UNIT-II

TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS)

Transdermal Drug Delivery System (TDDS) are defined as self contained, discrete dosage forms which are also known as "patches", when applied to the intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation.

Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation.

Advantages:

1) Hepatic first pass metabolism, salivary metabolism and intestinal metabolism are avoided.
2) The ease of usage makes it possible for patients to self-administer these systems.
3) In case of an emergency, removing the patch at any point of time during therapy can instantly stop drug input.
4) Since the composition of skin structurally and biologically is the same in almost all the humans, there is minimal inter and intra patient variation.
5) Drugs showing gastrointestinal irritation and absorption can be suitably administered through the skin.
6) Continuous, non-invasive infusion can be achieved for drugs with short biological half-lives, which would otherwise require frequent dosing.
7) Due to reduced frequency of dosing there is better patient compliance.
8) Therapeutic failures associated with irregularities in the dosing with conventional therapies can be avoided.
9) The adverse effects are minimized due to a steady and optimum blood concentration time profile.
10) The risks, pain and inconvenience associated with parenteral therapy are evaded.
11) The release is more prolonged than oral sustained drug delivery systems.
12) The drug release is such that there is a predictable and extended duration of activity.

Disadvantages:

1) There is possibility of skin irritation due to the one or many of the formulation components.

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2) Binding of drug to skin may result in dose dumping.
3) It can be used only for chronic conditions where drug therapy is desired for a long period of time including hypertension, angina and diabetes.
4) Lag time is variable and can vary from several hours to days for different drug candidates.
5) Cutaneous metabolism will affect therapeutic performance of the system.
6) Transdermal therapy is feasible for certain potent drugs only.
7) Transdermal therapy is not feasible for ionic drugs.
8) It cannot deliver drug in pulsatile fashion.

PRINCIPLE OF TRANSDERMAL PERMEATION

Earlier, skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration. Skin is the most intensive and readily accessible organ of the body as only a fraction of millimetre of tissue separates its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows:

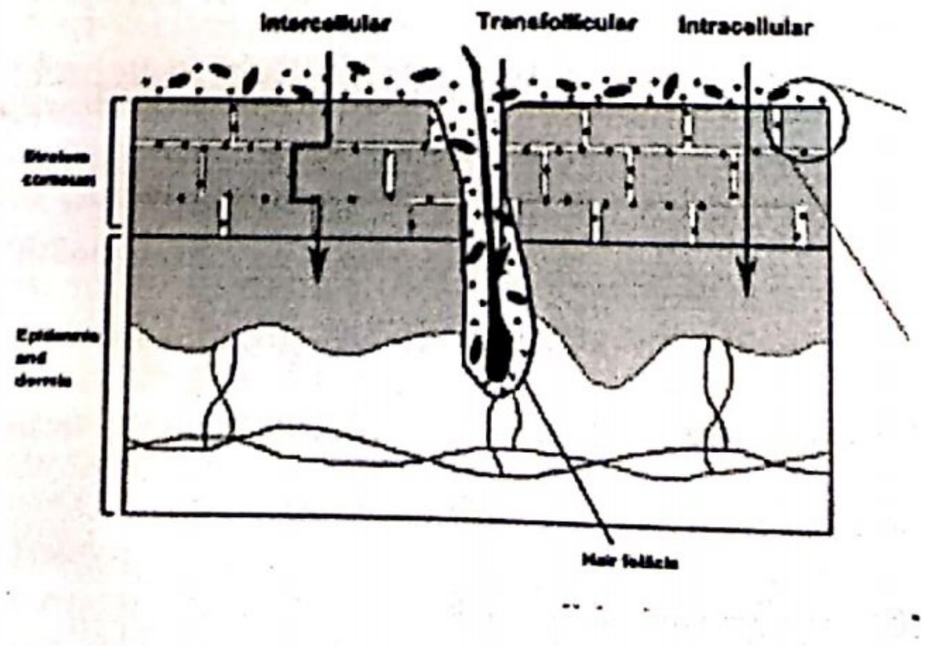
1) Diffusion of drug from drug reservoir to the rate controlling membrane.
2) Diffusion of drug from rate limiting membrane to stratum corneum.
3) Sorption by stratum corneum and permeation through viable epidermis.
4) Uptake of drug by capillary network in the dermal papillary layer.
5) Effect on target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

Routes of drug penetration through skin: In the process of percutaneous permeation, a drug molecule may pass through the epidermis itself or may get diffuse through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands. In the initial transient diffusion stage, drug molecules may penetrate the skin along the hair follicles or sweat ducts and then absorbed through the follicular epithelium and the sebaceous glands. When a steady state has been reached the diffusion through the intact *Stratum corneum* becomes the primary pathway for transdermal permeation. For any molecules applied to the skin, two main routes of skin permeation can be defined: Transepidermal route Transfollicular route.

