



Research Article

RECENT ADVANCES ON TRANSDERMAL DRUG DELIVERY SYSTEM

Nirja¹, Pawan Jalwal¹, Sumit Sigroha^{2*}, Sahil Kumar³

1. Department of Pharmaceutical Sciences, Baba Mastnath University,
Asthal Bohar, Rohtak-124001

2. Fitlife health care, gurgaon

3. Ph.D. Scholar, ISF College of Pharmacy, Moga

Abstract

Transdermal drug delivery is defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. There are two important layers of the skin: the dermis and epidermis. The outermost layer is approximately 100 to 150 micrometers thick and thin layer has no blood flow and includes a layer within it known as stratum corneum. This is the layer which is most important for transdermal drug delivery as its composition allows it to keep water within the body and foreign substances out. Beneath the epidermis, the dermis contains a system of capillaries that transport blood throughout the body. If the drug passes the stratum corneum layer then it can enter the blood stream. This process called passive diffusion. Lipid soluble substances readily pass through the intercellular lipid bi layers of the cell membrane whereas water soluble drugs are able to pass through the skin because of hydrated intracellular proteins. Using drug in this manner much more rapid and useful drug delivery is possible.

Keywords: Transdermal patches, epidermis, dermis, micrometer etc.

Introduction

Transdermal drug delivery is defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. Oral route is the most common route for drug delivery but due to the body's high metabolic activity, and changing chemical environment, limits the availability of a wide variety of drugs, including proteins and peptides. There are two important layers of the skin: the dermis and epidermis. The outermost layer is approximately 100 to 150 micrometers thick and thin layer has no blood flow and

includes a layer within it known as stratum corneum. This is the layer which is most important for transdermal drug delivery as its composition allows it to keep water within the body and foreign substances out. Beneath the epidermis, the dermis contains a system of capillaries that transport blood throughout the body. If the drug passes the stratum corneum layer then it can enter the blood stream. This process called passive diffusion. Lipid soluble substances readily pass through the intercellular lipid bi layers of the cell membrane whereas water soluble drugs are able to pass through the skin because of hydrated intracellular proteins. Using drug in this manner much more rapid and useful drug delivery is possible.

Rationale for Drug candidate used in Transdermal System

Transdermal patch is used when the patient has intolerable side effects including constipation and who is unable to take the oral medication and is requesting for an alternative. It is also used when the pain control might be improved by reliable administration. Transdermal patches are used for the drugs which have to be administered for long period of time or which causes adverse effects to the non-target tissues. The use of the transdermal patch is not suitable when the cure of acute pain is required and where the requirement of the dose is equal to or less than 30mg/24hrs. Transdermal delivery is an important option for delivering drugs with poor oral bioavailability and those that undergo extensive first-pass hepatic metabolism. It is also very useful delivery option for drugs with short half-lives or inconvenient dosing regimens and for the drugs with narrow therapeutic window. Transdermal patches are convenient, user friendly and painless and permit self administration. They offer multiday dosing, which improve patient compliance with the drug regimen. Administration of drug via transdermal patch produces a steady drug serum concentration without significant differences in peak and trough serum concentrations during the dosing interval. For some drugs this is associated with fewer systemic side effects. It avoids the need for invasive parenteral administration. It is an alternative route of administration if patients cannot tolerate oral dosage forms or if the drug causes gastrointestinal upset. It is suitable for the patients who are nauseous or unconscious. Drug therapy can be terminated rapidly. Commonly used dosage forms in patches were creams, lotions, ointments, gels.

Advantages of Transdermal Drug Delivery Systems

The positive features of drug delivery across the skin to achieve systemic effects

- Avoidance of first pass metabolism
- Avoidance of gastro intestinal incompatibility ☐
- Predictable and extended duration of activity
- Minimizing undesirable side effects ☐
- Provides utilization of drugs with short biological half lives TM
- Narrow therapeutic window

Disadvantages of Transdermal Drug Delivery

- Improving physiological and pharmacological response ☐
- Avoiding the fluctuation in drug levels ☐
- Inter and intra patient variations ☐
- Maintain plasma concentration of potent drugs
- Termination of therapy is easy at any point of time ☐
- Greater patient compliance due to elimination of multiple dosing profiles ☐
- Ability to deliver drug more selectively to a specific site
- Provide suitability for self administration ☐
- Enhance therapeutic efficacy

Despite decades of research, the barrier function of the stratum corneum still remains a problem, which makes the development of new transdermal drug delivery systems an interesting challenge. For dermal and transdermal drug delivery, vesicular systems as vehicles have been widely studied. Their drug permeation enhancing properties have been well established.

