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A REVIEW ON TRANSDERMAL PATCHES

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Abstract:
Transdermal drug delivery systems (TDDS) permit delivery of contained drug into the circulation via permeation through skin layers at a controlled rate. These systems ar simple to use and take away as and once desired. Skin is a good medium from that absorption of the drug takes place. numerous styles of transcutaneous patches are used to incorporate the active ingredients into the circulation system via skin. The patches are well-tried effective as a result of its giant a benefits over different controlled drug delivery systems. This review covers the introduction of transcutaneous drug delivery system, anatomy of skin, principles of transcutaneous permeation, numerous elements of pad, approaches of pad, unleash dynamics of drug from pad, benefits and drawbacks of pad.

Key words: *Transdermal Drug Delivery System, Transdermal Patches, Anatomy of Skin*

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INTRODUCTION:

Transdermal Drug Delivery System:

Medications of intense and perpetual infections have been achieved by delivery of drugs to patients utilizing different pharmaceutical measurement structures. This measurements structure is known to give a brief arrival of drug. But recently several technical advancements have been done and resulted in new techniques for drug delivery. These techniques are capable of controlling the rate of drug release. At present, the most common form of delivery of drug is the oral route, while this has a notable advantage of easy administration, it also has significant drawbacks – namely poor bioavailability due to hepatic metabolism (first pass) and tendency to produce rapid blood level spikes (both high and low) leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient [1].

To wear these challenges on every side is requirement for improvement of Extreme medicament distribution framework; which will enhances the helpful viability and wellbeing of drug by more exact (i.e. location particular), extraordinary and fleeting situation inside the body there by diminishing both the size and number of measurements. New drug delivery encipher are also essential for the delivery of novel, genetically engineered pharmaceuticals (peptide, proteins) to their site of action, without incurring significant immunogenicity or biological inactivation. Join of technique choicest often utilized has been Transdermal delivery – meaning transport of therapeutic substances through the skin for systemic effect. Methodically follower is percutaneous delivery, which is transport in to target tissue, with an attempt to avoid side effect [2]. Zoological a non-invasive technique, Transdermal delivery causes very little, if any, pain or risk of infection to the patient. These benefits are summarized in table 1.

Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects [3].

A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. Along with a predictable pharmacokinetic profile, the delivery rate of the drug from a Transdermal device into the bloodstream can be controlled. Therefore, constant drug levels can be achieved over extended periods of time without the extreme peak and trough fluctuations inherent in oral administration. With Transdermal devices, drug delivery can be localized and discontinuation of therapy can be achieved immediately by simply removing the patch. Non-medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists of two major sub-categories —therapeutic and cosmetic), aroma patches and weight loss patches, and patches that measure sunlight exposure.

Popular Transdermal Patch Applications

- Nicotine patch
- Fentanyl for severe pain
- Estrogen patches for hormone therapy
- Nitroglycerine for Angina
- Scopolamine for motion sickness
- Anti-hypertensive
- Anti-depressant
- Attention Deficit Hyperactivity Disorder (ADHD)
- Vitamin B12

Table1: Transdermal Drug Delivery Offers the Best of IV and Oral Administration

IV		Oral	TDDS
Reduced first-pass effects	Yes	No	Yes
Constant drug levels	Yes	No*	Yes
Self-administration	No	Yes	Yes
Unrestricted patient activity	No	Yes	Yes
Non-invasive	No	Yes	Yes

**Sometimes can be achieved with controlled release*

Transdermal Patch

Figure 2: A Transdermal Drug Delivery Patch

Transdermal drug delivery system is topically administered medicaments in the form of patch that deliver drug for systemic effect at predetermined and controlled rate. A Transdermal drug delivery device which may be of an active or passive design is a device which provides an alternative route for administering medication. These devices, allow for Pharmaceuticals to be delivered across the skin barrier [4]. In theory Transdermal patches work very simply. A drug is applied in relatively high dosage to the inside of patch, which is worn on the skin for an extended period of time. Trough a diffusion process, the drug enters the blood stream directly through the skin. Since there is high concentration on the patch low concentration in blood, the drug will keep diffusing into the blood for long period of time, maintaining the constant concentration of drug in the blood flow [5]. Transdermal drug delivery has many advantages over conventional drug delivery and can be discussed as follows

Advantages [6-15]

