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A Path for Horizing Your Innovative Work

TRANSDERMAL DRUG DELIVERY SYSTEM AS PROMINENT DOSAGE FORMS FOR THE HIGHLY LIPOPHILIC DRUGS.

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Abstract: An ideal dosage form would be maintaining the drug concentration in the blood at a constant level nearly coinciding with the minimum effective concentration (MEC) of drug throughout the treatment period. This leads to the concept of the controlled drug delivery. The primary objective of controlled drug delivery is to ensure safety and efficacy of the drugs as well as patients compliance. TDDS is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through skin in a predetermined and controlled rate. At present, the most common route for the delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks, namely poor bioavailability due to hepatic first pass metabolism and tendency to produce rapid blood level spikes, leading to a need for high and/ or frequent dosing, which can be inconvenient. To improve such characters transdermal drug delivery system (TDDS) was emerged which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific) placement within the body thereby reducing both the size and number of doses. Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy.

Key Words: TDDS, MEC, site specific, oral therapy.

INTRODUCTION

At present, the most common route for the delivery of drugs is the oral route. This has the notable advantage of easy administration, it also has significant drawbacks, namely poor bioavailability due to hepatic first pass metabolism and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be inconvenient. To overcome these difficulties there is a need for the development of new drug delivery system.[1]

Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy.[2]

The principal of transdermal drug transport is to deliver drug across epidermis to achieve systemic effect over a prolonged period of time.[3]

The human skin is a readily accessible surface for drug delivery. Skin of an average adult body covers a surface of approximately 2 m^2 and receives about one-third of the blood circulating through the body. Over the past decades, developing controlled drug delivery has become increasingly important in the pharmaceutical industry. The human skin surface is known to contain an average, 10-70 hair follicles and 200-250 sweat ducts on every square centimeters of the skin area. It is one of the most readily accessible organs of the human body. There is considerable interest in the skin as a site of drug application both for local and systemic effect.[4]

An ideal dosage form would be maintaining the drug concentration in the blood at a constant level nearly coinciding with the minimum effective concentration (MEC) of drug throughout the treatment period. This leads to the concept of the controlled drug delivery.

The primary objective of controlled drug delivery is to ensure safety and efficacy of the drugs as well as patients compliance. TDDS is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through skin in a predetermined and controlled rate.[5]

In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders and these show local action but occurrence of systemic side-effects with some of these formulations is indicative of absorption

through the skin this concept lead to the birth of TDDS. Moreover, it over comes various side effects like painful delivery of the drugs and the first pass metabolism of the drug occurred by other means of drug delivery systems. TDDS has been a great field of interest in recent times. Many drugs which can be injected directly into the blood stream via skin have been formulated by TDDS.[6]

Transdermal drug delivery systems (TDDS) are defined as self contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation. The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs.

Advantages[3, 4, 8, 9]

- Transdermal medication delivers a steady infusion of a drug over an extended period of time.
- An equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, e.g. the drug is given orally.
- Self administration is possible with these systems.
- They are easily and rapidly identified in emergencies (e.g. unresponsive, unconscious or comatose patient) because of their physical presence, features and identifying markings.
- They can be used for drugs with narrow therapeutic window.
- Longer duration of action resulting in a reduction in dosing frequency.
- Increased convenience to administer drugs which would otherwise require frequent dosing.
- Improved bioavailability.
- More uniform plasma levels and maintain plasma concentration of potent drugs.
- Reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval.
- Flexibility of terminating the drug administration by simply removing patch from the skin.
- Improved patient compliance and comfort via non-invasive, painless and simple application.
- Avoid inter and intra patient variation and enhance therapeutic efficacy.

Disadvantages[3, 5, 10]

- Many drugs especially drugs with hydrophilic structures permeate the skin too slowly to be of therapeutic benefit.
- The barrier function of the skin changes from one site to another on the

same person, from person to person and also with age.

- Only small, lipophilic drugs can be delivered currently through the skin.
- Drug molecule must be potent because patch size limits amount that can be delivered.
- Not suitable for high drug doses.
- Adhesion may vary with patch type and environmental conditions.
- Skin irritation and hypersensitivity reactions may occur.
- Drugs that require high blood levels cannot be administered.
- Along with these limitations the high cost of the product is also a major drawback for the wide acceptance of this product.

