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Transdermal Drug Delivery System

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Abstract

The transdermal route has numerous advantages over the more traditional drug delivery routes. The se include high bioavailability, absence of first pass hepatic metabolism, steady drug plasma conce ntrations, and the fact that therapy is noninvasive. The main obstacle to permeating drug molecule s is the outermost layer of the skin, the stratum corneum.This review describes enhancement techn iques based on drug/vehicle optimisation such as drug selection, prodrugs and ionpairs,supersaturate d drug solutions, eutectic systems, complexation, liposomes, vesicles and particles.

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 circulatio n. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug d elivery systems.Optimum therapeutic outcomes require not only proper drug selection but also effec tive drug delivery. The human skin is a readily accessible surface for drug delivery. Over the pas t three decades developing controlled drug delivery has become increasingly important in the phar maceutical industry. The pharmacological response, both the desired therapeutic effect and the unde sired 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 si te of action1. Tablets and injections have been the traditional way to take medications; new optio ns are becoming increasingly popular.

Advantages of Transdermal Drug Delivery Systems

1.Transdermal medication deliversa steady infusion of a drug over an extended period of time. Ad verse effects or therapeutic failures frequently associated with intermittent dosing can also be avoid ed..

2. Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific pro blems associated with the drug e.g., gastro-
intestinal irritation, low absorption,decomposition due to hepatic „"firstpass" effect, formation of met abolites that cause side dosing etc.

3.The simplified medication regimen leads to improved patient compliance and reduced inter & intr a –patient variability.

4Due to the above advantage, it is possible that an equivalent therapeutic effect can be elicited vi a transdermal drug input with a lower daily dose of the drug than is necessary, if, for example, the drug is given orally.

5 .At times the maintenance of the drug concentration within the diphase is not desired. Applicatio n and removal of transdermal patch produce optimal sequence of Pharmacological effect.6. Self ad ministration is possible with these systems.

7 .The drug input can be terminated at any pointof time by removing transdermal patch.

Disadvantages of Transdermal Drug Delivery 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 transder mal 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"s impermeability.
3 .Some patients develop contact dermatitis at the site of application for one or more of the syst em components, necessitating discontinuation.
4. Clinical need is another area that has to be examined carefully before a decision is made to d evelop atransdermal 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

ANATOMY AND PHYSIOLOGY OF SKIN:

The skin has evolved into an extremely efficient barrier, which prevents both excessive water loss from the body and the ingress of xenobiotics. It enables us to withstand a considerable range of environmental challenges. The reasons for this are manifold and may be summarized simply for t he purposes of this chapter. The outer layer of the skin, the stratum corneum, forms the rate-
controlling barrier for diffusion for almost all compounds. It is composed of dead, flattened, kerati n-
rich cells, the corneocytes. These dense cells are surrounded by a complex mixture of intercellular lipids

1. The stratified, a vascular, cellular epidermis;

2. Underlying dermis of connective tissues and ;

3. Hypodermis.

Epidermis

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

Stratum corneum :

This is the outermost layer of skin, also called horney layer. It is approximately 10mm thick whe n 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 r elatively impermeable. The stratum corneum is the principal barrier for penetration. The barrier nat ure of the horney layer depends critically on its constituents: 75 to 80%proteins, 5 to 15% lipids, and5 to 10%ondansetron material on a dry weight basis. Protein fractions predominantly contain a lpha-keratin (70%) with some beta-
keratin (10%) and cell envelope (5%).Lipid constituents vary with body site (neutral lipids, sphingo lipids, 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 0.06mm on the eyelids to 0.8mm on the palms. Going inwards, it consists of various layers as stratum lucidum, s tratum granulosum, stratum spinosum, and the stratum basale. In the basale layer, mitosis of the c ells constantly renews the epidermis and this proliferation compensates the loss of dead horney cel ls from the skin surface.

Dermis

Dermis is a 3 to 5mm thick layer and is composed of a matrix of connective tissuewhich contai ns 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 to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier

Hypodermis

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat s torage area.This layer helps to regulate temperature, provides nutritional support and mechanic prote ction. It carries principal blood vessels and nerves to skin and may contain sensory pressure organ s.