1. They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and another orally administered drugs.
2. They can substitute for oral administration of medication when that route is unsuitable, as with vomiting and diarrhea.
3. They avoid the first-pass effect, that is, the initial pass of s drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzymes.
4. They are noninvasive, avoiding the inconvenience of parenteral therapy.
5. They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration.
6. The activity of a drugs having s short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
7. Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.
8. They are easily and rapidly identified in emergencies (e.g., unresponsive, unconscious, or comatose patient) because of their physical presence, features, and identifying markings.
9. They are used for drugs with narrow therapeutic window.
10. Dose delivery unaffected by vomiting or Diarrhea At the same time transdermals drug delivery has few disadvantages that are limiting the use of transdermals delivery.

Disadvantages [6-15]

1. Only relatively potent small, lipophilic drugs are suitable candidates for Transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.
2. Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
3. The delivery system cannot be used for drugs requiring high blood levels.
4. The use of Transdermal delivery may be uneconomic.
5. Adhesion may vary with patch type and environmental conditions
6. The barrier function of the skin changes from one site to another on the same person, from person to person and with age for better understanding of Transdermal drug delivery, the structure of skin should be briefly discussed along with penetration through skin and permeation pathways.

Principles of Transdermal Permeation [8, 16]

Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration2. Skin is the most intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separates

its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows:
1. Diffusion of drug from drug reservoir to the rate controlling membrane.
2. Diffusion of drug from rate limiting membrane to stratumcorneum.
3. Sorption by stratum corneum and penetration through viable epidermis.
4. Uptake of drug by capillary network in the dermal papillary layer.
5. Effect on target organ

Brief review of skin structure [1, 7, 17, 18]
Skin:
The skin is largest and most external organ of body and hence provides a large surface area for drug application, combines with the mucosal lining of the respiratory, digestive, and urogenital tracts to form a capsule which separates the internal body structures from external environment. The pH of the skin varies from 4 to 5.6, Sweat and fatty acids secreted from sebum influence the pH of the skin surface. It is suggested that acidity of the skin helps in limiting or preventing the growth of pathogens and other organisms[24]. For an average 70 kg human with skin surface area of 1.8 m^2, a typical square centimeter covers 10 hair follicles, 12 nerves, 15 sebaceous glands, 100 sweat glands, and 3 blood vessels with 92 cm total length. The skin has several functions, which can be summarized as follows.

Functions of skin [8, 10]
1. Protection – from invasion by microbes, chemicals, physical agents (e.g. mild trauma, UV light), and dehydration.
2. Reflex action – due to sensory nerves to stimuli
3. Regulation of body temperature – regulate body temperature about 36.8°C (98.4°F) with variation of 0.5°C to 0.75°C.
4. Formation of vitamin D – fatty substance present in skin, 7- dehydrocholesterol, in presence of UV light from sun is converted to vitamin D.
5. Absorption – absorbs some drug with low molecular weight as well as toxic chemicals like mercury.
6. Excretion – excretes sodium chloride in sweat, urea when kidney function is impaired, and aromatic substances (e.g. garlic and other spices)

Anatomy and Physiology of skin [17, 18]
Human skin comprises of three distinct but mutually dependent tissues.