Optimum therapeutic outcomes require not only proper drug selection but also effective drug delivery. The human skin is a readily accessible surface for drug delivery. Over the past three decades, developing controlled drug delivery has become increasingly important in the pharmaceutical industry. Development of membrane permeation for effective Transdermal Delivery of ibuprofen desired therapeutic effect and the undesired adverse effect, of a drug is dependent on the concentration of the drug at the site of action, which in turn depends upon the dosage form and the extent of absorption of the drug at the site of action. Tablets and injections have been the traditional way to take medications; new options are becoming increasingly popular. One highly successful alternative delivery method is the transdermal. Skin of an average adult body covers a surface of approximately 2m² and receives about one-third of the blood circulating through the body. The deliver a drug into the body through transdermal layer of skin, it is necessary to understand about the skin.

Systems

- 1.The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult.
- 2.Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin impermeability.
- 3.Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.
- 4.Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.
- 5.The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

Mechanisms of Transdermal Permeation

For a systemically-active drug to reach a target tissue, it has to possess some physico-chemical properties which facilitate the absorption of the drug through the skin, and also the uptake of the drug by the capillary network in the dermal papillary layer

The rate of permeation, dQ/dt , across various layers of skin tissues can be expressed as.

$$dQ/dt = P_s (C_d - C_r) \dots\dots\dots (1)$$

Where, C_d and C_r are, respectively, the concentrations of skin penetrate in the donor phase (stratum corneum) and the receptor phase (systemic circulation); and P_s is the overall permeability coefficient of the skin and is defined by

$$P_s = \frac{K_s D_{ss}}{h_s} \dots\dots\dots (2)$$

Where, K_s = Partition coefficient of the penetrant
 D_{ss} = Apparent diffusivity of penetrant
 h_s = Thickness of skin

Thus, permeability coefficient (P_s) may be a constant since K_s ; D_{ss} and h_s terms in equation (2) are constant under the given set of conditions. A constant rate of drug permeation achieved, if $C_d > C_r$, then the equation (1) may be reduced to

$$dQ/dt = P_s \cdot C_d \dots\dots\dots(3)$$

And the rate of skin permeation (dQ/dt) becomes a constant, if the C_d value remains fairly constant throughout the course of skin permeation. To maintain the C_d at a constant value, it is critical to make the drug to be released at a rate (R_r) which is always greater than the rate of skin uptake (R_a), i. e., $R_r \gg R_a$ (Fig 1).

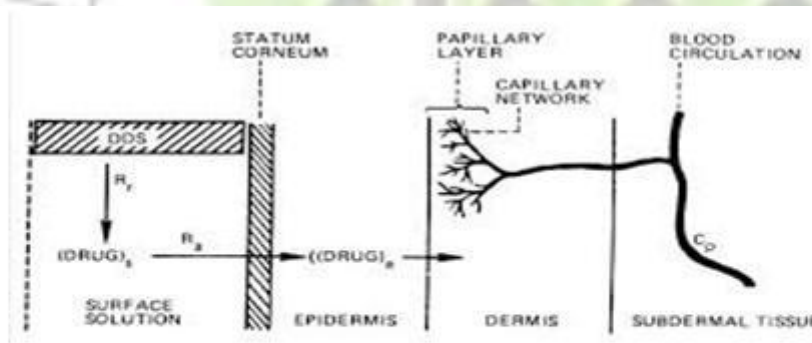


Fig 1: Relationship between the rate of drug release (R_r) from a transdermal drug delivery system (TDDS) and the rate of drug uptake (R_a) by the skin.