TRANSDERMAL DRUG PERMEATION

In order to design a successful transdermal drug delivery system (TDDS), it is important to understand the structure, physiology and function of the skin.[4]

Anatomy and physiology of skin

The skin is one of the most extensive organs of the human body covering an area of about $2m^2$ in an average human adult. This multilayered organ receives approximately one third of all blood circulating through the body.[5]Human skin comprises of three distinct but mutually dependent tissues:

(A) The stratified, vascular, cellular epidermis

(B) Underlying dermis of connective tissues

(C) Subcutaneous layer or hypodermis

Each layer has its own function and own importance in maintaining the integrity of skin and thereby the whole body structure.[6]

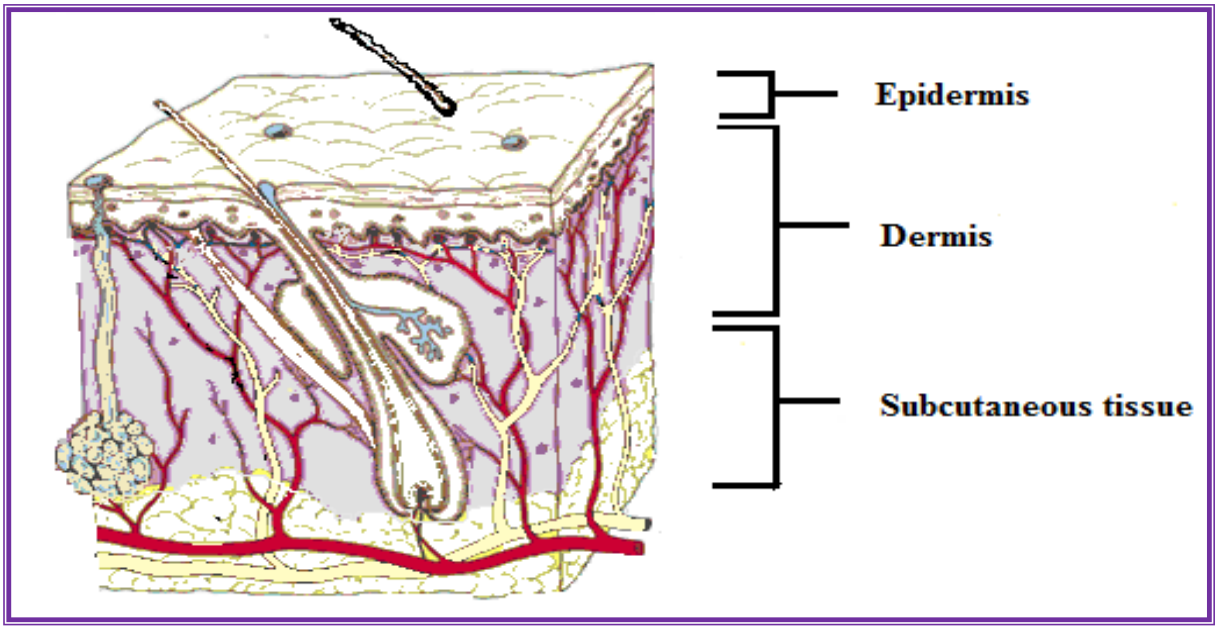

Figure1 Structure of human skin

The more common pathway through the skin is via the intercellular route.[12]

(A) The stratified, vascular, cellular epidermis

The multilayered epidermis varies in thickness depending on the cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Table 1 gives thickness, water permeability and diffusivity of water through epidermis. It consists of outer stratum corneum and viable epidermis.[4]

Epidermis results from an active epithelial basal cell population and is approximately 150 micrometers thick. It is the outermost layer of the skin and the process of differentiation results in migration of cells from the basal layer towards the skin surface. Below this layer are the other layers of the epidermis-the stratum lucidum, stratum granulosum, stratumspinosum and stratum germinativum. Together, these other layers constitute the viable epidermis.[5]

Table 1
Regional variations in water permeability of stratum corneum

Sr. No.	Skin region	Thickness (mm)	Permeation rate(mg/ cm^2/hr)	Diffusivity (cm^2/ sec × 10^{10})
1	Abdomen	15.00	0.34	6.00
2	Volar forearm	16.00	0.31	5.9
3	Back	10.5	0.29	3.5
4	Forehead	13.00	0.85	12.9
5	Forehead	5.00	1.70	7.4
6	Back of hand	49.00	0.56	32.3
7	Palm	400.00	1.14	535.00
8	Plantar	600.00	3.90	930.00

***a. Stratum corneum*[4]**

This is the outermost layer of skin also called ashorney layer. It is approximately 10mm thick whendry but swells to several times this thickness whenfully hydrated. It contains 10 to 25 layers of dead,keratinized cells called as corneocytes. It is flexible butrelatively impermeable. The stratum corneum is theprincipal barrier for penetration of drug. Thearchitecture of horney layer may be modeled as awall-like structure. In this model, the keratinizedcells function as protein “bricks” embedded in lipid“mortar”.