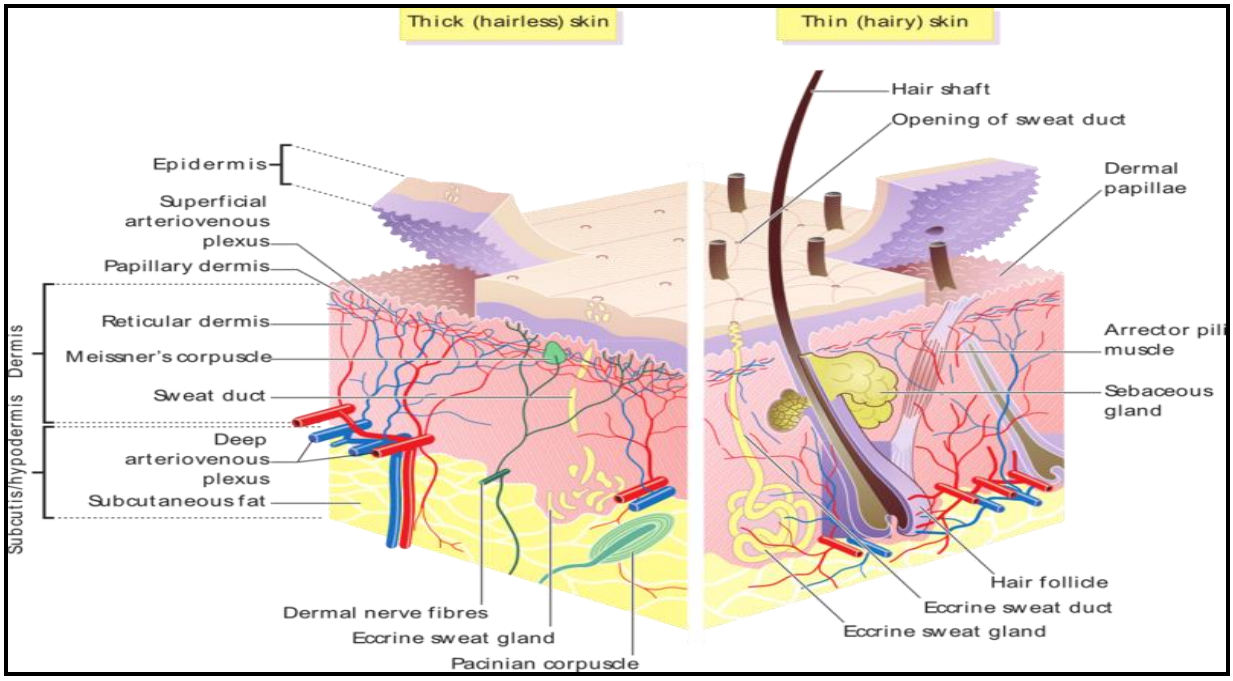


Fig3: Human Skin (T.S.) Structure

A) The stratified, a vascular, cellular epidermis, B) Underlying dermis of connective tissues, and C) Hypodermis.

A. Epidermis

The multilayered envelop of the epidermis varies in thickness, depending on cell size and number of cell layers, ranging from 0.8 mm on palms and soles down to0.06 mm on the eyelids. Stratum corneum and the remainder of the epidermis so-called viable epidermis cover a major area of skin. The epidermis contains no blood vessels and hence nutrients and waste products must diffuse across the dermo-epidermal layer in order to maintain tissue integrity. Likewise, molecules permeating across the epidermis must cross the dermo-epidermal layer in order to be cleared into the systemic circulation.. The source of energy for lower portions of epidermis is also glucose, and the end product of metabolism, lactic acid accumulates in skin. The epidermis contains four histological distinct layers which, from the inside to the outside, are