Transepidermal route: In transepidermal transport, molecules cross the intact horny layer. Two potential micro-routes of entry exist, the transcellular (or intracellular) and the intercellular pathway. Both polar and non-polar substances diffuse via transcellular and intercellular routes by

different mechanisms. The polar molecules mainly diffuse through the polar pathway consisting of "bound water" within the hydrated *stratum corneum* whereas the non-polar molecules dissolve and diffuse through the non-aqueous lipid matrix of the *stratum corneum*. Thus the principal pathway taken by a penetrant is decided mainly by the partition coefficient (log K). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophillic permeants (octanol/water log K > 2) traverse the *stratum corneum* via the intercellular route. Most molecules pass the *stratum corneum* by both routes.

Transfollicular route (Shunt pathway): This route comprises transport via the sweat glands and the hair follicles with their associated sebaceous glands. Although these routes offer high permeability, they are considered to be of minor importance because of their relatively small area, approximately 0.1% area of the total skin. This route seems to be most important for ions and large polar molecules which hardly permeate through the *stratum corneum.*



FACTORS AFFECTING TRANSDERMAL PERMEATION

1. **Partition coefficient:** Drugs possessing both water and lipid solubilities are favored. Lipid/water partition coefficient of 1 or more is required for optimal transdermal permeability.
2. **Molecular size and shape:** Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.
3. **pH conditions:** pH conditions of skin and in drug delivery system affect dissociation and permeation of drug molecule.
4. **Drug concentration:** permeation is passive diffusion process hence depends on drug conc. on surface of skin layer. More drugs are absorbed through percutaneous absorption when the drug is applied to a large surface area. Drug incorporated in an appropriate vehicle must interface skin in sufficient concentration.
5. **Release characteristics of drug delivery system:** Generally the more easily the drug is released from delivery system, the higher the rate of permeation. Drug substance should have greater physicochemical attraction to skin than to vehicle in which it is presented in order for the drug to leave in favor of the skin. Mechanism is depends on interfacial partition coefficient of drug from delivery system to skin tissue.
6. **Composition of drug delivery system:** It has great influence on absorption. It not only affects release rate but also permeability of stratum corneum by means of hydration, mixing with skin lipids or other promoting effects.
7. **Use of permeation enhancers:** Permeation can be improved by use of sorption or permeation promoters. Drug absorption enhanced by the vehicles that easily cover the skin surface, mix readily with sebum and bring drug in contact with sebum for tissue absorption.
8. **Reservoir effect of horny layer:** Horny layer or its deep layer can act as depot or reservoir. Absorption appears to be greater when drug is applied to skin with thin horny layer than with one that is thick. Thus, site of application affect degree of drug absorption. Generally, longer the period of time of medicated application is permitted to remain in contact with skin, the greater will be the absorption.
9. **Vehicles** that increase amount of moisture imbedded by the skin generally favor percutaneous absorption of drug. Oleaginous vehicles acts as moisture barrier through

which the sweat from the skin cannot pass and skin therefore remain occluded resulting in increased hydration of skin beneath the vehicle.

10. **Skin hydration:** Hydration of stratum corneum appears to increase rate of passage of certain substances that penetrate the skin. Increased absorption is probably due to softening of the tissues and the consequent sponging effect with an increase in size of the pore allowing greater flow of substance, large and small molecules through them. Hydration of stratum corneum can enhance the permeability of skin by as much as eight folds.
11. **Skin temperature:** skin permeation of acetyl salicylic acid and glucosteroids was raised ten folds when the environmental temp was raised from 10-37 °C.
12. **Skin metabolism:** Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.
13. **Skin conditions:** The intact skin itself acts as barrier but many agents like acids ,alkali cross the barrier cells and penetrates through the skin ,many solvents open the complex dense structure of horny layer. Solvents like methanol, chloroform remove lipid fraction, forming artificial shunts through which drug molecules can pass easily.
14. **Skin age:** It is seen that the skin of adults and young ones are more permeable than the older ones but there is no dramatic difference .Children shows toxic effects because of the greater surface area per unit body weight. Thus potent steroids, boric acid, hexachlorophene has produced severe side effects.
15. **Regional skin site:** Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration.

