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# TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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## INTRODUCTION

The Transdermal drug delivery system (TDDS) also known as patches are the dosage form designed to deliver a therapeutic amount of drug across the patient's skin. Throughout the last two decades transdermal patch has been proven technology that offers the variety of significant benefit over other dosage form. A skin patch uses a special membrane to control the rate at which liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. Transdermal delivery 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 which often causes undesirable side effects.

## ADVANTAGES

They can avoid first pass metabolism and gastrointestinal incompatibility. They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs. They are non invasive providing the inconvenience of parentral therapy. They avoid the fluctuation in drug levels. Maintains the plasma drug concentration of potent drug.

They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration. They have greater patient compliance due to elimination of multiple dosing profile. They have ability to deliver the drug to the specific site. They have fewer side effects than oral medication or supplements. Transdermal patch is easier to use and remember. These patches are cost effective. It is an alternate to the people who cannot take the supplements orally.

They are easily and rapidly identified in emergencies (for example, unresponsive, unconscious, or comatose patient) because of their physical presence, features, and identifying markings.

**DISADVANGTAGES**

Only potent drugs are suitable candidates for transdermal delivery because of natural limits of drug entry imposed by skin's impermeability. For example ionic drugs and drug formulation causing skin irritation are not suitable for transdermal drug delivery system.

Transdermal delivery cannot deliver the drug of large molecular size. TDDS cannot achieve high drug level in blood/plasma. The use of transdermal drug delivery may be uneconomical. The delivery system cannot be used for drugs requiring high blood levels.

Not practical, when the drug is extensively metabolized in the skin and when molecular size is great enough to prevent the molecules from diffusing through the skin.

**VARIOUS CATAGORIES OF DRUGS USED IN TRANDERMAL DELIVERY**

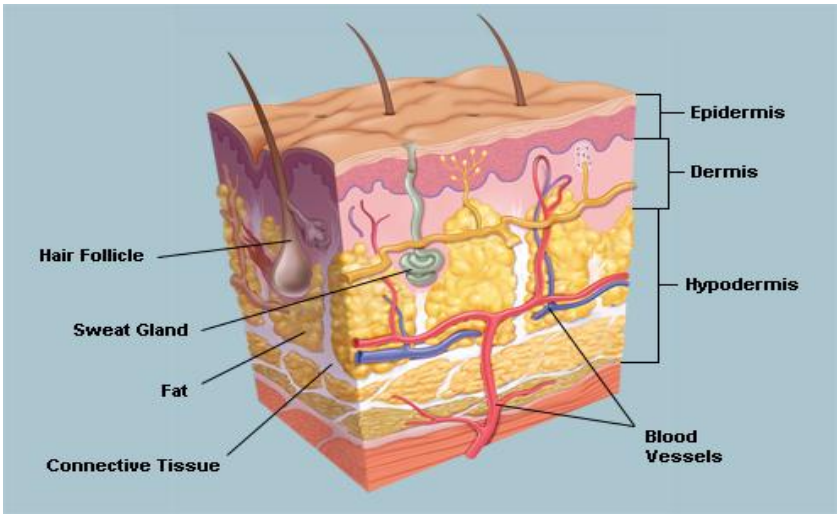
Antiemetics, Anesthetics, Painmanagement, Hormonal replacement therapy, Centeral nervous system, Cardiovascular, Antiasthemetic, Contraceptives, Antidiabeties, Urinary incontinence, Vaccine delivery, Protein and peptide based delivery.

**ANATOMY OF SKIN**

The skin of average adult body covers the surface area of approximately 2 sq.m and recives about one third of blood circulating in the human body and serve as a permeability barrier against transdermal absorption of various chemical and biological agent. The skin:

- Separates the underlying blood circulation network from the outside environment.
- Serve as a barrier against physical chemical and microbiological attacks.
- Act as thermostat in maintaining the body temperature.
- Protect against the penetration of UV rays.

As skin is the major factor in determining the various drug delivery aspects like permeation and absorption of drug across the dermis. So it is important to highlight the important characteristics of skin. The diffusion resistance of skin is greatly dependent on anatomy and ultrastructure. The composite structure of the skin is indicated by three distinct layers: epidermis, dermis and subcutaneous fat layer.




**Skin has two tissue layers: the epidermis and dermis as shown in fig.**

The outer epidermis is composed of stratified squamous epithelium while thicker dermis is made up of connective tissue. In all the epithelial tissue blood vessels are absent in the epidermis but present in the dermis.

Although two skin layers are firmly connected a burn can cause to separate forming a blister. For the purpose of drug delivery the skin structure can be divided into three distinct layer:

- The innermost subcutaneous fat layer
- The overlying dermis.
- The viable epidermis the outermost layer of the tissue (a nonviable epidermis layer) the stratum corneum.

**Epidermis**

The multilayered envelop of the epidermis varies in thickness, depending on cell size and number of cell layers, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Stratum corneum and the remainder of the epidermis, also called viable epidermis, cover a major area of skin.

**Stratum corneum**

It is the outermost layer of skin, also called horney layer. It is approximately 10 mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of parallel to the skin surface, lying dead, keratinized cells, called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration. The barrier nature of the horney layer depends critically on its constituents: 75 to

80% proteins, 5 to 15% lipids and 5 to 10% ondansetron material on a dry weight basis. Protein fractions predominantly contain alpha-keratin (70%) with some beta-keratin (10%) and cell envelope (5%). Lipid constituents vary with body site (neutral lipids, sphingolipids, polar lipids, cholesterol). Phospholipids are largely absent, a unique feature of mammalian membrane.

**Viable epidermis**

This is situated beneath the stratum corneum and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. It consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum, and the stratum basale. In the basale layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horney cells from the skin surface. As the cells produced by the basale layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratumcorneum.