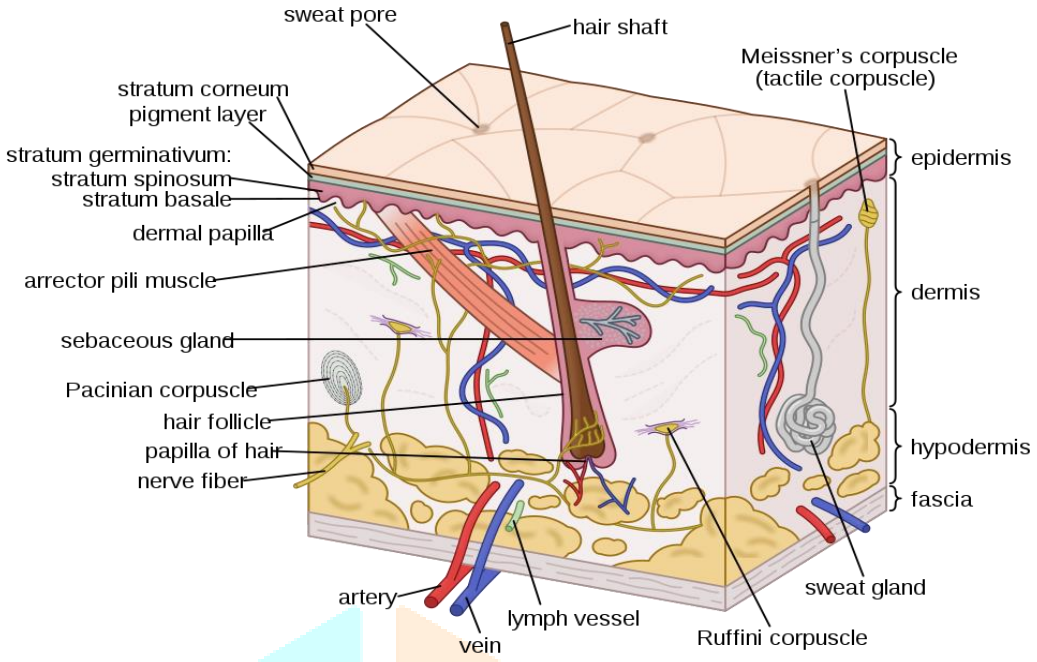

Fig :5: structure of human skin

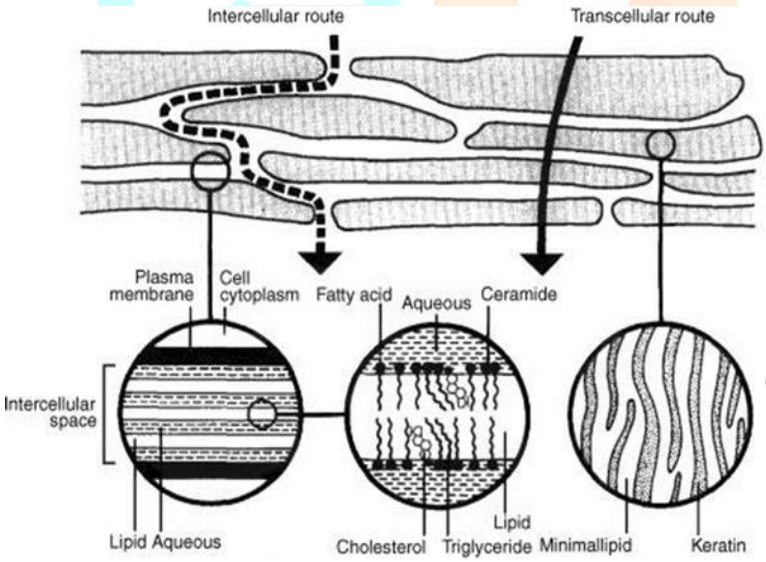

Fig 6: diagram of skin structure and macro routes of drug barrier at a fig penetration

Kinetics of Transdermal Permeation:

Knowledge of skin permeation kinetics is vital to the successful development of transdermal therap eutic systems. Transdermal permeation of a drug involves the following steps:

1.Sorption by stratum corneum.

2.Penetration of drug through epidermis.

3.Uptake of the drug by the capillary network in the dermal papillary layer.