***b. Viable epidermis*[4]**

This is situated beneath the stratum corneum andvaries in thickness from 0.06mm on the eyelids to0.8mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the stratumbasal. In the basale layer, mitosis of the cellsconstantly renews the epidermis and thisproliferation compensates the loss of dead horney cells from the skin surface.

(B) Dermis[4]

Dermis is 3 to 5mm thick layer and is composed of amatrix of connective tissue, which contains bloodvessels, lymph vessels and nerves. The cutaneousblood supply has essential function in regulation ofbody temperature. It also provides nutrients andoxygen to the skin while removing toxins and wasteproducts. Capillaries reach to within 0.2 mm of skinsurface and provide sink conditions for mostmolecules penetrating the skin barrier.

(C) Hypodermis[4]

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

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 do not contribute much for skin permeation. Therefore most neutral molecules pass through stratum corneum by passive diffusion. Regional variation in water permeability of stratum corneum showed in Table 1 and permeation of drug molecule through skin showed in Figure 2.

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.

Intracellular regions in stratum corneum are filled with lipid rich amorphous material. In dry stratum corneum intracellular volume may be 5% to 1% in fully hydrated stratum corneum.[4]

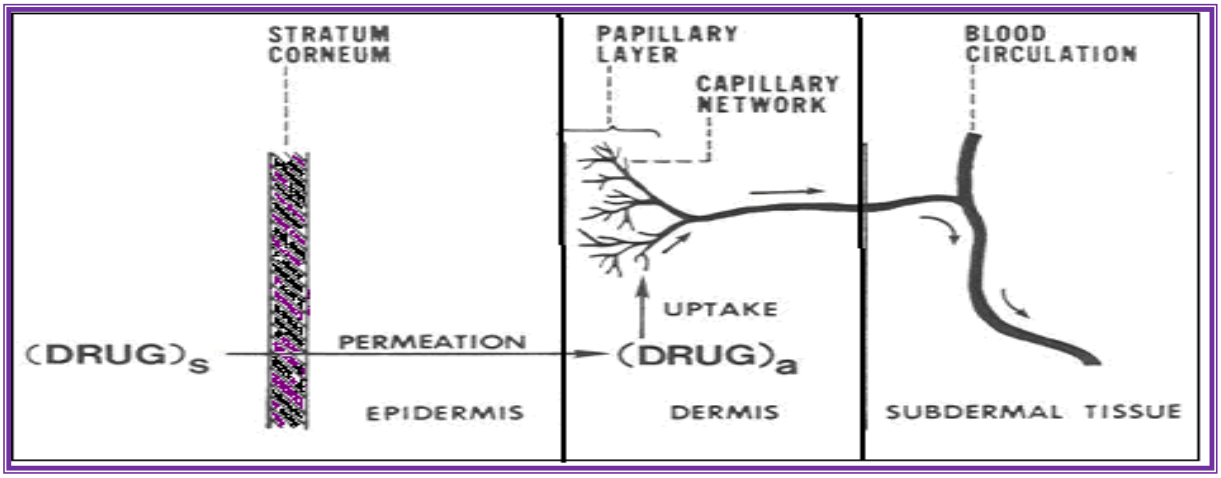

Figure 2 A multilayer skin model showing sequence of transdermal permeation

DRUG PENETRATION PATHWAYS[6]

There are critically three ways in which a drug molecule can cross the intact stratum corneum: via skin appendages (shunt routes); through the intercellular lipid domains; or by a transcellular route (Figure 3). A particular drug is likely to permeate by a combination of these routes, with the relative contributions of these pathways to the gross flux governed by the physicochemical properties of the molecule.