**Dermis**

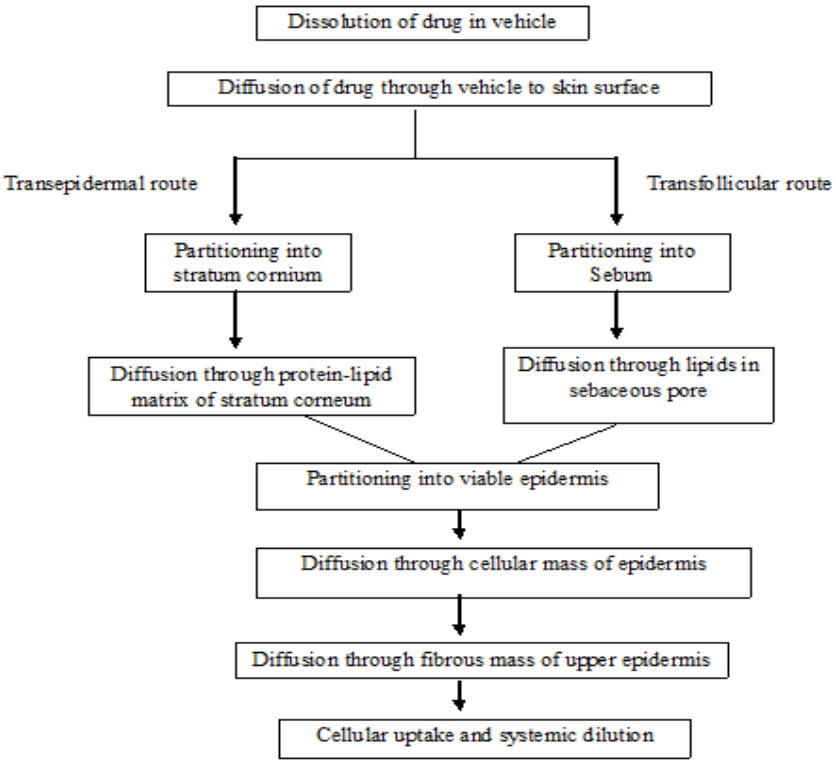
Dermis is a 3 to 5 mm thick layer and is composed of a matrix of connective tissue which contains blood vessels, lymph vessels and nerves. The continuous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of permeate very low, and the resulting concentration difference across the epidermis provides the essential driving force for transdermal permeation.

**Hypodermis**

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanic protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, the drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery, only penetration through stratum corneum is essential and then retention of drug in skin layers is desired.

**Mechanism of Percutaneous absorption**

It refers to the passage of medicinal substance through the skin. It is also defined as the penetration of substance from outside into the skin and through the skin into blood stream.




**Kinetics of Transdermal Permeation**

Transdermal permeation of a drug involves the following steps. **Sorption by stratum corneum,** Penetration of drug through viable epidermis, Uptake of the drug by the capillary network in the dermal papillary layer.

The rate of permeation across the skin (dQ/dt) is given by:

$$\frac{dQ}{dt} = Ps\ (Cd - Cr) \qquad \text{Equation- 1}$$

Where,

Cd = Concentration of skin penetrant in the donar compartment (e.g., on the surface of stratum corneum)

Cr = Concentration in the receptor compartment (e.g., body) respectively

Ps = The overall permeability constant of the skin tissue to the penetrant

$$\mathbf{Ps = \frac{KsDss}{hs}}$$

Equation- 2

Where

Ks is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system onto the stratum corneum,

Dss is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues and hs is the overall thickness of skin tissues. As Ks, Dss and hs are constant under given conditions, the permeability coefficient (Ps) for a skin penetrant can be considered to be constant.

From Eq.1 it is clear that a constant rate of drug permeation can be obtained only when Cd>>Cr i.e., the drug concentration at the surface of the stratum corneum (Cd) is consistently and substantially greater than the drug concentration in the body (Cr), then Eq. 1 becomes:

$$\frac{dQ}{dt} = P_s C_s$$ Equation- 3

Permeability coefficient = KsDss / hs = 1/ resistance

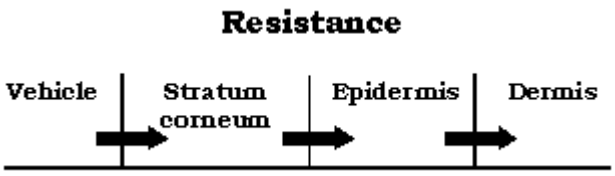
Resistance has many components

Vehicle

Stratum corneum (usually most significant)

Epidermis

Dermis




The resistance occurs one after another ‘in series’

Rtotal = Rvehicle + Rstratum corneum + Repidermis + Rdermis

$$\text{Total Permeability} = \frac{1}{R_{vehical}} + \frac{1}{R_{stratum\ corneum}} + \frac{1}{R_{epidermis}} + \frac{1}{R_{dermis}}$$

The membrane limited flux (J) under steady state condition is described by equation:

$$J = \frac{DK_{o/w}C}{h}$$ Equation- 4

Where,

J = Amount of drug passing through membrane system per unit area per unit time.

D = Diffusion coefficient with in the membrane

h = Membrane thickness

K = Membrane / vehicle partition coefficient

C = Concentration gradient across the membrane

**Factors affecting drug absorption**

**Skin Permeability**

Skin is durable because of the dermis, which is composed of connective tissue made up of fibers. Skin is selectively permeable; that is, skin allows only certain substances to enter the pores. The stratum corneum, the first layer of the epidermis, is a dense layer made up of dead, flattened cells that are filled with keratin (an insoluble protein). This layer of dead cells resists substances that are water-soluble or fat-soluble. In other words, the stratum corneum acts as the raincoat of the skin. If the epidermis is removed, the deeper layers of living cells, the dermis, act as a barrier to keep out fat-soluble substances. Because the skin has an oily secretion, medication applied to the skin surface is absorbed best if such medication is suspended or dissolved in oily media. Drugs combined with inorganic substances such as petroleum are not absorbed as well as drugs combined with synthetic ointment bases that are like sebaceous secretions.

**Drug Particle Size**

The size of the particles in the medication is an important factor in skin absorption. Very little absorption takes place if the particles in the skin medication are large and insoluble; for example, as in zinc oxide ointment. On the other hand, a great deal of absorption takes place when a solution such as oil of wintergreen in olive oil or in a lanolin base is rubbed on the skin.

**Degree of Skin Hydration**

Medication is absorbed by the skin better if the cornified layer (the top layer of the epidermis) is moist. Ointments soften the skin by wetting it, thus allowing the medication in the ointment to be absorbed into the skin easily. Another way to get moisture into the skin is to use an occlusive dressing over the skin lesion. An occlusive dressing is a dressing that prevents the loss of moisture from the skin's surface. This type of dressing can be made by placing an airtight plastic film (for example: Saran Wrap® or Handy Wrap®) over the medicated skin. Moisture is kept in the skin allowing the medicine to be absorbed into the skin. If a corticosteroid medication has been used, this medication will reduce skin inflammation

faster. The occlusive dressing has kept moisture on the skin as well as prevented the medication from evaporating.