Kinetics of transdermal permeation

→ Transdermal permeation of a drug involves the following steps
- i) Sorption by stratum corneum
- ii) Penetration of drug through viable epidermis
- iii) Uptake of the drug in the dermal papillary layer.

→ The rate of permeation ($d\theta/dt$) across the skin is given as -

$$\boxed{\frac{d\theta}{dt} = P_s (C_d - C_r)} \quad \text{---} (1)$$

Where, P_s = Overall permeability constant of the skin tissue to the drug / Penetrant

C_d = Concentration in the donor compartment (Surface of stratum corneum)

C_s = Concentration in receptor compartment (Body)

$$\boxed{P_s = \frac{K_s D_{ss}}{h_s}} \quad \text{---} (2)$$

Where,

K_s = Partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium into stratum corneum.

D_{ss} = Apparant diffusivity of penetrant molecule

h_s = Overall thickness of skin tissues

As K_s, D_{ss}, & h_s are constant under given conditions, the permeability coefficient (P_s) 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 ($C_d \gg C_r$) i.e the drug concentration at the surface of the stratum corneum (C_d) is greater than the drug concentration in the body (C_r), the eq. (1) becomes

$$\boxed{\frac{d\theta}{dt} = P_s C_d} \quad \text{---} (3)$$

→ The rate of skin permeation is constant provided magnitude of C_d remains fairly constant throughout the permeation.

→ for ~~Keeping~~ Keeping C_d constant the drug should be released from the device at a rate R_r ie either constant or greater than the rate of skin uptake R_a i.e $R_r \gg R_a$.

→ Since $R_r \gg R_a$, the drug concentration on the skin surface C_d is maintained at a level equal to or greater than the equilibrium solubility of the drug in the stratum corneum C_s i.e. $C_d \gg C_s$

→ Therefore a maximum rate of skin permeation is obtain and is given by the equation

$$\boxed{\left(\frac{dQ}{dt}\right)_m = P_s C_s} \quad \ldots\ldots (4)$$

→ From the above equation it can be seen that the maximum rate of skin permeation depends upon the skin permeability coefficient P_s and equilibrium solubility in stratum ~~corne~~ corneum C_s.

→ Thus skin permeation appears to be stratum corneum limited

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

$$\boxed{J = \frac{DCK_{o/w}}{h}}$$

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

D = Diffusion coefficient of drug within membrane

C = Concentration gradient across the membrane

K = Partion coefficient (membrane/vehicle)

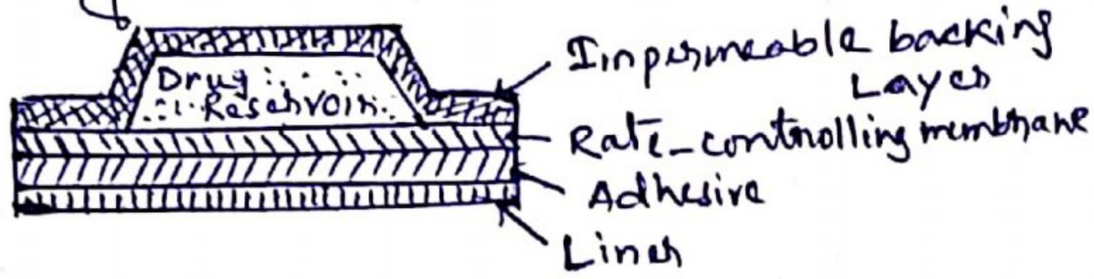
h = ~~Mem~~ Membrane thickness.

Classification of Transdermal drug delivery System :-

* The TDDS can be classified into 2 major categories -
  A) Rate-programmed systems (Transdermal patches)
  B) physical stimuli-activated transdermal dds

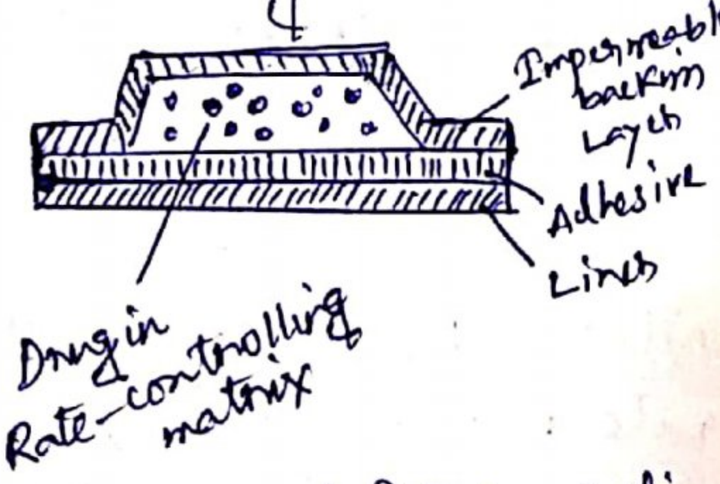
A) Rate-programmed Systems :- It is further classified as follows :-

(i) Drug in reservoir (Membrane type) - Membrane patches contain a delivery rate-controlling membrane between the drug reservoir and the skin.