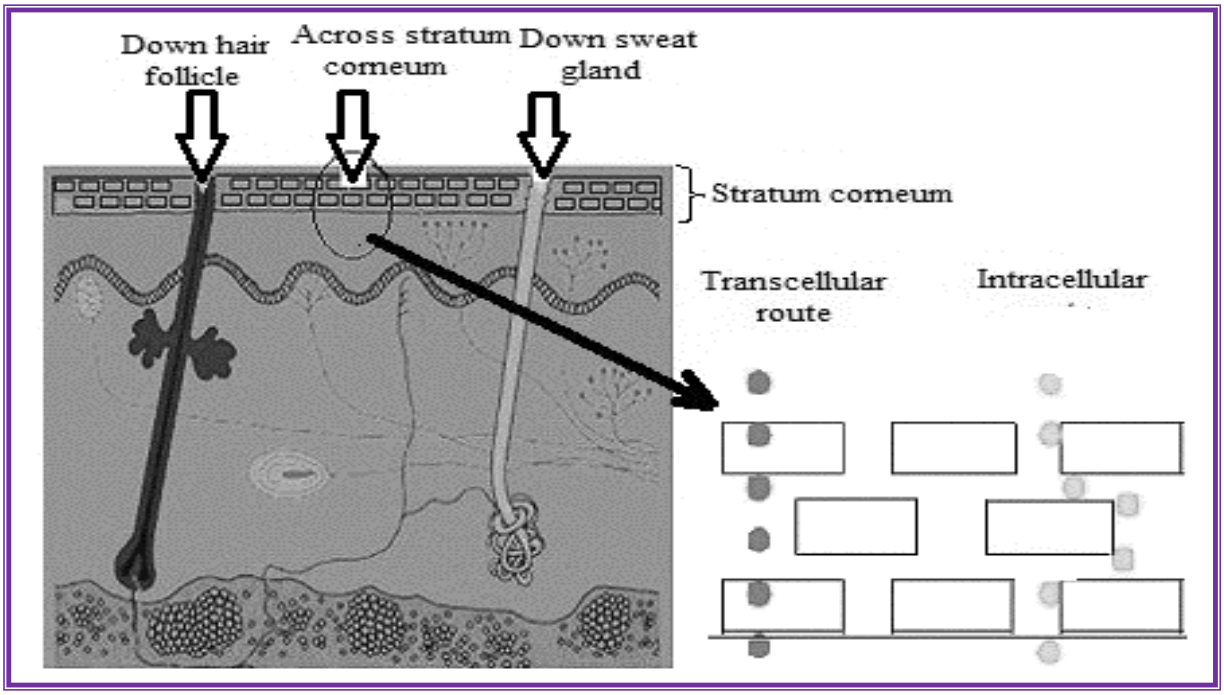

Figure 3 Permeation pathways through the skin

(A) The appendgeal route

Skin appendages provide a continuous channel directly across the stratum corneum barrier. However, their influence on drug penetration is hindered by a number of factors. The surface area occupied by hair follicles and sweat ducts are small (typically 0.1% of skin's surface area), therefore limiting the area available for direct contact of the applied drug formulation.

(B) Transcellular route

Drugs entering the skin via the transcellular route pass through corneocytes. Corneocytes containing highly hydrate keratin provide an aqueous environment from which hydrophilic drugs can pass. The diffusion pathway for a drug via the transcellular route requires a number of partitioning and diffusion steps.

(C) Intercellular route

The intercellular pathway involves drug diffusing through the continuous lipid matrix. This route is a significant obstacle for two reasons:

- Recalling the 'bricks and mortar' model of the stratum corneum, the inter-digitating nature of the corneocytes yields a tortuous pathway for intercellular drug permeation, which is in contrast to the relatively direct path of the transcellular route.
- The intercellular domain is a region of alternating structured bilayers. Consequently, a drug must sequentially partition into and diffuse through repeated aqueous and lipid domains. This route is generally accepted as the most common path for small uncharged molecules penetrating the skin.

Factors affecting transdermal drug delivery

(A) Physicochemical properties of permeant

1. Partition coefficient[6]

For molecules with intermediate partition coefficient (log K 1 to 3) and for highly lipophilic molecules (log K>3), the intercellular route will be almost the pathway used to traverse the stratum corneum. However, for these molecules a further consideration is the ability to partition out of the stratum corneum into the aqueous viable epidermal tissues. For more hydrophilic molecules (log K<1), the transcellular route probably predominates.

2. Molecular size[6]

A second major factor in determining the flux of a material through human skin is the size of the molecule. However, for simplicity the molecular weight is generally taken as an approximation of molecular size. It has been suggested that an inverse relationship existed between transdermal flux and molecular weight of the molecule.