**Contact Time**

Absorption of medication on the skin is increased if the medication is in contact with the skin for longer periods of time. Since all disease organisms are not killed at the same time, there is a gradual decrease in the number of organisms. The longer the medication is on the skin lesions, the more organisms will be killed.

**Partition coefficient**

The ratio of solubility of drug between lipid and water is known as partition coefficient and is important for absorption through skin. Compounds having lipid/water partition coefficient of 1 or greater have the highest diffusion rates through skin. The partition coefficient of a drug molecule can be altered by chemical modification of its functional groups, if this can be done without affecting the pharmacological activity of the drug. It has been established that membrane partition coefficient increases exponentially as the length of the lipophillic alkyl chain increases.

**pH conditions**

Applications of solutions whose pH values are very high or very low can be destructive to the skin. 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 permeability.

**Penetrant concentration**

Assuming membrane related transport, increasing concentration of dissolved drug causes a proportional increase in flux. At concentration higher than the solubility, excess solid drug functions as a reservoir and helps maintain a constant drug constitution for a prolonged period of time.

**Degree of Friction**

Skin medication can be absorbed better as the degree of friction is increased.

**Skin Temperature**

When the temperature of the skin increases, skin medication is absorbed faster. Also, in many cases heat alone is enough to kill disease organisms.

**Epidermal Damage**

The epidermal layer of the skin is the protective layer. Medication applied to an area in which this layer has been damaged means that there is nothing to keep the medication out; therefore, the medication will be absorbed quickly.

**Penetration Enhancers**

These are the compounds, which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant and are considered as an integral part of the formulations. To achieve and maintain therapeutic concentration of drug in the blood, the resistance of skin (stratum corneum) to diffusion of drugs has to be reduced in order to allow drug molecules to cross skin and to maintain therapeutic levels in blood. Enhancers increase the penetration by disrupting the structure of skin's outer layer 'stratum corneum' and increasing penetrant solubility. Disruption either by chemical means, may affect both intracellular and extracellular structure. Disruption may be due to protein denaturation, fluidization and randomization of intercellular lipids or intercellular delamination and expansion. The accelerants cause keratin to swell and leach out essential structural material from the stratum corneum, thus reducing the diffusional resistance and increasing the permeation of drugs through skin.

**Examples of permeation enhancers**

Sulphoxides (especially dimethylsulphoxide) and their analogues

Pyrrolidines

Fatty acid and alcohols

Azone and its derivatives

Surfactants – anionic, cationic and nonionic

Urea and its derivatives

Alcohols and glycols

**Factors Affecting Transdermal permeation**

There are three major factors which affect the transdermal permeation. These are as follows:

Physicochemical Properties of the Penetrant Molecules

Physicochemical Properties of the Drug Delivery System

Physiological and Pathological Conditions of the Skin

**1. Physicochemical properties of drug molecule**

**Partition coefficient**

Drug possessing both lipid and water solubility is absorbed through the skin. transdermal permeability coefficient shows a linear dependency on partition coefficient. A lipid/water partition coefficient 1 or greater is generally required for optimal transdermal permeability. The partition coefficient of a drug molecule may be altered by chemical modification of its functional groups. It can be done without affecting the pharmacological activity of the drug. It has been established that memberane partition coefficient increases exponentially as the length of lipophilic alkyl chain increases. The partition coefficient of a drug molecule may also be altered by varying the vehicle composition.

**pH conditions**

Application of solutions whose pH values are very high or very low can be destructive to the skin. With moderate pH values the flux of ionizable drugs can be affected by changes in pH that alter ratio of charged and uncharged species and their transdermal permeability.

**Penetrant concentration**

Assuming memberane related transport, increasing concentration of dissolved drug causes a proportional increase in flux. At the concentration higher than the solubility, excess solid drug function as a reservoir and helps maintain a constant constitution for prolonged period of time.

**2. Physicochemical properties of drug delivery system**

The drug delivery system vehicle do not increase the rate of penetration of a drug into the skin but serve as a carrier for drug:

Release characteristics: Solubility of drug in the vehicle determines the release rate. The mechanism of drug release depend upon the following factors:

Weather the drug molecule is dissolved or suspended in the delivery system.

The interfacial partition coefficient of the drug from delivery system to the skin tissues.
pH of the vehicle.

**Composition of the drug delivery system**

The composition of drug delivery system eg boundary layer, thickness, polymers, vehicle not only affect the rate of drug release, but also the permeability of the stratum corneum by means of hydration making with skin lipids or other sorption promoting effects. Eg: benzocaine permeation decreases with PEG of low molecular weight.

**Enhancement of transdermal permeation**

Majority of drugs will not penetrate skin at rates sufficiently high for therapeutic efficacy. In order to allow clinically useful transdermal permeation of most drugs the panertration can be improved by addition of a permeation promoter into the drug delivery systems.

**3. Physicochemical and pathological conditions of the skin**

Reservior effect of the horny layer: The horny layer, especially its deeper layers can sometimes act as a depot and modify the transdermal permeability of the drugs. The reservoir effect is due to the irreversible binding of a part of applied drug with the skin. The binding can be reduced by pretreatment of the skin surface with anionic surfactants.

**Lipid film**

The lipid film on the skin surface act as protective layer to prevent the removal of moisture from the skin and helps in maintaining the barrier function of the stratum corneum. Defatting of this film was found to decrease the transdermal absorption.

**Skin temperature**

Raising skin temperature results in an increase in rate of skin permeation. This may be due to: Solubility of skin in tissues.

**Increase vasodialation of the vessels.**

**Skin hydration**

Hydration of the stratum corneum can enhance transdermal permeability, although the degree of the penetration enhancement varies from drug to drug. Skin hydration can be achieved simply by covering or occluding skin with plastic shearing leading to accumulation of sweat and condensed water vapours. Occusion also reduces irreversible binding capacity of stratum corneum.

**Regional Variation**

Differances in the nature and thickness of barrier layer causes variation in permeability.

**Traumatic/pathological injuries to the skin**

Injuries that disrupt the continuity of the stratum corneum increases permeability due to increased vasodialation caused by removal of barrier layer.

**Cutaneous Drug Metabolism**

Catabolic enzyme present in the viable epidermis, may render the drug in active by metabolism and thus effect the topical bioavailability of the drug.