By doing so, the drug concentration on the skin surface (C_d) is maintained at a level which is always greater than the equilibrium (or saturation) solubility of the drug in the stratum corneum (C_{es}), i.e., $C_d \gg C_{es}$ and a maximum rate of skin permeation (dQ/dt) m , as expressed by equation (4), is thus reached:

$$[dQ/dt]_m = P_s C_{es} \dots\dots\dots(4)$$

Apparently, the magnitude of (dQ/dt) m is determined by the skin permeability coefficient

(P_s) of the drug and its equilibrium solubility in the stratum corneum (C_{es}).

Types of Transdermal Drug Delivery Systems
Membrane permeation controlled system

In this type of system, the drug reservoir is totally encapsulated in a shallow compartment moulded from a drug impermeable metallic plastic laminate and a rate controlling polymeric membrane e.g. Ethylene vinyl acetate with defined drug permeability. The drug molecules

are permitted to release only through the rate-controlling membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid-polymer matrix or suspended in a viscous liquid medium to form a paste like suspension. A thin layer of adhesive polymer is applied to the external surface of the rate controlling membrane to achieve an intimate contact of the transdermal system and the skin surface.

Matrix diffusion controlled system

In this approach, the drug reservoir is prepared by homogenously dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then moulded into a medicated disc with a defined surface area and controlled thickness. This drug reservoir containing polymer disc is then pasted on to an occlusive base plate in a compartment fabricated

from a drug impermeable plastic backing. The adhesive polymer is then spread along the circumference to form a strip of adhesive rim around the medicated disc.

Adhesive dispersion type system

This is a simplified form of the membrane permeation-controlled system. The drug reservoir is formulated by directly dispersing the drug in an adhesive polymer like Polyisobutylene and then spreading the medicated adhesive, by solvent casting or hot melt onto a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. On the top of the drug reservoir layer, thin layers of non-medicated, rate-controlling adhesive polymer of a specific permeability are applied to produce an adhesive diffusion - controlled delivery system.

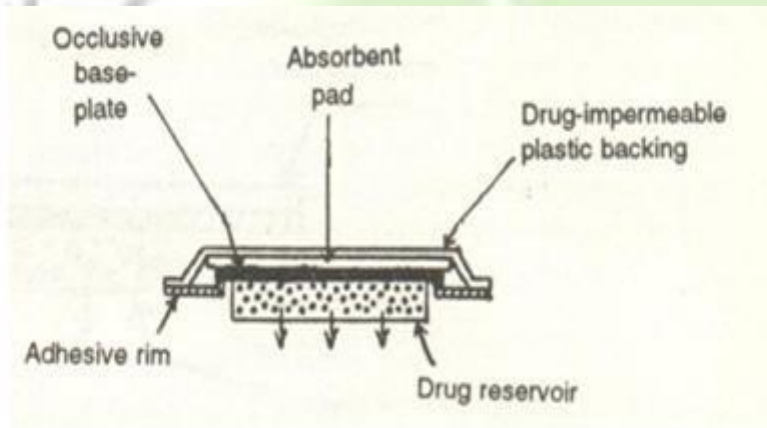


Figure 1.2: Cross sectional view of matrix diffusion controlled transdermal drug delivery system

