membrane partition coefficient} \]

Subscripts,

\[ S = \text{skin} \]

\[ S_{\text{c}} = \text{stratum corneum} \]

\[ e = \text{epidermis} \]

\[ p_d = \text{papillary layer} \]

\[ t = \text{transfer resistance} \]

\[ c_n = \text{peripheral blood flow rate} \]

The Transdermal permeability coefficient \((P_{sc})\) can be defined

\[
P_{sc} = \frac{1}{R_{sc}} = \frac{K_{pa} \cdot D_{pg}}{H_{sc}} \cdot \frac{1.16}{\left( -0.16/K_{p1} \cdot \frac{D_{pg}}{D_{tm}} \right) + 1 + 0.017 K_{p1} \cdot \frac{D_{tm}}{D_{pg}}} (3)
\]

Where,

\[ K_{pa} = \text{Distribution coefficient of the penetrant molecules between the} \]

\[ \text{Protein gel and the applied penetrant solution at equilibrium.} \]

\[ D_{pg} = \text{Diffusion of the penetrant molecule in protein gel.} \]
\( H^c \) = Thickness of the stratum corneum.

\( K_{pl} \) = Distribution coefficient of the penetrant molecule

\( D_{lm} \) = Diffusion of the penetrant molecules in lipid matrix.

If the drug is applied in simple solution form on to the skin surface in a simple solution form, the concentration of the drug (Cb) absorbed in to the body can be described by eqn. 4 if the pharmacokinetic pattern of the drug is known to follow, a simple one-compartment model.

\[
C_b = \frac{(Drug)_a}{V_d} \cdot \frac{K_a}{K_a - K_e} (e^{-K_c t} - e^{-K_e t})
\] (4)

Where,

\((Drug)_a\) = Amount of drug in the body.

\(V_d\) = Volume of distribution.

\(K_a\) = Rate constant for skin absorption.

\(K_e\) = Rate constant for drug elimination.

\(t\) = Time after drug administration.

The \(K_e\) rate term is replaced by a composite rate constant for drug elimination \(\beta\), if the pharmacokinetic pattern of the drug is best described by a multi-component open model.

If the drug is administered topically via a controlled release drug delivery system which releases the drug at a programmed rate of release and the rate of drug release from the drug delivery system is significantly slower than the rate of percutaneous absorption, then the process of drug release will play the rate controlling role to the blood level of a drug.
If the drug is released to the skin surface through a zero order drug delivery system, then at a steady state, a constant blood level will be achieved, which is a linear function of the rate of drug release \((K_0)\) and is inversely proportional to the rate constant for drug elimination \((K_e)\), and the volume of distribution \((V_d)\):

\[
InitialPhaseC_b = \frac{K_0}{K_e V_d} \left(1 - e^{-K_e t}\right)
\]  

\[
SteadyStateC_b = \frac{K_0}{K_e V_d}
\]

Eq. (6) indicates that the blood levels of a drug can be controlled in a desired therapeutic range by programming the magnitude of \(K_0\) value of the delivery system, (Since both \(K_e\) and \(V_d\) terms are the intrinsic pharmacokinetic properties of the drug molecule.)

On the other hand, if the drug is administered via a Transdermal drug delivery system that releases the drug molecules at the first order rate constant \((K_1)\) the blood level of the drug will be described by the equation. (7)

\[
C_b = \frac{K_1 (Drug)_{dds}}{(K_1 - K_e) V_d} \left(e^{-K_e t} - e^{-K_1 t}\right)
\]

In this case, \(C_b\) will be dependent on the drug dose level of the drug delivery system, \((Drug)_{dds}\).

Furthermore, if the drug is administered to the skin surface under a matrix diffusion-controlled process with the drug molecule released at a rate profile of \(Q\) versus \(t\) (or \(K_{1/2}\)), the blood drug level will be proportional to the square root of the drug dose level in the drug delivery system, \((Drug)_{dds}\).

\[
C_b = \frac{K_{1/2} (Drug)_{dds}^{1/2}}{(K_{1/2} - K_e) V_d} \left(e^{-K_e t} - e^{-K_{1/2} t}\right)
\]
1.7 *In Vitro* Evaluation Techniques

The aim of *in vitro* experiment in Transdermal Delivery is to understand and predict the delivery and penetration of a molecule from the skin surface into the body via the skin of living animal. Typically, this is achieved using a variety of skin diffusion cells and various experimental protocols. *In vitro*, an experimental design that will predict, exactly the penetration of the candidate molecule into the human body (*in-vivo*) should be used. The *in-vitro* evaluation involves the following three principal stages viz.,

- Delivery of the molecule to the skin surface.
- Passage of the molecule through the skin.
- Delivery of the molecule into the body *in vivo*, which is equal to the recovery of the molecule in *vitro*.