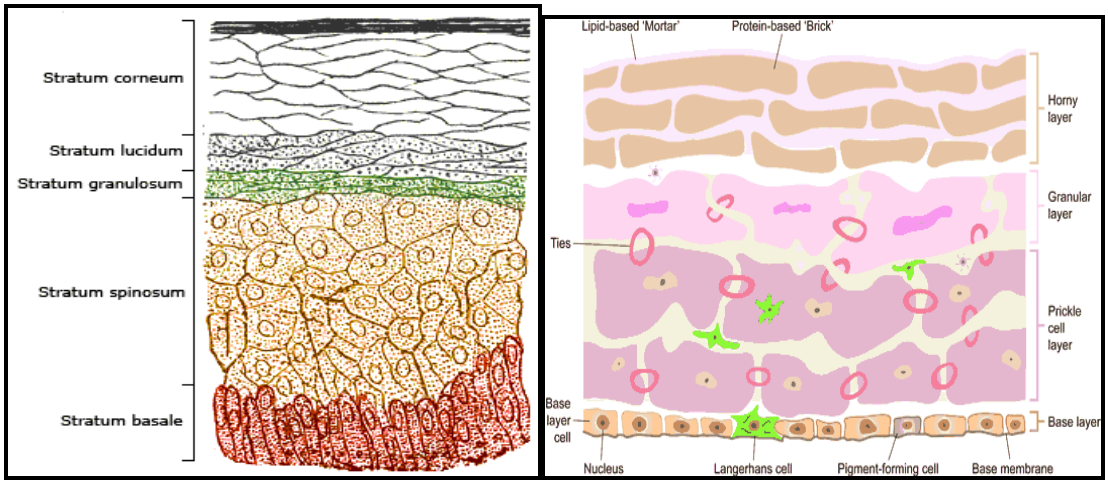
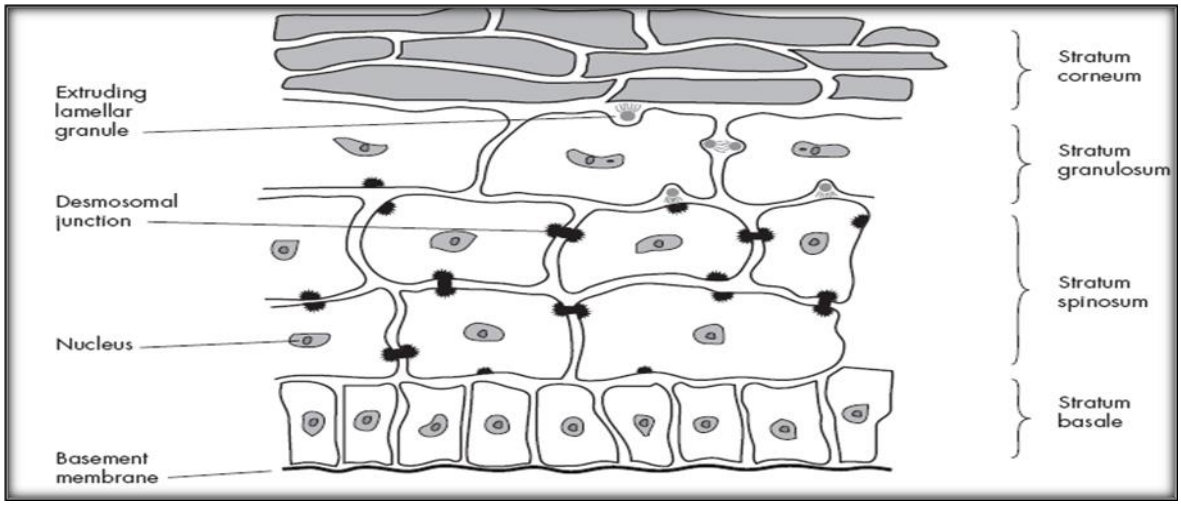


Fig 4: Microstructure of Stratum Corneum

- **Stratum Germinativum**(Growing Layer)
- **Malpighion Layer** (pigment Layer)
- **Stratum Spinosum**(Prickly cell Layer)
- **Stratum Granulosum**(Granular Layer)
- **Stratum Lucidum**



- **Stratum Corneum**(Horny Layer)

Fig 5: A Representation of Human Epidermal Cell Differentiation

- **Stratum Germinativum:**

Basal cells are nucleated, columnar. Cells of this layer have high mitotic index and constantly renew the epidermis and this proliferation in healthy skin balances the loss of dead horny cells from the skin surface.

- **Malpighion Layer:**

The basal cell also include melanocytes which produce the distribute melanin granules to the keratinocytes required for pigmentation a protective measure against radiation.

- **Stratum Spinosum:**

The cell of this layer is produced by morphological and histochemical alteration of the cells basal layers as they moved upward. The cells flatten and their nuclei shrink. They are interconnected by fine prickles and form intercellular bridge the desmosomes. These links maintain the integrity of the epidermis.

- **Stratum Granulosum:**

This layer is above the keratinocytes. They manufacturing basic staining particle, the keratinohylline granules. This keratogenous or transitional zone is a region of intense biochemical activity and morphological change.

- **Stratum Lucidum:**

In the palm of the hand and sole of the foot, and zone forms a thin, translucent layer immediately above the granule layer. The cells are non-nuclear.

- **Stratum corneum:**

This is the outermost layer of skin also called as horney layer. It is approximately 10mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of parallel to the skin surface lying dead, keratinized cells, called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration. Typically, it takes 14 days for a daughter cell from the stratum basale to differentiate into a stratum corneum cell, and the stratum corneum cells are typically retained for a further 14 days prior to shedding. Stratum corneum functions to avoid water loss and entry of foreign material including microorganisms. The barrier nature of thehorney layer depends critically on its constituents: 75-80%proteins, 5-15%lipids, and5-10%ondansetron material on a dry weight basis. Protein fraction pre dominantly contains alpha-keratin (70%) with some beta keratin (10%) and cell envelope (5%).