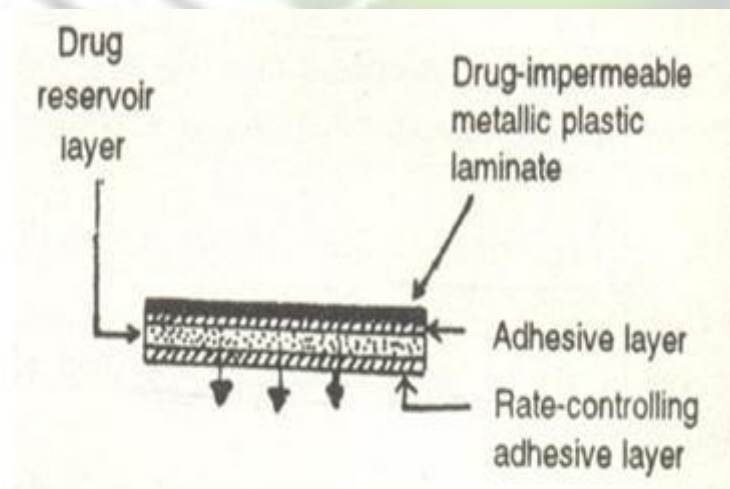


Figure 1.3: Adhesive dispersion type transdermal drug delivery system

Micro reservoir type or micro sealed dissolution controlled system

Here, the drug reservoir is formed by first suspending the drug solids in an aqueous solution of a water soluble liquid polymer and then dispersing the drug suspension homogeneously in a lipophilic polymer by high shear mechanical force to form a large number of micro reservoirs. These are unreachable microscopic spheres of drug reservoirs. This

thermodynamically unstable dispersion is stabilized quickly by immediate addition of cross linking polymers like Glutaraldehyde the polymer which produces a medicated polymer disc with a constant surface area and a fixed thickness. A transdermal therapeutic system is produced by positioning the medicated disc at the centre and surrounding it with an adhesive rim and then it is spread to the occlusive base plate with adhesive foam pad.

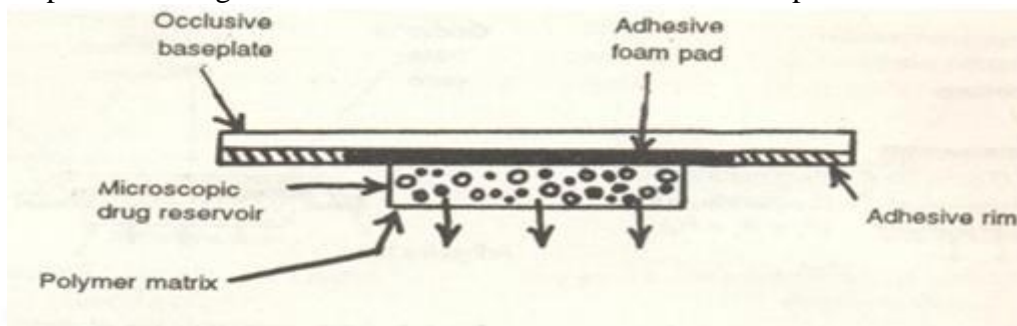


Figure 1.4: Microreservoir dissolution controlled transdermal drug delivery system

Various Methods for Preparation TDDS

Asymmetric TPX membrane method

A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive. These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°C to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a Gardner knife. After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs.

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.

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.

By using "IPM membranes" method

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymers and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.

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.

Aluminium backed adhesive film method

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custammade aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

Preparation of TDDS by using Proliposomes

The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. 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.

By using free film method

Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in desiccators until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.

Basic Components of Transdermal Drug Delivery System

The components of transdermal device include:

- 1.Polymer matrix
- 2.The drug
- 3.Permeation enhancers
- 4.Other excipients

1 .Polymer matrix:

The Polymer controls the release of the drug from the device. The polymer should be stable, non-reactive with the drug, easily manufactured into the desired product and inexpensive. The polymer and its degradation products must be non-toxic or non-antagonistic to the host. Possible useful polymers for transdermal devices are:

Table 1: Types of Polymers used in TDDS

Polymers	Examples
Natural Polymers	Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch
Synthetic Elastomer	Polybutadiene, Hydri rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadiene rubber, Neoprene etc.
Synthetic Polymers	polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethylmethacrylate, epoxy etc.

2. Drug:

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.

Physicochemical properties

1. The drug should have a molecular weight less than approximately 1000 daltons.
2. The drug should have affinity for both – lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin. Along with these properties the drug should be potent, having short half life and be none irritating.

3. Permeation Enhancers: These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. These may conveniently be classified under the following headings:

Solvents: These compounds increase penetration possibly by swelling the polar pathway and/or by fluidizing lipids. Examples include water alcohols – methanol and ethanol; alkyl methyl sulfoxides – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethyl acetamide and dimethyl form amide; pyrrolidones – 2 pyrrolidone, N-methyl, 2-pyrrolidone; laurocapram (Azone), miscellaneous solvents – propylene glycol, glycerol.