**Basic components of TDDS**

Polymer Matrix: Polymer is an integral and foremost important component of transdermal drug delivery system. Different classes of polymeric material have been used to achieve rate controlled transdermal delivery. The mechanism of drug release depends upon the physicochemical properties of the drug and polymer used in the manufacture of the device.

The following criteria should be satisfied for a polymer used in the transdermal drug delivery system:

Molecular weight, glass transition temperature, chemical functionality of the polymer must allow the diffusion and release of specific drug.

- The polymer should permit the incorporation of large amount of the drug.
- The polymer should not react physically or chemically with the drug.
- The polymer should be easily maintained and fabricated into the desired product and inexpensive.
- The polymer must be stable and must not decompose in the presence of the drug and other excipient used in the formulation at high humidity condition or at the body temperature.
- Polymers and its degradation product must be non toxic.

No single material may have all these attributes, certain excipients may be incorporated to alter the properties. Eg cosolvents such as ethanol, propylene glycol, PEG 4000 could be added to increase the drug solubility. Table shows useful polymer for transdermal delivery:

| Natural polymers | Synthetic Elastomer | Synthetic polymers |
|---|---|---|
| Cellulose derivatives | Polybutadiene | Polyvinyl alcohol |
| Zein | Hydrin Rubber | Polyethylene |
| Geatin | Polysiloxane | PVC |
| Proteins | Acrylonitrile | Polyacrylates |
| Shellac | Neoprene | Polyamide |
| Arabino Galactan | Chloroprene | Acetal copolymer |

Various techniques have been applied to modify the polymer properties and thus release rates:

**Cross Linked Polymers**

The higher the degree of crosslinking more dense the polymer and slower the diffusion of drug molecules through the matrix.

**Polymer Blends**

Polymers have been blended by varying ratios to combine the advantages of individual polymers. Advantages of polymer blend include easy fabrication of devices , manipulation of drug loading and other devices properties such as hydration, degradation rate and mechanical strength.

**Plasticizers**

Plasticizers have been known to reduce the stiffness of the polymer backbone thereby increasing the diffusion characteristics of the drug. Commonly used plasticizers are polyethylene glycol, polypropylene glycol, glycerol, dibutylphthalate.

**Drug Structure**

Judicious choice of drug plays an important role in successful development of transdermal product. For the drug selections following factors are considered:

**Physicochemical properties**

The drug should have some degree of solubility both in oil and water i.e should be greater than 1mg/ml. The drug has to transfer from primarily lipid rich environment into one which is largely aqueous in nature. This will be optimal for drugs which posses balanced lipophilic-hydrophillic characterstics and also have reasonable solubility in both lipid and aquous phases. Extremely lipophilic material can form a reservoir in stratum corneum, from which the drug may get slowly released even after the system is removed from the skin and this is not desirable as far as the aim is rapid termination of therapy. The compound having log P value in between 1 and 2 are good candidates for trandermal drug delivery. Eg: For compounds having log P>2, there are potential problem in achieving steady state plasma concentration in a reasonable time span. This is due to the drug being held up in the stratum corneum where reservoir of drug can be established.

The substance should have melting point less than $200^0$F.

Concentration grade across the memberane is directly proportional to log solubility of the drug in lipid phase of the membrane, which inturn is directly proportional to reciprocal of the melting point.

The melting point should be low for better TDDS.

Substances having the molecular weight less than 1000 unit are suitable. A saturated aqueous solution of drug should have a pH value between 5 and 9. Those drugs that are highly acidic or alkaline are not suitable for TDDS because they get ionized rapidly at physiological pH and ionized material generally penetrate the skin poorly.

Hydrogen bonding groups should be less than 2.

**Biological Properties**

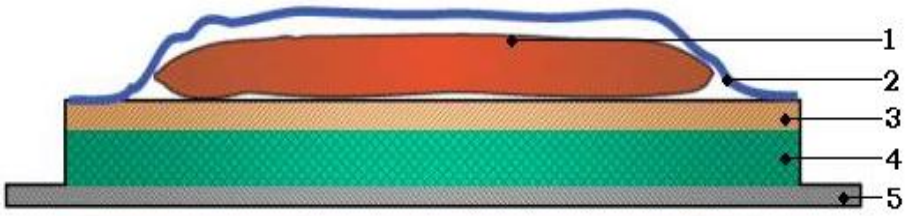
- Drug should be very potent i.e should be effective in few mgs per day.
- The drugs should have short biological half life.
- Because skin is very efficient barrier to the ingress of materials, allows only a small amount of drug to penetrate over a period of time.
- The drug should have short biological half life.
- The drugs having long half life, plasma level build up slowly over a longer period of time than desired.
- Drug should be non irritant and non allergic to skin.
- The drug should not stimulate an immune reaction to the skin.
- Tolerance to drug must not develop under near zero order release profile of transdermal delivery. The drug should not get extensively metabolized in the skin.

| • **Technology** | **Polarity** | **Molecular weight(g/mole)** | **Log P** | **Melting Point( $^0$C)** | **Daily dose(mg/day)** |
|---|---|---|---|---|---|
| Passive DIA | Neutral | <500 | Near 2 | <150 | **<10** |
| Gel | Neutral | <500 | Near 2 | <150 | **<20** |
| Thermal | Neutral | <500 | Near 2 | <150 | **<15** |
| Iontophoresis | Ionic | No Limit | <1 | No Limit | **<20** |
| Sonophoresis | Neutral | No Limit | No Limit | No Limit | **<20** |
| Microporation | All | No Limit | No Limit | No Limit | **<30** |

Table shows summary of physicochemical and clinical properties of molecules for various transdermal technology.

**Components of Transdermal Patch**

There are five components of trandermal patch as shown on fig:




1. Drug reservior
2. Backing laminate
3. Rate controlling membrane
4. Adhesive layer
5. Release liner (peel strip)

1. Drug Reservior Components: It must be compatible with the drug and must allow for drug transport at the desired rate. If an ointment is used, drug reservoir must posses the desired viscosity attributes to ensure the reliable manufacturing process. It must posses the desired adhesive and cohesive properties to hold the system together. Material used are: Mineral oil, polyisobutylent, colloidal silica, HPC.

2. Backing Laminates: The primary function of backing laminate is to provide the support.
   Important Characterstics:
   They should be able to prevent the drug from leaving the dosage form through the top.
   Must be impermeable to drug and permeation enhancers.
   Should have low moisture vapour transmission rate.
   Must have optimal elasticity, flexibility and tensile strength.
   Must be chemically compatible with the drug, enhancer, adhesive and other excipients.
   Must allow printing and adhesive lamination.