3. Solubility/melting point[6]

It is well known that most organic materials with high melting points have relatively low aqueous solubility at normal temperature and pressure. The lipophilic molecules tend topermeate through the skin faster than more hydrophilic molecules. However, while lipophilicity is a desired property of transdermal candidates, it is also necessary for the molecule to exhibit some aqueous solubility since topical medicaments are generally applied from an aqueous formulation.

4. Ionization[6]

According to pH-partition hypothesis, only the unionized forms of the drug can

permeate through the lipid barrier in significant amounts.

5. Penetrant concentration[9]

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

6. Diffusion coefficient[4]

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.

7. Other factors[6]

Beyond the factors mentioned above, there are other molecular properties that can affect drug delivery through the skin. Drug binding is a factor that should be born in mind when selecting appropriate candidates. Interactions between drug substances and the tissue can vary from hydrogen bonding to weak Van der Waals forces and the effect of drug binding (if any) on flux across the tissue will vary depending on the permeant, e.g. with a poorly water soluble drug in an aqueous donor solution, significant binding to the stratum corneum may completely retard drug flux. Consequently, there will be a delay between applying a drug to the surface of the tissue and its appearance in a receptor solution (*in vitro*) or the blood (*in vivo*).Depending on the type of formulation selected, other factors may be important in a transdermal delivery system. For example, if the drug is suspended then the particle size may become a key regulator of flux.

(B) Physicochemical properties of the drug delivery system

1. Release characteristics[9]

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

- Whether the drug molecules are dissolved or suspended in the delivery systems.
- The interfacial partition coefficient of the drug from the delivery system to the skin tissue.
- pH of the vehicle.

2. Composition of the drug delivery systems[9]

The composition of the drug delivery systems, e.g. boundary layers, thickness, polymers, vehicles not only affects the rate of drug release, but also the permeability of the stratum corneum by means of hydration, making with skin lipids, or

other sorption promoting effects, e.g. benzocaine permeation decreases with PEG of low molecular weight.

***3. Enhancement of transdermal permeation*[9]**

Majority of drugs will not penetrate skin at rates sufficiently high for therapeutic efficacy. In order to allow clinically useful transdermal permeation of most drugs, the penetration can be improved by the addition of a permeation promoter into the drug delivery systems.[10]

(C) Physiological factors

***1. Skin barrier properties in the neonate and young infant*[6]**

The skin of newborns is known to be relatively susceptible to irritants, other variables related to stratum corneum function such as pH and stratum corneum hydration may enhance the irritant potential to newborn skin. Skin surface pH values in newborns are significantly higher in all body sites than those in adult skin, but stabilize at values similar to adults within the first month. There are also significant changes in the metabolic capacity of infants, whether full or preterm and adult levels of cutaneous enzyme activity are not observed until 2 months or even 6–12 months of age which may additionally account for the sensitivity of baby skin to irritants. The skin surface of thenewborn is slightly hydrophobic and relatively dry and rough when compared to that of older infants. Stratum corneum hydration stabilizes by the age of3 months.

***2. Skin barrier properties in aged skin*[6]**

There are changes in the physiology of aged skin (>65 years). The corneocytes are shown to increase in surface area which may have implications for stratum corneum function due to the resulting decreased volume of intercorneocyte space per unit volume of stratum corneum. The moisture content of human skin decreases with age. There is a flattening of the dermoepidermal junction and, consequently, the area available for diffusion into the dermis is diminished.

***3. Race*[6]**

Racial differences between black and white skins have been shown in some anatomical and physiological functions of the skin although data is relatively sparse. In black skin, increased intracellular cohesion, higher lipid content and higher electrical skin resistance levels compared to whites have been demonstrated. Black skin appears to have a decreased susceptibility to cutaneous irritants, but this difference is not detected instripped skin, suggesting the stratum corneum modulates the different racial response toirritants. Black skin responds with a

decrease in blood flow and hence less erythematic than Hispanics or Caucasians.

4. Body site[6]

It is readily apparent that skin structure varies to some degree over the human body. However, the relative permeability of different skin sites is not simply a function of stratum corneum thickness as different permeants exhibit varied rank orders through different skin sites. It is apparent that genital tissue usually provides the most permeable site for transdermal drug delivery. The skin of the head and neck is also relatively permeable compared to other sites of the body such as the arms and legs.

5. Skin temperature[6]

The human body maintains a temperature gradient across the skin from around 37 ºC to around 32 ºC at the outer surface. Since diffusion through the stratum corneum is a passive process, elevation of the skin temperature can induce structural alterations within the stratum corneum, and these modifications can also increase diffusion through the tissue.