Surfactants: These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.

Anionic Surfactants: Dioctyl sulphosuccinate, Sodium lauryl sulphate, especially Decodecylmethylsulphoxide

Nonionic Surfactants: e.g. PluroF127, PluronicF68 etc

Bile Salts: e.g. Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

Binary system: These systems apparently open up the heterogeneous multilaminar pathway as well as the continuous pathways. e.g. Propyleneglycol-oleic acid and 1, 4-butane diol-linoleic acid.

Miscellaneous chemicals: These include urea, a hydrating and keratolytic agent; N, N-dimethyl-m-toluamide; calcium thioglycolate; anticholinergic agents. Some potential

permeation enhancers have recently been described but the available data on their effectiveness sparse.

The rate of drug transport across the skin (stratum corneum) follows Ficks law of diffusion and can be explained by the following equation:-

$$J = \frac{K \cdot D \cdot \Delta C}{H}$$

Where J is the steady state flux across the stratum corneum

K is the partition coefficient of the drug between skin and the formulation medium.

D is the diffusion constant or coefficient of the drug molecule in the stratum corneum.

ΔC is the concentration difference across the stratum corneum.

H is thickness of the stratum corneum.

4. Other Excipients

a) Adhesives: The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive which can be positioned on the face of the device or in the back of the device and extending peripherally. Adhesive systems should fulfill those criteria.

- (i) Should not irritate or sensitize the skin
- (ii) Should not leave an unwashable residue on the skin.
- (iii) Should adhere to the skin aggressively, should be easily removed.

The face adhesive system should also fulfill the following criteria.

- (i) Physical and chemical compatibility with the drug, excipients and enhancers of the device
- (ii) The delivery of simple or blended permeation enhancers should not be affected. Eg. Poly isobutylenes, acrylic and silicones.

b) Backing membrane: Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is impermeable substance that protects the product during use on the skin e.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminium foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc) etc.

The main purpose of developing alternative drug delivery technologies is to increase efficiency and safety of drug delivery and provide more convenience for patient. Substantial research

to the development of technologies that meet the requisite criteria for delivering the drug through a non invasive route. One of such technologies is transdermal drug delivery. Transdermal drug delivery is non invasive delivery of medication from the surface of the skin the largest and most accessible organ of the human body through its layers, to the circulatory system. Medication delivery is carried out by a patch that is attached to the body surface. Transdermal patch is a medicated adhesive pad that is designed to release the active ingredient at a constant rate over a period of several hours to days after application to the skin. It is also called skin patch. A skin patch uses a special membrane to control the rate at which the drug contain within the patch can pass through the skin and into the blood stream. The first transdermal patch was approved by the FDA in 1979. It was a patch for the treatment of motion sickness. In the mid 1980s, the pharmaceutical companies started the development of nicotine patch to help smokers quit smoking and within a few months at the end of 1991 and beginning of 1992. The FDA approved for nicotine patches. Today drugs administrated through skin patches include scopolamine (for motion sickness), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerine (for angina), lidocaine to relieve the pain of shingles (herpes zoster). Non medicated patches include thermal and cold patches, weight loss patches, nutrient patches, skin care patches (therapeutic and cosmetic), and aroma patches, and patches that measure sunlight exposure.

General clinical considerations in the use of TDDS

The patient should be advised of the following general guidelines. The patient should be advised of the importance of using the recommended site and rotating locations within the site. Rotating location is important to allow the skin to regain its normal permeability and to prevent skin irritation. TDDS should be applied to clean, dry skin relatively free of hair and not oily, inflamed, irritated, broken. Wet or moist skin can accelerate drug permeation time. Oily skin can impair the adhesion of patch. If hair is present at the site, it should be carefully cut, not wet shaved nor should a depilatory agent be used, conducted during the past several years has lead