This permeation can be possible only if the drug possesses certain physiochemical properties. The rate of permeation across the skin is given by-

$$\frac{dQ}{} = P\ s\ (Cd - Cr)$$

dt

Where,

Cd and Cr are the concentration of the skin penetrant in the donor compartment i.e. on the surface of stratum corneum and in the receptor compartment i.e. body respectively. Ps is the overall permeability coefficient of the skin tissue to the penetrant. This permeability coefficient is given by the relationship:

$$Ps = \frac{Dss\ Ks}{hs}$$

Where,

Ks is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system on to 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 equation (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 Cdis consistently and substantially greater than the drug concentration in the body Cr. The equation becomes:

$$\frac{dQ}{dt} = PsCd$$

The rate of skin permeation is constant provided the magnitude of Cdremains fairly constant throughout the course of skin permeation. For keeping Cdconstant the drug should be released from the device at a rate Rr i.e. either constant or greater than the rate of skin uptake Rai.e. Rr>> Ra.

Since Rr>> Ra, the drug concentration on the skin surface Cdis maintained at a level equal to or greater than the equilibrium solubility of the drug in the stratum corneum Csi.e. Cd>>Cs. Therefore a maximum rate of skin permeation is obtained and is given by the equation:

$$(dQ/dt)m = PsCs$$

From the above equation it can be seen that the maximum rate of skin permeation depends upon the skin permeability coefficient Psand is equilibrium solubility in the stratum corneum Cs. Thus skin permeation appears to be stratum corneum limited .

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Basic components of transdermal drug delivery system -

1. Polymer membrane partition controlled TDDS

2. Polymer matrix diffusion controlled TDDS

3. Micro reservoir dissolution controlled TDDS

MEMBRANE PERMEATION – CONTROLLED SYSTEMS

In this type of system, the drug reservoir is totally encapsulated in a shallow compartment moulded from a drugimpermeable metallic plastic laminate and a rate controlling polymericmembrane which may be micro-porous or non porous e.g., ethylene vinyl acetate (EVA) copolymer, with a defined drug permeability property. In the drug reservoir compartment, drug solids are either dispersed in a solid polymer matrix or suspended in an unleachable, viscous liquid medium such as silicone fluid to form a paste like suspension.

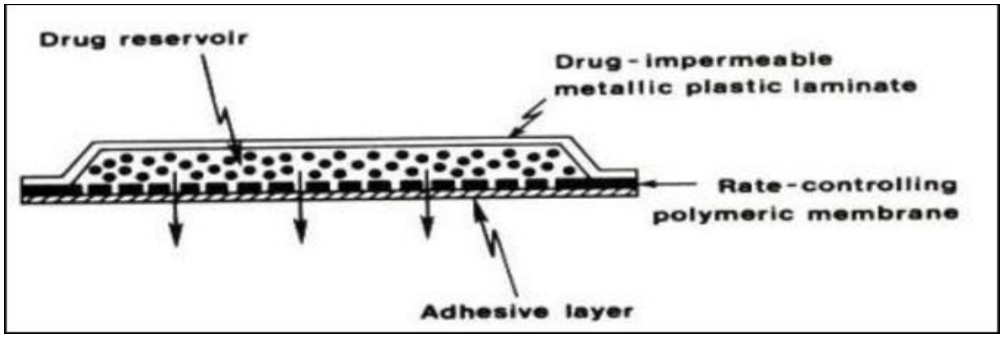

Figure : 1 Membrane permeation type TDDS.

ADHESIVE DISPERSION TYPE SYSTEMS

This is a simplified form of the membrane permeation controlled system. As represented in the dr ug reservoir is formulated by directly dispersing the drug in an adhesive polymer Eg. Poly (isobut ylene) or poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent Impact factor casting or hot melt, on to the flat sheet of drug impermeable metallicplastic backing to form a thin drug reservoir layer. On top of the drug reservoir layer, thin layers of nonmedicated, rate controlling adhesive polymer of a specific permeability and constant t hickness are applied to produce an adhesive diffusion-controlled delivery system