6. Skin condition[4]

Acids and alkalis, many solvents like chloroform, methanol damage the skin 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.

7. Blood supply[4]

Changes in peripheral circulation can affect transdermal absorption.

8. Skin metabolism[4]

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

Basic components of TDDS[2, 9]

A. Polymer matrix/ Drug reservoir
B. Drug
C. Permeation enhancers
D. Pressure sensitive adhesive (PSA)
E. Backing laminates
F. Rate controlling membrane
G. Release liner
H. Other excipients like plasticizers and solvents

(A) Polymer matrix

Polymers are the backbone of a transdermal drug delivery system. Systems for transdermal delivery are fabricated as multilayered 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 and/or

rate-controlling membrane. Polymer selection and design must be considered when striving to meet the diverse criteria for the fabrication of effective transdermal drug delivery systems. The main challenge is in the design of a polymer matrix, followed by optimization of the drug loaded matrix not only in terms of release properties, but also with respect to its adhesion-cohesion balance, physicochemical properties, compatibility and stability with other components of the system as well as with skin.

The polymers utilized for TDDS can be classified as:

- **Natural polymers:** e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber, chitosan, starch, etc.
- **Synthetic elastomers:** e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, styrene-butadiene rubber, neoprene, butylrubber, polysiloxane, etc.
- **Synthetic polymers:** e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate, epoxy, ethyl cellulose, hydroxy propyl cellulose etc.

The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose and hydroxyl propylmethylcellulose are used as matrix formers for TDDS. Other polymers like EVA, silicon rubber and polyurethane are used as rate controlling membrane.[2, 5]

(B) Drug

The most important criteria for TDDS are that the drug should possess the right physicochemical and pharmacokinetic properties.[2]

The selection of drug for transdermal drug delivery depends upon various factors.[9]

Physicochemical properties[9, 13]

- The drug should have some degree of solubility in both oil and water (ideally greater than 1 mg/ml).
- The substance should have melting point less than 200 °F. Concentration gradient across the membrane is directly proportional to the log solubility of drug in the lipid phase of membrane, which in turn is directly proportional to the reciprocal of melting point.
- Substances having a molecular weight of less than 1000 units are suitable.
- A saturated aqueous solution of the drug should have a pH value between 5 and 9. Drugs highly acidic or alkaline in solution are not suitable for TDD;

because they get ionized rapidly at physiological pH.

- Hydrogen bonding groups should be less than 2.
- Partition coefficient (Log P) should be between 1 and 3.
- Skin permeability coefficient should be less than 0.5×10^{-3} cm/ h.

- ***Biological properties***[3, 9, 13]
- Drug should be very potent, i.e. it should be effective in few mgs per day (ideally less than 25 mg/day).
- The drug should have short biological half life.
- The drug should be non-irritant and non-allergic to human skin.
- The drug should be stable when in contact with the skin.
- The drug should not stimulate an immune reaction to the skin.
- Tolerance to drug must not develop under near zero order release profile of transdermal delivery.
- The drug should not get irreversibly bound in the subcutaneous tissue.
- The drug should not get extensively metabolized in the skin.
- Drugs, which degrade in the GIT or are inactivated by hepatic first-pass effect, are suitable candidates for transdermal delivery.
- Drugs, which have to administer for a long period of time or which cause adverse effects to non-target tissues can also be formulated for transdermal delivery.
- Therapeutic index should be low.

(C) Permeation enhancers

The stratum corneumis the principal barrier to drug permeation across the skin. Consequently, there has been a concerted effort to investigate and develop novel strategies of maximizing the amount of permeant crossing this barrier. Innovative approaches focus on altering the drug-vehicle interaction to enhance partitioning into the stratum corneum or modifying the structure of the stratum corneum to make it less resistance to drug diffusion.[14]

When a drug does not possess ideal physicochemical properties, manipulation of the drug or vehicle to enhance diffusion becomes necessary. The approaches that have been investigated are discussed below.[15]

- **Methods for enhancing transdermal drug delivery**[13, 16, 17]

Skin penetration can be enhanced by following methods:

1. Drug and vehicle interactions

i. Selection of correct drug or prodrug
ii. Chemical potential adjustment

iii. Ion pairs and complex coacervates
iv. Eutectic systems

2. Stratum corneum modification

i. Hydration
ii. Chemical penetration enhancers

3. Stratum corneum bypassed or removed

i. Microneedle based devices
ii. Needle-less injection
iii. Radio frequency
iv. Suction ablation
v. Skin abrasion