since later can remove stratum corneum and affect the rate and extent of drug permeation. Use of skin lotion should be avoided at the application site, because lotions affect the hydration of skin and can alter partition coefficient of drug. Patient should not physically alter TDDS, since this destroys integrity of the system. The protecting backing should be removed with care not to touch fingertips. The TDDS should be pressed firmly against skin site with heal of hand for about 10 seconds. A TDDS should be placed at a site that will not subject it to being rubbed off by clothing or movement. TDDS should be left on when showering, bathing or swimming. A TDDS should be worn for full period as stated in the product's instructions followed by removal and replacement with fresh system. The patient or caregiver should clean the hands after applying a TDDS. Patient should not rub eye or touch the mouth during handling of the system. If the patient exhibits sensitivity or intolerance to a TDDS or if undue skin irritation results, the patient should seek re-evaluation. Upon removal, a used TDDS should be folded in its half with the adhesive layer together so that it cannot be reused. The used patch discarded in a manner safe to children and pets.

Fundamentals of skin permeation

Until the last century the skin was supposed to be impermeable with exception to gases. However, in the current century the study indicated the permeability to lipid soluble drugs. Also it was recognized that various layers of skin are not equally permeable i.e. epidermis is less permeable than dermis. After a large controversy, all doubts about stratum corneum permeability were removed and using isotopic tracers, it was suggested that stratum corneum greatly hamper permeation.

a) Stratum corneum as skin permeation barrier

The average human skin contains 40-70 hair follicles and 200-250 sweat ducts per square centimeter. Especially water-soluble substances

pass faster through these ducts; still these ducts don't contribute much for skin permeation. Therefore most neutral molecules pass through stratum corneum by passive diffusion.

Series of steps in sequence

1. Sorption of a penetrant molecule on surface layer of stratum corneum.
2. Diffusion through it and viable epidermis and finally reaches to dermis and then
3. The molecule is taken up into the microcirculation for systemic distribution.

b) Permeation pathways

Percutaneous absorption involves passive diffusion of the substances through the skin. A molecule may use two diffusional routes to penetrate normal intact skin, the appendageal route and the epidermal route. as shown below.

a) Appendageal route

Appendageal route comprises transport via sweat glands and hair follicles with their associated sebaceous glands. These routes circumvent penetration through the stratum corneum and are therefore known as "shunt" routes. This route is considered to be of minor importance because of its relatively small area, approximately 0.1 % of the total skin area.

b) Epidermal route

For drugs, which mainly cross-intact Horny layer, two potential micro routes of entry exists, the transcellular (intracellular) and intercellular pathways.

I. Transcellular: Transcellular pathway means transport of molecules across epithelial cellular membrane. These include passive transport of small molecules, active transport of ionic and polar compounds and endocytosis and transcytosis of macromolecules.

➤ **II. Paracellular:** Paracellular pathway means transport of molecules around or between the cells. Tight junctions or similar situations exist between the cells. The principal pathway taken by a permeant is decided mainly by the partition coefficient ($\log k$). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophilic permeants traverse the

corneum via the intercellular route. Most permeants permeate the stratum corneum by both routes. However, the tortuous intercellular pathway is widely considered to provide the principal route and major barrier to the permeation of most drugs.

Enhancement of penetration: Combating skin barrier

To overcome the stratum corneum barrier problem for transdermal delivery of the drugs to achieve effective plasma concentration, need arises to search the techniques, which combat this problem and enhances the transdermal penetration of drugs. These techniques are broadly divided into three categories:

1. Physical penetration enhancement: This class mainly includes different methods which share the common goals to disrupt stratum corneum structure in order to create 'holes' big enough for molecules to permeate. Two of the better-known technologies include iontophoresis and sonophoresis. A new technology for macromolecule delivery is microneedle-enhanced delivery.

2. Chemical penetration enhancement: These are the substances that help promote drug diffusion through the stratum corneum and epidermis and are referred to as penetration enhancer, accelerants, adjuvants, or sorption promoters.

3. Biochemical penetration enhancement: Biochemical means of penetration enhancement include using prodrug molecules, chemical modification, enzyme inhibition and the usage of vesicles or colloidal particles.

Properties that influence transdermal drug delivery

The effective transdermal drug delivery can be formulated by considering three factors as drug, skin and the vehicles. So the factors affecting can be divided in two classes as biological factors and physicochemical factors.