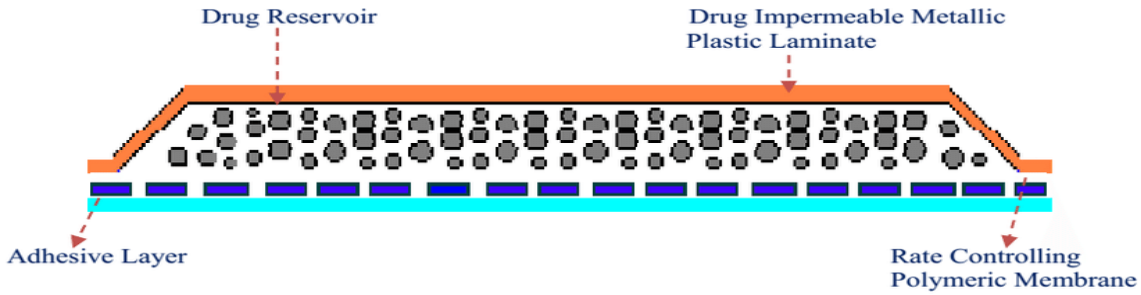

Figure 2:Adhesive Dispersion Type System

MATRIX DIFFUSION CONTROLLED SYSTEMS

In this approach, the drug reservoir is prepared byhomogeneously dispersing drug particles ina hydr ophilic or lipophilic polymer matrix. The resultant medicated polymer is then molded into a medic ated disc with a defined surface area and controlled thickness. The dispersion ofdrug particles in t he polymer matrix can be accomplishedby either homogeneously mixing thefinely ground drug parti cles with a liquid polymer or a highly viscous base polymer followed by cross linking of the pol ymer chains or homogeneously blending drug solids with a rubbery polymer at an elevated temper ature

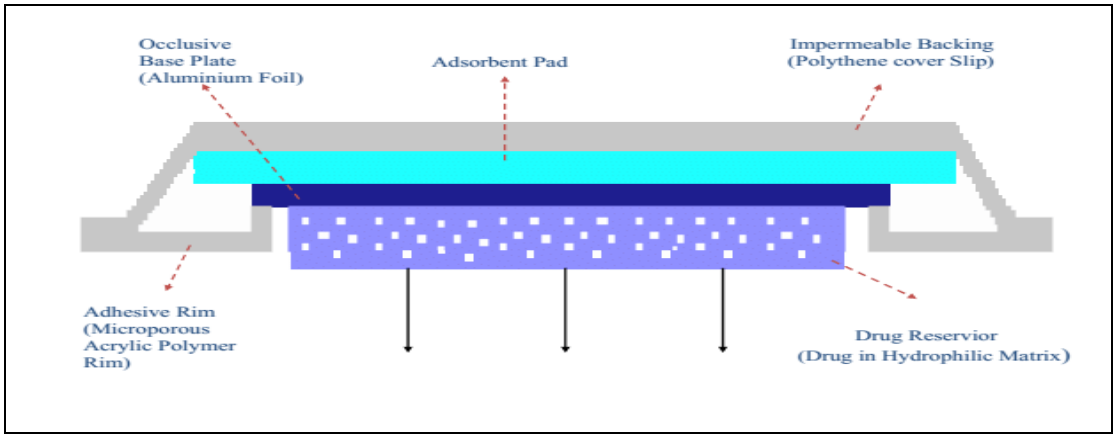

Fig 03: Matrix diffusion controlled type TDDS.

MICRO-RESERVOIR TYPE OR MICRO-SEALED DISSOLUTION CONTROLLED SYSTEMS

This can be considered a combination of the reservoir and matrix diffusion type drug delivery sys tems. Here the drug reservoir is formed by first suspending the drug solids in an aqueous solutio n of a water soluble liquid polymer and thendispersing the drug suspension homogeneously in a li pophilic polymer viz. siliconeelastomers by high energy dispersion technique to form several discret e, unleachable microscopic spheres of drug reservoirs. The quick stabilization of this thermodynami cally unstable dispersion is accomplished by immediately cross linking the polymer chains in situ which produces a medicated polymer disc with a constant surface area and a fixed thickness.

Origins 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 re cognized that various layers of skin are not equally permeable i.e. epidermis is less permeable tha n 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.

B- Intracellular verse transcellular diffusion

Intracellular regions in stratum corneum are filled with lipid rich amorphous material. In dry stratu m corneum intracellular volume may be 5% to 1% in fully hydrated stratum corneum.

C. 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 epid ermal route.

1. Appendageal route:

Appendageal route comprises transport via sweat glands and hair follicles with their associated seb aceous 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 relati vely small area, approximately 0.1 % of the total skin area.