The drug permeates by dissolution & diffusion through microporous membranes, which control drug flux by the size & tortuosity of pores in the membrane. Several materials like silicones, high-density polyethylene can be used as rate-controlling membranes. The membrane should be permeable only to the drug & enhancer (if present) and should retain other excipients. In drug reservoir compartment, it can be in the form of solution, suspension or gel or dispersed in a solid polymer matrix.
A definite requirement for a reservoir system is that it should permit Zero-order release of the drug over the delivery period.

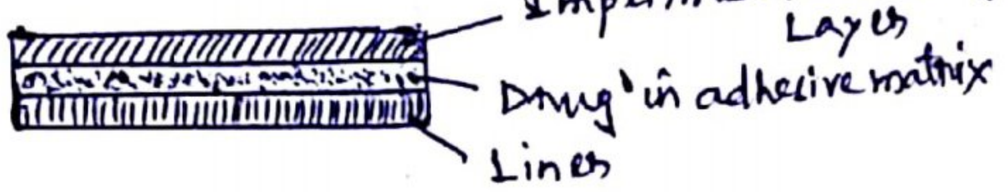
(ii) Drug in Matrix — In this system, the drug is uniformly dispersed in a polymeric matrix (hydrophilic or lipophilic), through which it diffuses to the skin surface. The polymeric matrix may comprise of silicone elastomers, PVA, PVP etc. Several steps are involved in the drug delivery process—



(a) Dissociation of drug molecules from the crystal lattice.
(b) Solubilization/partitioning of the drug in polymer matrix.
(c) Diffusion of drug molecules through the matrix to the surface of the skin.

The diffusion rate of the drug within the matrix must be much greater than the diffusion rate in the skin.

(iii) Drug in Adhesive matrix — These are the simplest systems of involve formulating the drug and enhancers (if present), in an adhesive mixture that is subsequently coated onto a backing membrane, such as a polyester film, to produce an adhesive tape. Such systems have certain disadvantages-

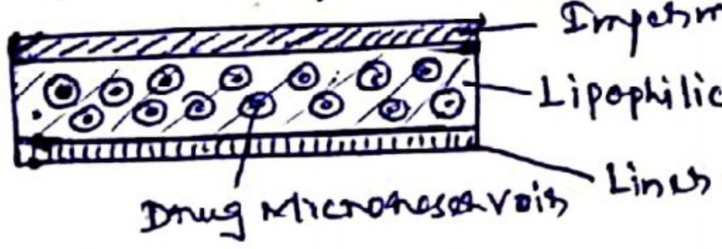


a) Chemical interactions resulting in interference with adhesive performance, breakdown of active species or formation of new chemical entities.

b) Physicochemical characteristics of drug & adhesive may provide different release rates of hydrophilic & hydrophobic drugs. Eg- Silicone adhesives are typically lipophillic, which limits solubility of hydrophilic drugs within adhesive matrix.

c) Incorporation of other excipients, like permeation enhancers into this systems may alter drug release rates and adhesive properties.

(iv) Drug in Microreservoir — This drug delivery system is a combination of reservoir and matrix-dispersion system. The drug reservoir is formed by first suspending the drug in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unleachable, microscopic spheres of drug reservoirs.



(v) Mixed Monolithic-Reservoir Devices (Hybrid patches) — These systems comprises of drug-polymer matrix layered on the skin side by a rate-controlling membrane. Drug release is controlled initially by the membrane but as the drug gets depleted, the rate is controlled by diffusion of drug through a thicker layer of polymer matrix.

Physical-Stimuli Activated TDDS :- Besides the transdermal patches, transdermal delivery of damgs is also possible through the use of physical stimuli and includes different methods such as—

(i) Structure-based system— An example of this type of TDDS is microneedles developed by Alza. It is also called as microflux which consists of a thin titanium screen with 200 μm long microprojections attached to the underside. Such microneedles when applied to the skin, create superficial pathways through the stratum corneum but donot cause any pain. Drug can either be coated into the micro projections for bolus delivery or attached to a damg reservois for continuous or ~~iontophoretic~~ iontophoretic applications. This system could be usefor for delivering vaccines, small molecules.