4. Electrically assisted methods

i. Electroporation
ii. Iontophoresis
iii. Ultrasound (Phonophoresis, Sonophoresis)
iv. Magnetophoresis
v. Laser radiation and photomechanical waves
vi. Thermophoresis

5. Vehicles and particles

i. Micro or Nanocapsules
ii. Nanoemulsions/submicron emulsions/miniemulsions
iii. Solid lipid nanoparticles
iv. Multiple emulsions
v. Microemulsions
vi. Liposome
vii. Niosomes
viii. Transfersomes
ix. Ethosome
x. Aquasomes

(D)Pressure sensitive adhesive (PSA)

A PSA is a material that helps in maintaining an intimate contact between transdermal system and the skin surface[21]. PSA is a material that adheres with no more than applied fingerpressure, is aggressively and permanently tacky, exerts a strong holding force and should be removable from a smooth surfacewithout leaving a residue. Adhesion involves a liquid-likeflow resulting in wetting of the skin surface upon the applicationof pressure and when pressure is removed, the adhesive setsin that state. Acrylic-, poly isobutylene- and silicone-based adhesives are usedmostly in the design of transdermal patches. The selectionof an adhesive is based on a numberof factors, including the patch design and drug formulation. Forreservoir systems with a peripheraladhesive, an incidental contactbetween the adhesive and thedrug or penetration enhancersmust not cause instability of thedrug, penetration enhancer, or the adhesive. In the case of reservoirsystems that include a face adhesive,the diffusing drug must notaffect the adhesive.For matrix designs in which the adhesive, the drug and the penetration enhancers must be compounded,the

selection will be more complex. The physicochemical characteristics of a drug-adhesive combination- such as solubility and partition coefficient and adhesive characteristics such as the extent of cross-linking will determine the choice of adhesive for a drug. When formulating a PSA, a balance of four properties must be taken into account: tack, peel adhesion, skin adhesion and cohesive strength.[22]

- **Polyisobutylene (PIB)[23]**

These are characterized by a low solvent capacity for drugs. PIBs are often used in membrane-controlled systems where the initial burst of drug released from the adhesive layer should be limited. 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 because atomized for each system.

- **Polyacrylates[22,23]**

Polyacrylatesare most widely used pressure sensitive adhesives. 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.[23]Acrylic esters are represented by the general formulaCH_2= CH-COOR. The nature of the R group determines the properties of each ester and the polymer it forms. Polymers of this class are amorphous and are distinguished by their water-clear color in solution and stability towardaging. As is typical of polymer systems, the mechanical properties of acrylic polymers improve as the molecular weight increases.

Table 2
Glass transition temperatures of acrylate polymers

Polymer	T_g (°C)
Methyl acrylate	6
Ethyl acrylate	-24
Propyl acrylate	-45
Isopropyl acrylate	-3
n-Butyl acrylate	-50
Hexyl acrylate	-57
Heptyl acrylate	-60
2-Ethylhexyl acrylate	-65
2-Ethylbutyl acrylate	-50
Dodecyl acrylate	-30

- **Silicones**[22]

Silicone PSAs comprise polymer or gum and a tackifying resin. Medical-grade silicone adhesives contain a low viscosity dimethylsiloxane polymer, which has a terminal silanolgroup.[22]They are characterized by low allergenicity. Similar to PIBs, silicones dissolve most drugs poorly and regulate tackiness and cohesion through polymer size. Molecular weight of silicones, however, can be hard to control during storage of drug-adhesive formulations, since drugs containing amine groups can catalyze further polymerization in silicone adhesives retaining residual silanol groups. To address this problem, special silicones have been developed that are rendered resistant to amine-catalyzed condensation through end-capping of silanol functional groups.[23] Unlike acrylic-, rubber- and PIB-based adhesives, medical-grade silicone adhesives do not contain organic tackifiers, stabilizers, antioxidants, plasticizers, catalysts, or other potentially toxic extractables. The properties of silicone-based PSAs such as tack, peel adhesion, skin adhesion and cohesion can be modified or customized by varying the resin-polymer ratio.[22]

- **Hot-melt PSAs (HMPSAs)**[22]

Typical PSAs include a volatile organic solvent for reducing the viscosity of the composition to a coatable room-temperature viscosity. After the product is coated, the organic solvent is removed by evaporation. When they are heated, HMPSAs melt to a viscosity suitable for coating, but when they are cooled they

generally stay in a flawless state. HMPSAs are advantageous over solvent-based systems because they

- Do not require removal and containment of the solvents
- Do not require special precautions to avoid fire
- Are amenable to coating procedures other than those commonly used with solvent-based systems
- They are more easily coated into full thickness with minimal bubbling, which often results with solvent-containing PSAs.