In general *in vitro* Transdermal delivery experiments are conducted on either vertically or horizontally arranged diffusion cells. The diffusion cells should be designed so that they satisfy the following requirements.

A. All materials should be assessed for their ability to absorb or adsorb the test penetrant.

B. Donor compartment.

- Easy access to deliver the penetrant to the skin.
- Stirred if possible.
- Temperature controlled.
- Control of evaporation for volatile vehicles and penetrants.

C. Membrane.

- For the study of penetration kinetics only human skin should be used.
- For vehicle/device release studies other barriers may be used,

- The skin sample should contain both stratum comeum and viable epidermis.

- A molecule of known penetration kinetics should be used prior to the test molecule to assess barrier function.

- Where applicable, metabolic viability of the epidermis must be assessed.

D. Receptor compartment

- Either flow-through or static.

- Temperature controlled.

- Sufficient volume to maintain infinite sink conditions.

- Stirred without obvious formation of boundary layers.

- Receptor fluid

- Should not compromise barrier function.

- Should be of favorable partitioning characteristics.

- Capable of maintaining epidermal viability where necessary.

Keeping all these features in mind, the In-vitro Transdermal cells should be developed. These cells provide a valuable tool in both guiding in vivo Transdermal drug delivery and for the testing of toxic or injurious compounds.
Figure 3.1 Glass Diffusion Cell