1. Epidermal route:

For drugs, which mainly cross intact horney 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 membra ne. These include passive transport of small molecules, active transport of ionic and polar compou nds and endocytosis and transcytosis of macromolecules.

ii) Paracellular**:** Paracellular pathway means transport of molecules around or between the cells. Ti ght 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 permeant s traverse the stratum corneum via the intercellular route. Most permeants permeate the stratum co rneum by both routes. However, the tortuous intercellular pathway is widelyconsidered to provide t he principal route and major barrier to the permeation of most drugs.

Factors affecting drug delivery system:

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

A. Biological factors

i) Skin condition: Acids and alkalis, many solvents like chloroform, methanol damage the skin cell s and promote penetration. Diseased state of patient alters the skin conditions. The intact skin is better barrier but the above mentioned conditions affect penetration.

ii) 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 factor affecting penetration of drug in TDDS.

iii) Blood supply: Changes in peripheral circulation can affect transdermal absorption.

iv) Regional skin site: Thickness of skin, nature of stratum corneum and density of appendages v ary site to site. These factors affect significantly penetration.

v) Skin metabolism: Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.

vi) Species differences: The skin thickness, density of appendages and keratinization of skin vary s pecies to species, so affects the penetration.

B. Physicochemical factors

i) 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 transd ermal delivery.

ii) 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 dependi ng on the pH and pKa or pKb values. The proportion of unionized drug determines the drug con centration in skin. Thus, temperature and pH are important factors affecting drug penetration.

iii) Diffusion coefficient: Penetration of drug depends on diffusion coefficient of drug. At a consta nt temperature the diffusion coefficient of drug depends on properties of drug, diffusion medium a nd interaction between them.

iv) Drug concentration: The flux is proportional to the concentration gradient across the barrier an d concentration gradient will be higher if the concentration of drug will be more across the barrie r.

v) Partition coefficient: The optimal partition coefficient (K) is required for good action. Drugs wit h high K are not ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated.

vi) Molecular size and shape: Drug absorption is inversely related to molecular weight, small mole cules penetrate faster than large ones

Ideal molecular properties for transdermal drug delivery

From the above considerations we can conclude with some observations that can termed as ideal molecular properties for drug penetration. They are as follows.

- An adequate solubility in lipid and water is necessary for better penetration of drug (1mg/ ml).
- Optimum partition coefficient is required for good therapeutic action.
- Low melting point of drug is desired (<200°C).
- The pH of the saturated solution should be in between 5 to 9.

Constituents used in TDDS

The main constituents of a transdermal patch are:

i. Release Liner

Protects the patch during storage. The liner is removed prior to use.

ii. Drug reservoir

The most important part of TDDS is drug reservoir. It consists of drug particles dissolved or disp

ersed in the matrix. To make the drug soluble, solvents and cosolvents are used. Theeffect of sol vent and cosolvent should be considered while doing selection.

iii. Adhesive

Serves to adhere the components of the patch together along with adhering the patch to the skin. The adhesive must posses sufficient adhesion property so that the TDDS should remain in place for a long time. Pressure sensitive adhesives are commonly used for transdermal patch to hold t he skin. Commonly used adhesives are silicone adhesives, poly isobutylenes adhesives and poly acr ylate based adhesives.

iv. Membrane

Membrane controls the release of the drug from the reservoir and multi-layer patches. It may or may not contain rate-controlling membrane. It should be flexible enough not to split or crack on bending or stretching. Some of rate-controlling membranes are polyethylene sheets, ethylene vinyl acetate copolymer and cellulose acetat e.

v. Backing

Protects the patch from the outer environment. The backing layer should be impermeable to drug and penetration enhancers. It serves a function of holding the entire system and protects drug rese rvoir from atmosphere. The commonly used backing materials are polyesters, aluminized polyethyle ne terepthalate and siliconized polyethylene terepthalate.

Conclusion:

Successful transdermal drug application requires numerous considerations. Bearing in mind that the basic functions of the skin are protection and containment, it would seem exceptionallydifficult to target the skin for drug delivery.he brief overview of the different antihypertensive.

Drugs revealed that, by delivering through the transdermal route improves bioavailability as well i mprove the patient compliance by many fold. But the demerit is that, all the antihypertensive dru gs cannot be given as transdermal delivery because the drug should have specificphysicochemical p roperty which should be suited to permeate through skin. The development of success TDDS depends on proper selection of drug, polymer as well as other additives.

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