   Backing memberane are composed of pigmented layer, an aluminium vapour coated layer, a plastic film (polyethylene, polyvinyl chloride, polyester) and heat seal layer.

   Rate Controlling Memberane: Rate controlling memberane in transdermal devices governs the drug release from the dosage form. Memberane made from natural polymeric material such as chitosan show great promise for use as rate controlling memberanes. Recently composite poly-2-hydroxyethyl methacrylate(PHEMA) memberanes have been evaluated as rate controlling barriers for transdermal application.

3. Adhesive Layer: The fasting of all transdermal devices to the skin using pressure sensitive adhesive that can be positioned on the face or in the back of device is necessary.

   Both adhesive layer should fulfill the following criteria:

   Drug not cause irritation, sensitization or imbalance in the normal skin flora during its contant with the skin.

   Should adhere to the skin aggressively.

   Should be easily removeable without leaving an unwashable residue.

   The face adhesive system should also fulfill the following criteria:

   Should be physically and chemically compatible with the drug.

   Should allow the delivery of simple absorption enhancers.

   Should not determine the adhesive properties as drug enhancer and excepients permeate into the adhesive.

   The three major classes of polymers evaluated for potential medical application in TDDS include:

   Polyisobutylent type pressure sensitive adhesive.

   Acrylic type pressure sensitive adhesive.

   Sillicon type pressure sensitive adhesive.

4. Release Liner: The release liner has to be removed before the application of transdermal system, and it prevents the loss of drug that has migrated into adhesive layer during storage. It also helps to prevent the contamination. It is composed of base layer, which may be nonocclusive or occlusive and a release layer made up of silicon Teflon. Other material include polyesters, foil, mylar and metalized laminates.

Ideal Product Requirement: An ideal product for transdermal delivery should fulfill the following critaria:

- It should have the shelf life up to 2 years.
- The patch should be of small size i.e it should be of less than 40 $cm^2$
- It should have convenient dosage frequency i.e from once a day to once a weak.
- It should be cosmetically acceptable.
- Packing should be simple i.e minimum number of steps should be required to apply the system.
- Release liner should be of easy removable.

- No residue i.e. cold flow around the edge of patch in storage or other application to skin or beneath the patch after removal.

Consistent biopharmaceutical performance **(**i.e., precision of required pharmacokinetic and pharmacodynamic response between individuals and in the same individual over time**).**

**PATCH DESIGN AND TECHNOLOGY**

- There are two major types of transdermal drug delivery product:
- Thin flexible coloured and nearly invisible matrix patches.
- Flexible coloured or transparent liquid or semisolid filled reservoir patches.

Four major types of transdermal patches are as follows:

1. Single layer drug in adhesive.
2. Multi layer drug in adhesive.
3. Reservior
4. Matrix.

**These are explained as follows**

1. Single layer drug in adhesive: The adhesive layer of this system also contains the drug. In this type of patches the adhesive layer not only serves to adhere the various layer together, along with entire system to the skin but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.
2. Multi Layer Drug In Adhesive: The multi layer drug in adhesive is similar to the single layer system in that both adhesive layer are also responsible for the releasing of the drug. But it is different however that it adds another layer of drug in – adhesive, usually separated by a membrane. This patch also has a temporary liner – layer and a permanent backing.
3. Reservior: Reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the backing layer. In this type of system the rate of release is zero order.
4. Matrix: The matrix system design is charactersized by inclusion of semi solid matrix containing a drug solution or suspension which is in a direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semi solid matrix.

**Methods of Formulation of Transdermal Patch**

**1. Circular teflon mould method**

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butylphthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular teflon mould. The moulds are to be placed on a leveled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored for another 24 hrs at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. The type films are to be evaluated within one week of their preparation.

**2. Mercury substrate method**

In this method drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10- 15 minutes to produce a homogenous dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation.

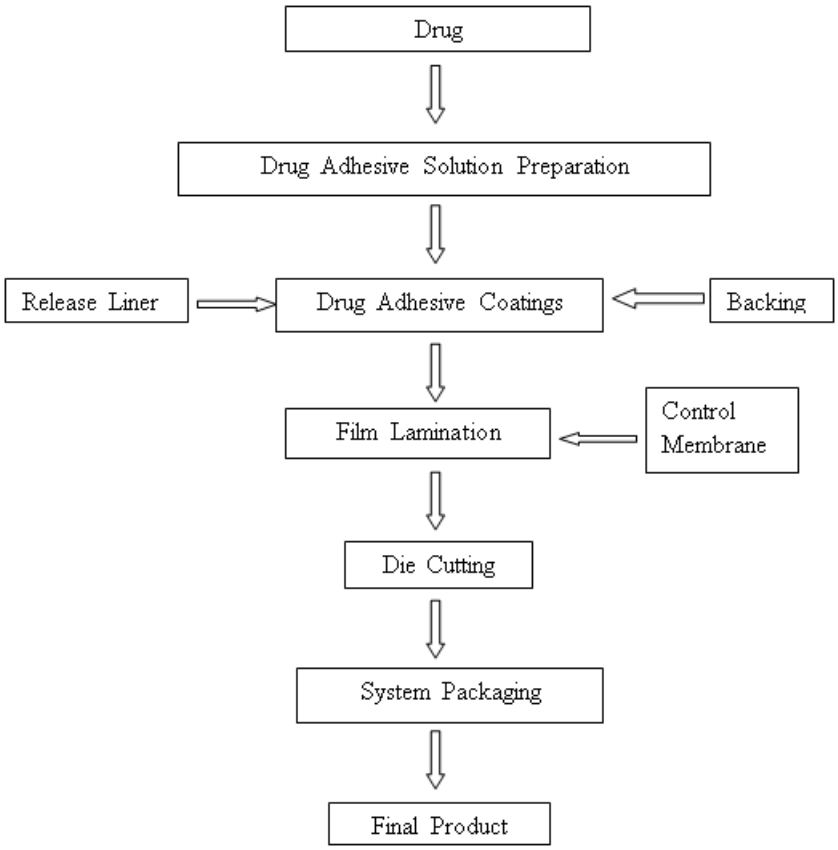
**3. By using "EVAC membranes" method**

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol, carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

**4. Preparation of TDDS by using Proliposomes**

The proliposomes are prepared by carrier method using film deposition technique. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70°C temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20-30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C,

after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders (proliposomes) are placed in a desiccator over night and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.