Figure 3.2 Vertical Diffusion Cell

Figure 3.3 Valia-Chien Skin Permeability System

Figure 3.4 Flow Through Diffusion Cell

FIGURE 3: TYPICAL DIFFUSION CELLS
Figure 3.5 Side-by-Side Permeability Cell

Figure 3.6 Glass Diffusion Cell consisting of a Lower Chamber With a Side arm

Figure 3.7 Skin Permeation Evaporation Cell

FIGURE 3: TYPICAL DIFFUSION CELLS
### 1.3 MARKETED FORMULATIONS

#### 1.3.1 TRANSDERMAL DRUG DELIVERY SYSTEMS – MARKETED FORMULATIONS

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Trade name / Manufacturer/ Design</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Scopolamine | Transderm-Scop (formerly Transderm-V)  
A film 0.2mm thick and 2.5 cm² with four layers. (1) A backing layer of tan coloured, aluminized, polyester film; (2) A drug reservoir of scopolamine, mineral oil, and polyisobutylene; (3) A microporous polypropylene membrane that controls the rate of delivery; (4) An adhesive formulation of mineral oil, polyisobutylene and scopolamine. A protective peel strip of siliconized polyester. | For prevention of nausea and vomiting associated with motion sickness. Programmed to deliver 0.5 mg of scopolamine over 3 days. |
| Nitroglycerin | Nitrocine (Schwarz Pharma)  
Nitroglycerin in a laminated matrix composed of polyvinyl chloride/polyvinyl acetate copolymer, di-(2-ethyl hexyl) phthalate, isopropyl palmitate, colloidal silicone dioxide, aluminium foil laminate, polyethylene foam and acrylic adhesive to provide a continuous source of active ingredient. Each unit is sealed in polyester foil-polyethylene-laminate. The bandage portion consists of medical grade acrylic-based adhesive backed with polyethylene | For treatment of angina pectoris. Designed to deliver for 24 hours. |
<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Trade name / Manufacturer/ Design</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>Transderm-Nitro (Ciba-Geigy) Four layered patch (1)Tan colored backing layer (Aluminized plastic) (2)Drug reservoir containing nitroglycerin adsorbed on lactose colloidal silicone dioxide, and silicone medical fluid.(3) An Ethylene -Vinylacetate copolymer membrane that is permeable to nitroglycerin.(4)A layer of hypoallergenicSilicone adhesive</td>
<td>For treatment of angina pectoris. Designed to provide controlled release of nitro - glycerin for a 12 hour period</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Prostep (Ledrle Laboratories) Nitroglycerin in a hydrogel matrix. Contains (1)Foam tape and acrylate adhesive,(2) Backing foil, Gelatin and low density Polyethylene coating. (3) Nicotine gel matrix.(4) Protective foil with well. (5) Release liner which overlies the adhesive layer and must be removed prior to use. System is packed in child resistant pouches.</td>
<td>For treatment of Angina pectoris. Designed to provide a controlled release of Nitroglycerin for a 24 hour period</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Nitrodisc (Searle) A patented Microseal drug Delivery system consisting of a solid, nitroglycerin impregnated polymer bonded to a flexible, nonsensitizing adhesive bandage. Inactive ingredients are Lactose, isopropyl palmitate, mineral oils, polyethylene glycol, water, silicone rubber, plasticizers, Aluminium foil laminate, polyethylene foam and acrylic adhesives.</td>
<td>For treatment of Angina pectoris. Designed to provide a controlled release of Nitroglycerin for a 12 hour period</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Deponit (Wyeth-Ayerst) Nitroglycerin in a matrix system</td>
<td>Same as above.</td>
</tr>
<tr>
<td>Therapeutic Agent</td>
<td>Trade name / Manufacturer/ Design</td>
<td>Comments</td>
</tr>
<tr>
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</tr>
<tr>
<td>Nitroglycerin</td>
<td>Nitro-dur (Key) Nitroglycerin in a gel like matrix sealed in a polyester foil-polyethylene laminate</td>
<td>Same as above</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Mimitran (3M Riker) Nitroglycerin in adhesive sealed in foil/polymer laminate</td>
<td>Provides a controlled release of drug for 24 hours</td>
</tr>
<tr>
<td>1. Clonidine</td>
<td>Catapress –TTS (Coehring-Ingelheim) Catapres-TTS(Coehring-Ingelheim) Reservoir Type Four Layered patch (1) Backing Layer; (2) Drug reservoir; (3) Rate controlling membrane;</td>
<td>Designed to Delivery Clonidine at a Constant rate for seven days</td>
</tr>
<tr>
<td>2. Estradiol</td>
<td>Estraderm (Alza/Ciba-Giegy) Reservoir Type, Four layered patch (1). Transparent; (2) backing layer; (3) Drug reservoir; (4) Rate controlling Membrane; (5) Adhesive layer</td>
<td>Designed to release 17β-Estradiol continuously applied twice weekly over a cycle of three weeks.</td>
</tr>
<tr>
<td>Estracombi</td>
<td>Ciba</td>
<td>Estradiol and Norethisterone acetate for relief of menopausal symptoms and the prevention of post menopausal osteoporosis. Duration 3-4 days.</td>
</tr>
<tr>
<td>Therapeutic Agent</td>
<td>Trade name / Manufacturer/ Design</td>
<td>Comments</td>
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<tr>
<td>------------------</td>
<td>----------------------------------</td>
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</tr>
<tr>
<td>10. Nicotine</td>
<td>Habitrol (Basel Pharmaceuticals)</td>
<td>Designed for a systemic delivery of 21, 14, or 7 mg per day over 24 hours.</td>
</tr>
<tr>
<td>11. Nicotine</td>
<td>Nicoderm (Alza corporation for marion Dow Inc.)</td>
<td>To treat nicotine dependence and smoking cessation. Designed to provide 21, 14, or 7 mg nicotine per day over a 24 hour period.</td>
</tr>
<tr>
<td></td>
<td>Nicotrol (Mc Neil Consumer Products)</td>
<td>Designed for a systemic delivery of 15, 10, or 5 mg per day over 24 hours.</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Nicabate (Merion Merrell Dow)</td>
<td>Duration -1 day. To treat nicotine dependence and smoking cessation.</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Nicotinell (Ciba Geigy)</td>
<td>Same as above.</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Nicorette (Kabi Pharmacia)</td>
<td>Duration -16 hours. Same as above.</td>
</tr>
<tr>
<td>Therapeutic Agent</td>
<td>Trade name / Manufacturer / Design</td>
<td>Comments</td>
</tr>
<tr>
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</tr>
<tr>
<td>Testosterone</td>
<td>Testaderm (Alza US)</td>
<td>Designed for a systemic delivery of testosterone.</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Frandol Tape (Nitto Electric Comp.)</td>
<td>Duration - 1 day For the treatment of angina pectoris.</td>
</tr>
</tbody>
</table>