(ii) Iontophoresis — This system implies delivery of ionic damgs into the body by means of an electric current. An ionised damg in solution is placed on the skin. The damg is applied under an electrode of the same charge as the damg. An electrical potential difference is established thus driving the ions into the skin. Like electrical charges repel. Therefore, application of a positive current will drive positively charged damg molecules away from the electrode & into the tissues. Similarly, a negative current will drive negatively charge ions into tissues. Eg- cortisol, Lidocaine, Insulin have been delivered in this way.

(iii) Electroporation — Skin electroporation creates transient aqueous pores in the lipid by application of high voltage of electrical pulses of approx 100-1000 V/cm for short time (milliseconds). These pores provide pathways for damg penetration that travel straight through the horney layer. This technology has been successfully used to enhance skin permeability of molecules with differing lipophilicity & size with molecular weight greater than 7000 Dalton.

(iv) Sonophoresis / Phonophoresis - This type of drug delivery system utili. ultrasonic energy (at low frequency) the disturbs the lipid packing in stratum corneum by cavitation and activate or trigger the delivery of drug from a polymeric drug delivery device through skin into systemic circulation. Sonicators operating at frequencies in the range of 20 KHZ to 3 MHZ are avi available commercially & can be used for sonophoresis.

FORMULATION OF TRANSDERMAL DRUG DELIVERY SYSTEM/ MATERIALS EMPLOYED IN TDDS

Various components of a transdermal drug delivery system are

1. **Drug substance:** For successfully developing a transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery:
   - The drug should have a molecular weight less than 1000 Daltons.
   - The drug should have affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conductive to successful drug delivery via the skin.
   - The drug should have low melting point.
   - The drug should be potent, having short half life and be non-irritating.
   - The drug should not be irritant and non allergic to human skin.
   - The drug should be stable when contact with the skin.
   - The drug should not get extensively metabolized in the skin.

2. **Polymer matrix:** Polymers are the backbone of transdermal drug delivery system. System for transdermal delivery are fabricated as multi layered polymeric laminates in which a drug reservoir or a drug polymer matrix is sandwiched between two polymeric layers, an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive, or rate controlled membrane. Ideal properties of a polymer to be used in a transdermal system:
   - Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
   - The polymer should be stable, nontoxic, and inexpensive.
   - The polymer and its degradation products must be non-toxic or non-antagonistic to the host.
   - The mechanical properties of the polymer should not deteriorate excessively when large amounts of active agent are incorporated into it.

Some commonly used polymers for TDD are:

- ❖ Natural Polymers: Cellulose derivatives, Zein, Gelatin, Proteins, Shellac, Starch
- ❖ Synthetic Elastomers: Polybutadiene, Polysiloxane, Acrylonitrile, Neoprene, Chloroprene, Silicon rubber
- ❖ Synthetic Polymers: Polyvinyl alcohol, Polyethylene, Polyvinyl Chloride, Polyacrylates, Polyamide

3. **Penetration Enhancers:** These are compounds which promote the skin permeability by altering the skin as barrier to the flux of a desired penetrate. Ideal properties of penetration enhancers are:
   - It should be compatible with all drugs and excipients.

- Upon removal of the material, the skin should immediately and fully recover its normal barrier property.
- The enhancer should not cause loss of body fluids, electrolytes or other endogenous materials.
- The chemical should formulate into all the variety of preparations used topically.
- It should be odourless, tasteless, colourless and inexpensive.

Permeation enhancers can enhance the skin permeability by a variety of mechanisms, including-

a) Interaction with intercellular lipids leading to disruption of their organization and increasing their fluidity.
b) Extraction of lipids from the stratum corneum.
c) Displacement of bound water.
d) Loosening of horny cells.
e) Enhancing solubility.
f) Increasing partitioning into the stratum corneum.
g) Interaction with intercellular protein, and keratin denaturation.