Biological factors

➤ **Skin condition:** Acids and alkalis, many solvents like chloroform, methanol damage

stratum the skins cells and promote penetration. Diseased state of patient alters the skin conditions. The intact skin is better barrier but the above mentioned conditions affect penetration.

- Skin age: The young skin is more permeable than older. Childrens are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug in transdermal drug delivery system (TDDS).
- Blood supply: Changes in peripheral circulation can affect transdermal absorption.
- Regional skin site: Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration.
- Skin metabolism: Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.
- Species differences: The skin thickness, density of appendages and keratinization of skin vary species

Physicochemical factors

- Skin hydration: In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. So use of humectant is done in transdermal delivery.
- Temperature and pH: The permeation of drug increase ten folds with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pK_a or pK_b values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factors affecting drug penetration.
- Diffusion coefficient: Penetration of drug depends on diffusion coefficient of drug. At a constant temperature the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.
- Drug concentration: The flux is proportional to the concentration gradient across the barrier and concentration gradient will be

higher if the concentration of drug will be more across the barrier.

- Partition coefficient: The optimal partition coefficient (K) is required for good action. Drugs with high K are not ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated.
- Molecular size and shape: Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.

Ideal molecular properties for transdermal drug delivery

- Ideal molecular properties for drug penetration are as follows;
- An adequate solubility in lipid and water is necessary (1mg/ml).
- Optimum partition coefficient is required for good therapeutic action.
- Low melting point of drug is desired ($<200^\circ\text{C}$).
- The pH of the saturated solution should be in between 5 to 9.
- Molecular weight less than 500 Daltons
- Low dose deliverable per day
- Less oral bioavailability
- Half life less than 10 hr

References:-

- 1.Dermatology. (4th edition.). Elsevier Inc. ISBN 1-4160-3185-5.
- 2.Ghosh TK, Jasti BR, Abraham W. Transdermal and Topical drug delivery systems. Theory and Practice of contemporary Pharmaceutics .CRC press; 2004 .p. 423-454.
- 3.Aulton.M.E, Pharmaceutics; The science of dosage form design, second edition, Churchill Livingston, Harcourt publishers-2002.
- 4.Barry, B.W. Dermatological Formulations: Percutaneous Absorption. Marcel Dekker, New York .(1983) .p .35-38
- 5.Bronaugh, R.L, Maibach, H. I.Percutaneous Absorption, 4th edition. Marcel Dekker, Jain, N. K., Controlled and Novel Drug Delivery, CBS Publishers, and Distributors, 2002, 107.
- 6.Chien, YW, Novel drug delivery systems,