## APPROACHES TO DEVELOPMENT OF TRANSDERMAL THERAPEUTIC SYSTEMS

Several technologies have been developed to provide rate control over the release and transdermal permeation of drugs. The technologies can be classified into four approaches as follows:

### Memberane Moderated System

In this system drug reservoir is totally encapsulated in a shallow compartment model from a drug-immpermeable metallic plastic laminate and a rate controlling polymeric memberane as shown in fig. The drug molecules are permitted to release only through rate controlling polymeric memberane. In the drug reservoir compartment drug solids are either dispersed in a solid polymer matrix or suspended in a unleachable viscous liquid medium eg: silicone fluid

to form paste like suspension. The rate limiting memberane can be microporous or a nonporous polymeric memberane. Eg: external surface of polymeric memberane, a thin layer of drug compatible, hypoallergic adhesive polymer. Eg: Sillicon or polyacrylate adhesive may be applied to achieve an intimate contact of transdermal therapeutic system with the skin surface. The rate of drug release from this type of transdermal drug delivery system may be tailored by varying the polymer composition, permeability coefficient or thickness of rate limiting memberane and adhesive. Several transdermal therapeutic system have been mineralized from this technology and are best used in the development of nitroglycerine transdermal therapeutic system for once a day medication of angina pectoris of scopolamine releasing transdermal therapeutic system (Transderm-Scop system/cibba) for three day protection of motion sickness and of clonidine releasing transdemal therapeutic system (Catapress-TTS/Boehringer Ingelheim).

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

$$dQ/dt = \frac{CR}{\delta_a}$$

$$\frac{dQ}{dt} = C \frac{r}{\frac{1}{Pm}+\frac{1}{Pa}} \qquad 1.$$

Where Cr is the drug concentration in the reservoir compartment Pa and Pm are permeability coefficient of the adhesive layer and the rate controlling memberane respectively. For a microporous memberane Pm is the sum of permeability coefficient across the pores and the polymeric material. Pm and Pa are defined as follows:

$$Pm = \frac{\frac{Km}{r} d.Dm}{\delta_a} \qquad 2.$$

$$Pa = \frac{\frac{K_a}{m}.Da}{\delta a} \qquad 3$$

Where Km/r and Ka/m are the partition coefficient for the interfacial partitioning of drug from reservoir to the membrane and from membrane to adhesive respectively. Dm and Da are diffusion coefficient in rate controlling membrane and adhesive layer respectively. δm and δa are thickness of rate controlling memberane and adhesive layer respectively. In the case of microporous membrane, the porosity and tortuosity of membrane should also be taken into consideration in calculation of Dm and δm values. By substituting equation 2 and 3 in equation 1 gives:

$$\frac{dQ}{dt} = K\frac{m}{r}Ka/_{m}.\text{Dm.Da/}$$

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

The membrane permeation controlled transdermal drug delivery technology has also been applied to development of transdermal therapeutic system for controlled percutaneous absorption of estradiol and prostaglandin derivative.

**Adhesive Diffusion-Controlled System**

It is a simplified version of membrane moderated drug delivery system. Instead of completely encapsulating the drug reservoir I a compartment fabricated from a drug-impermeable metallic plastic backing, in this system the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and than spreading the medicated adhesive, by solvent casting onto flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. On the top of 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. The rate of drug release is defined as:

$$\frac{dQ}{dt} = K\frac{a}{r}.Da.\frac{Cr}{\delta a}$$

Where Ka/r is the partition coefficient for interfacial partitioning of the drug from reservoir layer to the adhesive layer. The type of transdermal drug delivery system is best illustrated by development and marketing of nitroglycerin released transdermal therapeutic system (Deponit system/Pharma Schwarts) in Europe and of isosorbidedinitrate releasing transdermal therapeutic system (Frandol tape/Toaeiyo) in Japan for one day medication of angina pectoris.

**Matrix Dispersion Type Systems**

In this approach, the drug reservoir is formed by homogeneously dispersing the drug solids in hydrophilic or lipophillic polymer matrix and the medicated polymer is then molded into medicated disc wth a defined surface area and controlled thickness. This drug reservoir containing polymer disc is than glued onto an occlusive baseplate in a compartment fabricated from a drug impermeable plastic backing. Instead of applying the adhesive polymer directly on surface of medicated disc, the adhesive polymer is spread on to the

circumference to form a strip of adhesive ring around the medicate disc. The rate of drug release from the matrix dispersion type transdemal therapeutic system is defined as:

$$\frac{dQ}{dt} = \left(\frac{ACpDp}{2t}\right)$$

Where A is the initial drug loading dose dispersed in the polymer matrix and Cp and Dp are the solubility and diffusibility of the drug in the polymer. In the view of fact that only a drug species dissolved in the polymer can release, so, practically Cp is equal to Cr.

At the steady state, a Q versus $t^{1/2}$ drug release profile is obtained as defined by:

$$\frac{Q}{t^{1}/_{2}} = [(2A - Cp)CpDp]^{1}/_{2}$$

This type of transdermal drug delivery is exemplified by the development and marketing of nitroglycerine-releasing transdermal therapeutic system( Nitro-Dur system/Key) which has been approved by FDA for once a day medication of angina pectoris.

**Microreservior System**

This type of drug delivery system an be considered as a combination of reservoir and matrix dispersion type drug delivery systems. In this approach drug reservoir is formed by first suspending the drug solids in an aquous solution of water soluble polymer and then dispersing homogeneously the drug suspension in lipophillic polymer, by high shearing mechanical force, to form thousand of unleachable, microscopic sphere of drug reservoir. This thermodynamically unstable dispersion is quickly stabilized by immediately croslinking the polymer chains in situ, which produces a medicated polymer disc with a constant surface area and fixed thickness,. A transdermal therapeutic system is produces in which the medicated disc is positioned at the center and surrounded by an adhesive rim as shown in fig. This technology has been successfully utilized in the development and marketing of nitroglycerin releasing transdemal therapeutic system for once a day treatment of angina pectoris.