Some commonly used absorption enhancers for TDDS are:

- ❖ Surfactants: Na-lauryl sulfate, Na-deoxycholate. Na-glycocholate
- ❖ Fatty acids: Oleic acid
- ❖ Cyclodextrins: γ- and β-Cyclodextrins
- ❖ Chelating agents: EDTA, Polyacrylates
- ❖ Positively charged polymer: Chitosan salts, Trimethyl chitosan

4. Other excipients:

a) ***Solvents:*** Various solvents such as chloroform, methanol, acetone, isopropananol, and dichloromethane, are used to prepare drug reservoir. In addition plasticizers such as dibutyl pthalate, propylene glycol are added to provide plasticity to the transdermal patch.

b) ***Pressure sensitive adhesive:*** A Pressure Sensitive Adhesive (PSA) is a material that helps in maintaining an intimate contact between transdermal system and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tacky, and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue. PSA should be physicochemical and biologically compatible and should not alter drug release. The PSA can be positioned on the face of the device or in the back of the device and extending peripherally.

PSAs used in commercially available Transdermal systems include polyacrylate, polyisobutylene, and polysiloxane.

- *Polyacrylates,* are most widely used. In general, all acrylic adhesives are polar in character, allowing them to absorb moisture readily and to maintain adhesion to wet skin. They also dissolve most drugs well, enabling high drug loading of polyacrylate matrices.
- *Polyisobutylenes (PIBs)*, in contrast, are characterized by a low solvent capacity for drugs. PIB-based adhesives are mixtures of high and low molecular weight polymers, which provide cohesion and tackiness, respectively. By adjusting the composition of the PIB formulation, cold flow and adhesiveness can be customized for each system.
- *Silicone*, adhesives are characterized by low allergenicity. Similar to PIBs, silicones dissolve most drugs poorly and regulate tackiness and cohesion through polymer size.

c) ***Backing laminates:*** While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipient compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer. However, an overemphasis on the chemical resistance may lead to stiffness and high occlusivity to moisture vapor and air, causing patches to lift and possibly irritate the skin during long wear. They should a low moisture vapour transmission rate. They must have optimal elasticity, flexibility and tensile strength. eg: aluminum vapour coated layer, a plastic film and heat real layer.

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

EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM

The evaluation methods for transdermal dosage form can be classified into following types:

A. Physicochemical evaluation

B. *In vitro* evaluation

C. *In vivo* evaluation

A. Physicochemical Evaluation

1) **Interaction studies:** The drug and the excipients must be compatible with one another to produce a product that is stable. The interaction between drug and excipients affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are taken out by Thermal analysis, FT- IR, UV and chromatographic techniques by comparing their physicochemical properties like assay, melting point, wave numbers, and absorption maxima.

2) **Thickness of the patch:** The thickness of the drug loaded patch is measured in different points by using a digital micrometer and the average thickness and standard deviation is determined to ensure the thickness of the prepared patch. The thickness of transdermal film is determined by travelling microscope dial gauge, screw gauge or micrometer at different points of the film.

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

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

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

$$\% \text{ Moisture content} = [(\text{Initial weight} - \text{Final weight}) / \text{Final weight}] \times 100$$

6) **Percentage Moisture Uptake**: Weighed films are kept in desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in desiccators until a constant weight is achieved. % moisture uptake is calculated as given below.

$$\%\text{Moisture uptake} = [(\text{Final weight} - \text{Initial Weight}) / \text{Initial Weight}] \times 100$$

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

8) **Content uniformity test:** 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

9) **Polariscopic examination:** A specific surface area of the piece is to be kept on the object slide of Polariscope and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch.

10) **Water vapor transmission studies (WVT):** For the determination of WVT, weigh one gram of calcium chloride and place it in previously dried empty vials having equal diameter. The polymer films are pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then, the vials are accurately weighed and placed in humidity chamber maintained at 68 % RH. The vials are again weighed at the end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch.

$$WVT = W / ST$$

W is the increase in weight in 24 hr, S is area of film exposed (cm2), T is the exposure time.

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

$$\% \text{ constriction} = [(I_1 - I_2) / I_1] \times 100$$

Where, I_1 = Initial length of each strip, I_2 = final length of each strip.

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

13) **Peel Adhesion test:** In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to

a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180° angle, and the force required for tape removed is measured.

14) **Tack properties test:** It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer.

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

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

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

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

B. *In Vitro* Evaluation

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

16) **In vitro skin permeation studies:** An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Westar rats weighing 200 to 250g was taken. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin is thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and is placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell is maintained at 32 ± 0.5°C using a thermostatically

controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or HPLC.

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

C. *In Vivo* Evaluation

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

Animal models: Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, rabbit, guinea pig etc. Various experiments conducted lead us to a conclusion that hairless animals are preferred over hairy animals in both in vitro and in vivo experiments.

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

18) **Skin Irritation study:** Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface ($50cm^2$) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

The Future

Pharmacist