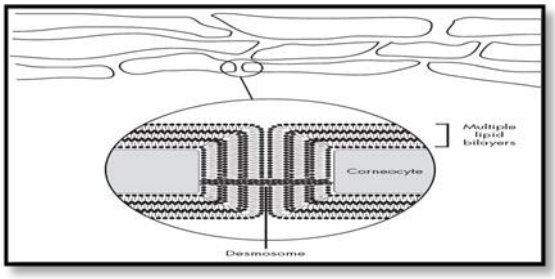


Fig 6: A Representation of the 'Brick And Mortar' Model Of Human Stratum Corneum

Lipid constituents vary with body site (neutral lipids, sphingolipids, polar lipids, cholesterol). Phospholipids are largely absent, a unique feature of mammalian membrane. The architecture of horney layer may be modeled as a wall-like structure. In this model, the keratinized cells function as a protein "bricks" embedded in lipid "mortar." The lipids are arranged in a multiple bi layers, and it has been suggested that there is sufficient amphipilic material in the lipid fraction, such as polar free fatty acids and cholesterol, to maintain a bi layer form.

In the basal layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horney cells from the skin surface. As the cells produced by the basal layer move outward, they alter morphologically and histochemically, undergoing keratinization to form the outermost layer of stratum corneum.

B. Dermis

Dermis is 3 to 5mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels, and nerves. The cutaneous 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. The blood supply thus keeps the dermal concentration of a permeate very low, and the resulting concentration difference across the epidermis provides the essential driving force for Transdermal permeation.

C. Hypodermis (Subcutaneous Fat Layer)

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

For Transdermal drug delivery 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.

Fundamentals of skin permeation [8]

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 like electrolytes. 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. Thus, the stratum corneum acts as a passive, but not inert, diffusion medium. 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.
3. The molecule is taken up into the microcirculation for systemic distribution.

Table 2: Regional Variation in Water Permeability of Stratum Corneum

Sr. No.	Skin Region	Thickness (µm)	Permeation ($mg/cm^2/hr$)	Diffusivity ($cm^2/secx\ 1010$)
1	Abdomen	15	0.34	6.0
2	Volar forearm	16	0.31	5.9
3	Back	10.5	0.29	3.5
4	Forehead	13	0.85	12.9
5	Scrotum	5	1.70	7.4
6	Back of hand	49	0.56	32.3
7	Palm	400	1.14	535
8	Plantar	600	3.90	930

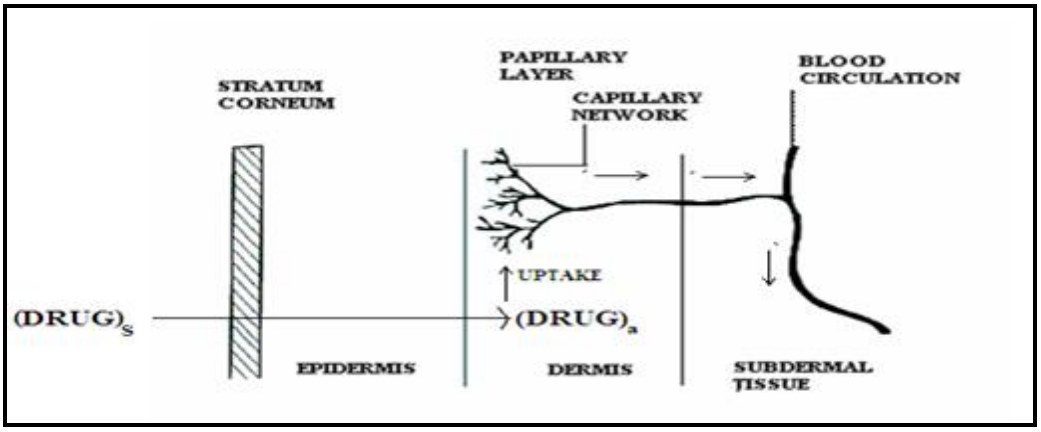


Fig7: A Multilayer Skin Model Showing Sequence of TDDS.