The rate of drug release from microreservior drug delivery system is defined by:

$$\frac{dQ}{dt} = DpDs\alpha$$

Where α'=δ'/β'. δ' is the ratio of drug concentration in the bulk of elution solution over the drug solubility in the same medium and β' is the ratio of drug concentration at the outer edge of polymer coating membrane over the drug solubility in the same polymer composition. $K_1$, Km and Kp are the partition coefficient for the interfacial partitioning of drug from the liquid compartment to the polymer matrix, from the polymer matrix to the polymer coating membrane and from the polymer coating membrane to elution solution (or skin), respectively. $S_1$ and Sp are the solubilties of drug in the liquid compartment and in the polymer matrix. Δ1, δp and $\delta_d$ are the thickness of the liquid layer surrounding the drug particles, the polymer coating membrane around the polymer matrix and the hydrodynamic diffusion layer surrounding the polymdr coating membrane. B is the ratio of drug concentration in the inner edge of interfacial barrier over the drug solubility in the polymer matrix.

Release of drug from the microreservior type drug delivery system can follow either a partition control or matrix diffusion control process depending on the relative magnitude of $S_1$ and Sp.

Development of other types of potential drug delivery systems are also undergoing for possible applications in the transdermal controlled infusion of drugs.

Eg: Development of protoplastic memberane and hydrophilic polymeric reservoir .Both of them are drug solution saturated porous polymer matrix

## EVALUATION OF TRANDERMAL PATCH

### (A) Physical evaluation

(i) Drug content uniformity: It is determined by taking specific no. of patches and completely dissolving then in specific media. Resulting solution is filtered out through membrane filter. The samples so obtained is analyzed by HPLC or U.V. spectrophotometer.

(ii) Determination of surface pH : Specific number of patches are kept in contact with distilled water and excess water is drained and pH noted by pH meter.

(iii) Holding endurance: It is calculated by cutting the patch in specific size by using sharp blade. Holding endurance was determined by repeatedly following a small strip of the patch at the same place till it broke. The no. of time the patch could be folded at the same place without breaking gave the value of holding endurance.

(iv) Thickness of patches: The thickness of transdermal patches is measured using micrometer screw gauge.

(iv) Weight of patches: Specific number of patches of each formulation are weighed individually in digital balance and calculated standard deviation.

(v) Moisture content: The prepared patches are cut into strips of specific size. The strips are then weighed individually and kept in a dessicator containing activated silica at 300°C for 12 hours. The films are reweighed individually until a constant weight is obtained.
Percentage (%) of moisture content = Loss in wt./ Initial wt. x 100

(vi) Water absorption studies: Transdermal films are into strips of specific size. A strip is weighed and kept in a dessicator at 400 C for 24 hours, removed and exposed to 75% RH (Containing saturated solution of sodium chloride) at room temperature weight is taken until a constant weight is obtained. Water absorption capacity = Increase in weight / Initial weight x 100.

(vii) Drug carrier Interaction: Thin layer chromatography (TLC) or HLPC method is used for the drug carrier interaction studies.

(viii) Tack properties: Tack is the ability of a polymer to adhere to a substrate with little contact pressure. It is depends on the molecular weight and composition of polymer. Test of tack includes.
(a) Thumb tack test: This is a subjective test in which evaluation is done by pressing the thumb briefly into the adhesive.
(b) Rolling ball tack test: This test involves measurement of the distance that a stainless steel ball travels along an upward – facing adhesive. The less tacky the adhesive for they will travel.
(b) Quick stick (Peel-tack) test: The Peel force required to break the bond between on adhesive and substrate is measured by pulling the force away from the substrate at 90° at a speed of 12inch/min
(c) Probe tack test: The force required to pull a probe away from on adhesive at a fixed rate is recorded at tack.

(IX) Peel adhesion properties: Peel adhesion is the force required to remove an adhesive coating from a test substance. It is tested by measuring the force required to pull a single

coated tape, applied to a substance at 180° angle. It should not damage the skin and no residue on the skin.

(X) Shear strength properties: Shear strength is the measurement of the cohesive strength of an adhesive polymer. Adequate cohesive strength of a device will mean that the device will not slip on application and will leave no residue on removal. It is determined by measuring the time it takes to pull on adhesive coated tape off a stainless steel plate when a specified weight is hung from the tape which pulls the tape in a direction parallel to the plate.

(XI) Tensile strength: The mechanical properties are determined using plastic tensile test performed using an instron instrument.

(B)Invitro method: These are valuable techniques for screening and for measuring fluxes partition coefficients and diffusion coefficients because the investigator can closely control laboratory conditions.

(i) In-vitro permeation studies K-C cell (Keshary –chain) diffusion cell is used if skin of rats are used. Hairless skin is used and skin is thoroughly cleaned of any adhering tissues or blood vessels and equilibrated for an hour in pH 7 buffer before running for experiment. The K.C. cell or skin piece was mounted between the compartment of the diffusion cell and donor compartment and epidermal part of skin upward or toward donor compartment. The patch to be tested was placed on skin. Specific butter media at 370° C + 10° C is used as receptor phase and stirred with magnetic stirrer. Specific amount of sample withdrawn at regular period through the sampling port and fresh receptor fluid was added. Absorbance of sample is measured spectrophotometrically at against blank. The cumulative amount of drug permeated is plotted against

(i) In-vitro drug release studies: A modified dissolution apparatus consisting of a jacketed vertical glass beaker 18cm long and 48cm in diameter was used for assessment of the release of drug from patches in the specific amount of formulation of buffer solution. The patch to be evaluated is struck on to the depression (15mm internal diameter and 1.5mm depth) on a teflon block fabricated for the purpose and is put into the glass beaker containing the dissolution medium. The apparatus was equilibrated to 37 + 20 C and operated at 50 rpm. Specific amount of sample pipetted out on regular interval of time. Sample is filtered out through filter paper and finally membrane filtered sample is analyzed by the HPLC or U.V. spectrophotometer.

(B) In-Vivo methods: 1 In vivo evaluation of trandermal patch can be carried out using – i) Animal models ii) Human Volunteers

(i) Animal models: In Vivo animals models are preferred because considerable time and resources are required to carry out studies in humans. Some of the species are used : mouse, rat, guinea pig, rabbit, rat, cat, dog, pig, house, monkey small hairy animals (e.g. rat, rabbit) or rhesus monkey is most reliable. For in vivo evaluation of transdermal patches standard radiotracer methodology used. The application site is generally the abdomens which are the least hairy site on the animal body. The compound is applied after light clipper showing of the site.

ii) Human models: Human subjects should give pertinent information with minimum risk to the subjects within responsible period. It is first described by Fieldman and Maibach. They includes determination of percutaneous absorption by an indirect method of measuring radioactivity in excreta following topical application of the labeled drug. 14C is generally used for radio labeling. Determination of absorption following topical administration requires the investigator to know the amount of radioactivity retained in the body or excreted by routes. The percentage of dose absorbed transdermally is then calculated as.