### 1.8.2 DOSAGE FORMS AND MARKETED PRODUCTS OF DICLOFENAC SODIUM / DIETHYL AMMONIUM.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Product</th>
<th>Dosage Form</th>
<th>Company name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac Sodium</td>
<td>Diclofax</td>
<td>Oral Tablets</td>
<td>Torrent</td>
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<tr>
<td></td>
<td>Diclonac</td>
<td>Oral tablets</td>
<td>Diclonac</td>
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<tr>
<td></td>
<td>Difisal</td>
<td>Oral tablets</td>
<td></td>
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<tr>
<td></td>
<td>Dilofen</td>
<td>Enteric coated Tablets</td>
<td>P&amp;B Labs</td>
</tr>
<tr>
<td></td>
<td>Fenac</td>
<td>Oral tablets</td>
<td>Core</td>
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<tr>
<td></td>
<td>Mobinak</td>
<td>Enteric coated tablets</td>
<td>Creslands</td>
</tr>
<tr>
<td></td>
<td>Nac - SR</td>
<td>Sustained release tablets</td>
<td>Systopic</td>
</tr>
<tr>
<td></td>
<td>Promax</td>
<td>Oral tablets</td>
<td>Aristo</td>
</tr>
<tr>
<td></td>
<td>Product</td>
<td>Dosage Form</td>
<td>Company name</td>
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<tr>
<td></td>
<td>Relaxyl</td>
<td>Enteric coated tablets</td>
<td>Franco Indian</td>
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34
<table>
<thead>
<tr>
<th>Drug</th>
<th>Product</th>
<th>Dosage Form</th>
<th>Company name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac Sodium</td>
<td>Voveran</td>
<td>Oral tablets</td>
<td>Hindustan Geigy</td>
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<tr>
<td></td>
<td>Voveran S.R.</td>
<td>Sustained release tablets</td>
<td>Hindustan Geigy</td>
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<tr>
<td></td>
<td>Zobid</td>
<td>Enteric coated tablets</td>
<td>S.G. Pharma</td>
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<tr>
<td></td>
<td>Promax injection</td>
<td>Injection</td>
<td>Aristo</td>
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<tr>
<td></td>
<td>Voveran injection</td>
<td>Injection</td>
<td>Hindustan Geigy</td>
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<tr>
<td></td>
<td>Zobid injection</td>
<td>Injection</td>
<td>S.G. Pharma</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Product</th>
<th>Dosage Form</th>
<th>Company name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac diethyl ammonium</td>
<td>Diclonac</td>
<td>Gel</td>
<td>Lupin</td>
</tr>
<tr>
<td></td>
<td>Diclonac</td>
<td>Gel</td>
<td>Lupin</td>
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<tr>
<td></td>
<td>Voveran</td>
<td>Emulgel</td>
<td>Hindustan Geigy</td>
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<tr>
<td></td>
<td>Inac</td>
<td>Gel</td>
<td>B.P.R.L</td>
</tr>
<tr>
<td></td>
<td>Diclomax</td>
<td>Gel</td>
<td>Torrent</td>
</tr>
<tr>
<td></td>
<td>Diclomol</td>
<td>Gel</td>
<td>Win-Medicare</td>
</tr>
<tr>
<td></td>
<td>HaloranSR</td>
<td>Gel</td>
<td>Hindustan anti biotics</td>
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</tbody>
</table>
### 1.8.3 Dosage Forms and the Marketed Products of Ketorolac Tromethamine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Product</th>
<th>Dosage Form</th>
<th>Company name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketorolac tromethamine</td>
<td>Zorovon</td>
<td>Oral tablets</td>
<td>Sun Pharmaceuticals</td>
</tr>
<tr>
<td></td>
<td>Zorovon SR</td>
<td>Sustained release</td>
<td>Sun Pharmaceuticals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tablets</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zorovon Injection</td>
<td>Injection</td>
<td>Sun Pharmaceuticals</td>
</tr>
<tr>
<td>Disket</td>
<td>Tablets</td>
<td>Alkem</td>
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</tr>
<tr>
<td>Kelac</td>
<td>Tablets</td>
<td>Alkem</td>
<td></td>
</tr>
<tr>
<td>Nodine</td>
<td>Tablets</td>
<td>Protec</td>
<td></td>
</tr>
<tr>
<td>Torvin</td>
<td>Injection</td>
<td>Torrent</td>
<td></td>
</tr>
<tr>
<td>Ketanov</td>
<td>Tablets &amp; Injection</td>
<td>Ranbaxy</td>
<td></td>
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