Hot-melt adhesives are based on thermoplastic polymers that may be compounded or uncompounded (see Table 3).

Table 3

Thermoplastic hot-melt pressure-sensitive adhesives

Thermoplastic hot-melt pressure-sensitive adhesives.	
Compounded	Ethylene vinyl acetate copolymers Paraffin waxes Low-density polypropylene Styrene-butadiene copolymers Ethylene-ethacrylate copolymers
Uncompounded	Polyesters Polyamides Polyurethanes

(E) Backing laminates[22]

When designing a backing layer, the developer must give chemical resistance of the material foremost importance. Excipient compatibility also must be seriously 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. The most comfortable backing may be the one that exhibits the lowest modulus or high flexibility, good oxygen transmission and a high moisture-vapor transmission rate. In a novel modification to the conventional design, a patch was fabricated in which the backing itself acted as a reservoir for the drug.

(F) Rate controlling membrane[22]

Reservoir-type transdermal drug delivery systems contain an inert membrane enclosing an active agent that diffuses through the membrane at a finite controllable rate. The release rate-controlling membrane can be nonporous so that the drug is released by diffusing directly through the material or the material may contain fluid-filled micropores, in which case the drug may additionally diffuse through the fluid, thus filling the pores. In the case of nonporous membranes, the rate of passage of drug molecules depends on the solubility of the drug in the membrane and the membrane thickness. Hence, the choice of membrane material must conform to the type of drug being used. By varying the composition and thickness of the membrane, the dosage rate per area of the device can be controlled.

(G) Release liner[23, 24]

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. 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 or occlusive and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metalized laminates.

(H) Plasticizer and solvents[25]

Plasticizer

In transdermal systems, plasticizers are used to improve the brittleness of the polymer and to provide flexibility. They are generally non-volatile organic liquids or solids with low melting temperature and when added to polymers, they cause changes in definite physical and mechanical characteristics of the material. Upon addition of plasticizer, flexibilities of polymer macromolecules or macromolecular segments increase as a result of loosening of tightness of intermolecular forces. Many of polymers used in pharmaceutical formulations are brittle and require the addition of plasticizer into the formulation. The plasticizers with lower molecular weight have more molecules per unit weight compared to the plasticizers with higher molecular weight. These molecules can more easily penetrate between the polymer chains of the film forming agent and can interact with the specific functional groups

of the polymer. By adding plasticizer to a polymeric material, elongation at break, toughness and flexibility are expected to increase; on the other hand tensile stress, hardness, electrostatic chargeability, and glass transition temperature are expected to decrease.

Table 4

Plasticizers used in transdermal films

Group	Hydrophilic/ Lipophilic	Plasticizer
Glycerol and esters	Hydrophilic	Glycerine, Glycerine triacetate, Glyceryl tributyrate
Glycol derivatives	Hydrophilic	Propylene glycol, Polyethylene glycol
Phthalic acid esters	Lipophilic	Diethyl phthalate, Dibutyl phthalate
Sebacic acid esters	Lipophilic	Diethyl sebacate, Dibutylsebacate
Oleic acid esters	Hydrophilic	Oleiloleate
Sugar alcohols	Hydrophilic	Sorbitol
Citric acid esters	Hydrophilic	Triethyl citrate, Tributyl citrate
Tartaric acid esters	Lipophilic	Diethyl tatarate

Solvents

Various solvents are used to solve or disperse the polymer and adhesive or drug used in preparation of transdermal system. Among those chloroform, methanol, acetone, isopropanol and dichloromromethane are used frequently.

Types of transdermal drug delivery system[13]

A. Single-layer Drug-in-Adhesive

The adhesive layer of this system contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

B. Multi-layer Drug-in-Adhesive

The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. One of the layers is for immediate release of the drug and other layer is for control release of drug from the reservoir. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane. This patch also

has a temporary liner-layer and a permanent backing.

C. Reservoir

Unlike the single-layer and multi-layer drug-in-adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system the rate of release is zero order.

D. Matrix

The matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it. It is also known as a monolithic device.

E. Vapour patch

In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hr. The vapour patches release essential oils and is used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market.

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