% Dose absorbed =Total radioactivity exerted after topical Administration/ Total radioactivity exerted by intervenes Administration

The procedure takes 5-7 days for completion. Other following method used are as:

(a) Reservoir technique: It makes use of the relationship between stratum cornium reservoir function and in vivo percutaneous absorption to predict in vivo penetration. This method involves a simple, short exposure of the skin to the compound under study followed by removal of the stratum corneum by tape stripping and analysis of the content of the compound in the stratum corneum. For this analysis, it is possible to predict the amount of drug that will penetrate over a longer period of time.

(b) Mass balance technique: The application site is covered with an occlusive chamber, the chamber being replaced by a new one after a particular time interval. The site is also subjected to washing at these time. Radio labeling techniques are used and the chamber, washing and the faces and urine of the patients are subjected to analysis. This technique includes achievement of Mars balance between the applied close and exertion level and measurement for predicting percutaneous.

(c) Cutaneous toxicological evaluation: The major cutaneous toxicological reaction and the method are Contact dermatitis: It can be either contact irritant or contact allergic dermatitis.

(d) Contact irritant dermatitis: It results from direct toxic injury to cell membrane, cytoplasm or nuclei. This is generally manifested (to show, clearly especially a feeling) by inflammation and itching and can occurs from the drug, vehicle and absorption enhancer. Contact irritant dermatitis involves use of animals like rabbis and guinea pig. A major part of the screening deals with testing in humans. Two types of protocols are used.

a.) Ten day primary skin irritation test: A panel of ten subjects has the test agent applied daily for two weeks at the site to be used in clinical situation. The test agent is left in place over the weekend between the first and second five days of repeated application, Adverse reaction consists of erythemia and scaling which are graded daily prior to the re- application of the agent on a 0 to 3 scale of none, mild, moderate and servers or a 0 to 6 scale to permit more discrimination.

b.) Twenty one day skin irritation test: Same procedure as about is repeated but there are 25 volunteers and application is on a daily basis for 5 day a week for 21 day. The following test are the newer methodologies for assessing cutaneous toxicity and are noninvasive procedure.

(a) Laser Doppler: This test is based upon the fact that as a laser light beam passes through a specimen. It is scattered when it impinges (strike or fall against) upon either static structure or moving object. Light beam scattered in static tissue will not undergo any frequency shift while those encountering moving object will. Doppler effect by illuminating the skin with a monochromatic laser light and electronically process. the frequency of the back scattered light collected by a photo editor system at the skin surface, a continuous measure of the red cell flux. In this micro- vascular bed can be obtained. The irritation will lead to an increase in cutaneous flow and thus increased red cell flux.

(b) Evaporative water loss measurement: Contact irritation also disturbs the skin barrier and causes an excessive water loss from the damaged surface than can be measured by means of evaporimetry.

(c) Contact allergic dermatitis: Contact allergic dermatitis involves a fast immunological reaction to an antigen. The antigen is viewed to be a complex formation an externally applied compound and skin proteins. The reaction easily distinguished clinically from contact irritation types of reaction. Two protocols are employed-

(I) 25 volunteers and low grade dermatitis is included in them by application of 1- 5% Sodium lauryl sulphate to enhance penetration and maximize any allergic potential. In first 5 day in two weeks and closed test is performed.

(II) 75-200 volunteers under occlusive patch test for 5 applications. The test agent is applied in between 24 hr. rest or 48 hr. without rest. After 7-10 day rest period, challenge is done by

closed patch testing, interpretation of result. Agent show an allergenic potential may still be used by millions of patients with adverse effect.

## RECENT ADVANCEMENTS IN TRANSDERMAL DRUG DELIVERY

Today many chemical and physical approaches have been applied to increase the efficacy of material transfer across the skin. These are termed Novel due to recent development with the satisfactory results in the field of drug delivery.

Improvement in the physical and chemical permeation enhacement technologies has led to renew interest in transdermal drug delivery. Some of these novel advancement in the drug delivery system include: ionotophoresis, electroporation, ultrasound and microporation using electrical current/voltage, radiofrequency and microneedles to open the skin.

### New Technologies inTransdermal Drug Delivery

#### 1. Iontophoresis

Iontophoresis passes a few milliamperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. Mainly used of pilocarpine delivery to induce sweating as part of cystic fibrosis diagnostic test. Iontophoretic delivery of lidocaine appears to be a promising approach for rapid onset of anesthesia.

### A no. of factors influence the iontophoretic transport of drug

a). The pH of the Medium: As the ionization of the drug is controlled by the pH transport is optimum in the pH range in which the drug is fully ionized although uncharged species can be carried out by electroosmotic solvent flow.

b.) The nature of the other ions in the formulation, which compete the transport of the current.

c.) The current density: The drug flux is proportional to the current density but the allowable density is limited by safety and patient tolerance to about 0.5mA $cm^{-2}$ .

d.) The Molecular Weight: Larger drug have lower transport number and so are delivered less effectively. As the drug size increases, the importance of ionic transport decreases and drug becomes predominantly carried by electroosmotic solvent flow.

e.) Concentration of drug in delivery system: The drug concentration at the donar side is increased, the flux across the skin increases.

f.) Physiological Variations: A major advantage of ionotophoresis is that relatively low level of variation is observed. This is probably due to the fact that the applied voltage is adjusted to achieve specific current and this will take amount of much variability between the subjects due to site, age and color of skin.

**2. Electroporation**

Electroporation is a method of application of short, high-voltage electrical pulses to the skin. After electroporation, the permeability of the skin for diffusion of drugs is increased by 4 orders of magnitude. The electrical pulses are believed to form transient aqueous pores in the stratum corneum, through which drug transport occurs. It is safe and the electrical pulses can be administered painlessly using closely spaced electrodes to constrain the electric field within the nerve-free stratum corneum.

Although DNA introduction is most commonly used for electrophoresis, it has been used as isolated cells for introduction of enzymes and more recently tissue elecroporation has begun to be explored with potential application including enhanced chemotheraphy, gene therapy and transdermal drug delivery.

**3. Sonophoresis**

This technique uses high frequency ultrasonic waves. Recent studies have shown that ultrasound can increase upto 900 times the ability of protein the size of insulin to penetrate the skin. Using a transdermal patch design in conjugation with ultrasound can provide an improved method for insulin delivery.