- Drugs and the Pharmaceutical Sciences, Vol.50, Marcel Dekker, New York, NY;1992;797
- 7.Roberts MS, Targeted drug delivery to the skin and deeper tissues: role of physiology, solute structure and disease.Clin Exp Pharmacol Physiology 1997 Nov; 24(11):874-9.
- 8.Ansel.H.C, Loyd.A.V, Popovich.N.G, Pharmaceutical dosage forms and drug delivery systems, Seventh edition, Lippincott Williams and Willkins publication(1983) p.565 -596.
- 9.Brahmankar.D.M, Jaiswal.S.B, Biopharmaceutics and pharmacokinetics A Treatise. Vallabh Prakashan, Delhi1995, 335-371.
- 10.Banker, G. S and Rhodes, C. T Modern pharmaceuticals, third edition, New York, Marcel Dekker, Inc, 1990.
- 11.Jain.N.K, Controlled and novel drug delivery, first edition, CBS publishers and distributors, New Delhi.1997.
- 12.Mathiowitz.Z.E, Chickering.D.E, Lehr.C.M, Bioadhesive drug delivery systems; fundamentals, novel approaches and development, Marcel Dekker, Inc New York.
- 13.Proksch, E; Brandner, JM; Jensen, JM (2008). "The skin: an indispensable barrier." *Experimental Dermatology* **17** (12): 1063–72.
- 14.Madison, KC. (2003). "Barrier function of the skin: "la raison d'être" of the epidermis". *J Invest Dermatol* **121** (2): 231–41
- 15.Johnson, J.M. and Proppe, D.W. Cardiovascular adjustments to heat stress. In: Handbook of Physiology. Section 4: Environmental Physiology (Fregly, M.J. and Blatteis, C.M. eds), pp. 215–243.
- 16.Vyas SP, Khar RK. Controlled Drug Delivery: Concepts and Advances. Vallabh Prakashan. 1st edition;2002:411- 447
- 17.Naik A, Kalia YN and Guy RH. Transdermal drug delivery: overcoming the skin's barrier function. Pharm Science Technology Today. 2000; 3(9):318-326.
- 18.Chein YW. Transdermal Drug Delivery, In : Swarbick J. editor, Novel Drug Delivery Systems, New York: Marcel Dekker. 2nd edition . 2005;50:301–380.
- 19.Barry B. Transdermal drug delivery, In: Aulton ME, editor, Pharmaceuticals: the science of dosage form design. Churchill Livingstone Ltd. 2002:499–533.
- 20.Barry BW. Dermatological Formulations: New York. Marcel Dekker. 1983; 18:95–120.
- Roberts MS, Targeted drug delivery to the skin and deeper tissues: role of physiology, solute structure and disease.Clin Exp Pharmacol Physiol 1997 Nov; 24(11):874-9.
- 21.Ryan D. Gordon, and Tim A. Peterson, transdermal drug delivery , drug delivery technology,
- 22.Dubey V, Mishra D, Nahar M, Jain NK. Vesicles as tools for the modulation of skin permeability Drug Delivery. 2007; 4(6):579-593.
- 23.Hadgraft J, Guy R. In Transdermal Drug Delivery, Marcel Dekker, Inc., New York and Basel. 1989; 35:296.
- 24.Schreier R, Bouwstra J. Liposomes and niosomes as topical drug carriers: dermal and transdermal drug delivery. J Control Release. 1994; 30(1):1-15.
- 25.Keleb E, Sharma RK, Mosa EB, Aljahwi AZ. Transdermal drug delivery system- design and evaluation. Int J Adv Pharm Sci. 2010; 1:201-211.
- 26.Hadgraft J, Guy R. In Transdermal Drug Delivery, Marcel Dekker, Inc., New York and Basel. 1989; 35:296.
- 27.Vyas SP, Khar RK. Controlled Drug Delivery: Concepts and Advances. Vallabh Prakashan. 1st edition;2002:411- 447
- 28.Naik A, Kalia YN and Guy RH. Transdermal drug delivery: overcoming the skin's barrier function. Pharm Science Technology Today. 2000; 3(9):318-326.
- 29.Chein YW. Transdermal Drug Delivery, In: Swarbick J. editor, Novel Drug Delivery Systems, New York: Marcel Dekker. 2nd edition. 2005; 50:301–380.
- 30.Barry B. Transdermal drug delivery, In: Aulton ME, editor, Pharmaceuticals: the science of dosage form design. Churchill Livingstone Ltd. 2002:499–533.

31. Barry BW. Dermatological Formulations: New York. Marcel Dekker. 1983; 18:95–120.
32. Bodae HE, De Hnn FHN. Drug permeation enhancement: Theory and Application, In: Hsieh DS editor, Drugs and Pharmaceutical Sciences, New York: Marcel Dekker. 1994; 62:59–90.
33. Rawat AS, Senthil MK, Khurana B, Mahadevan N. Proniosome gel: a novel topical delivery system. Int J Recent Adv Pharm Res. 2011; 3(1):1-10.
34. Benson HAE. Transdermal drug delivery: penetration enhancement techniques. Current Drug Delivery. 2005; 2(1):23-33.
35. Prausnitz MR. Microneedles for Transdermal Drug Delivery. Advanced Drug Delivery Review. 2004; 56(5):581-587.
36. Pfister WR, Hsieh DS. Permeation enhancers compatible with transdermal drug delivery systems. Part I: selection and formulation considerations. Med Device Technol. 1990;1(5):48-55

Corresponding Author:

Sumit Sigroha

Fitlife health care, gurgaon

E-mail- sigroha007@gmail.com

Phn:- +91-9466205824