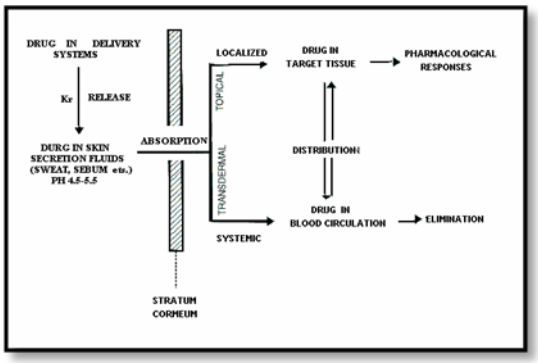


Fig8: Percutaneous Absorption of Drugs for Localized Therapeutic Action in the Skin Tissues or For Systemic Medications in the Tissues.

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.

- **Intracellular verses trans cellular diffusion**

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.

B. Permeation pathways [1, 8]

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

- **Appendageal route**

Appendageal route comprises transport via sweat glands and hair follicles with their associated sebaceous glands (shown as no.1&3 in fig.5). 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.

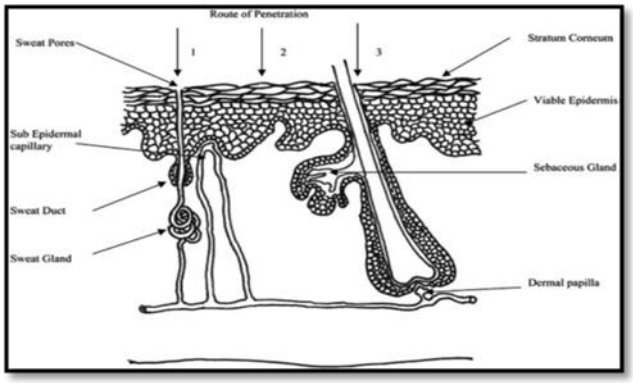


Figure 9: Routs for drug permeation.

- **Epidermal route (shown as no.2 in fig.8)**

For drugs, which mainly cross-intact horney layer, two potential micro routes of entry exists, the transcellular (intracellular) and intercellular pathways. (Fig.6)

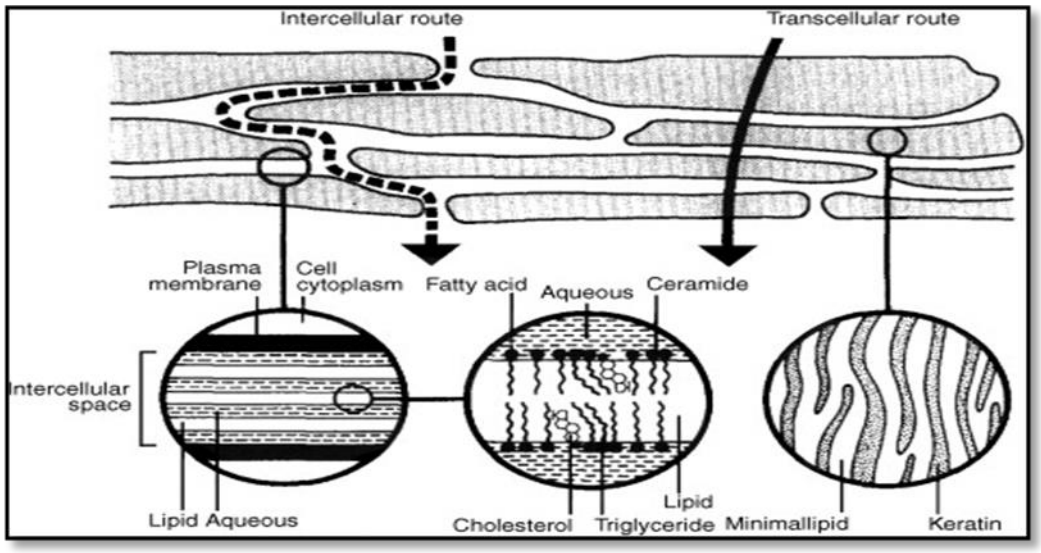


Fig. 10: Epidermal Routes for Drug Permeation

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 (o/w log k >2) traverse the stratum corneum via the intercellular route. Most permeate the stratum corneum by both routes. However, the tortuous intercellular pathway is widely considered to providethe principal route and major barrier to the permeation of most drugs.

Kinetic of Transdermal Permeation [21]

Knowledge of skin permeation kinetics is vital to the successful development of Transdermal therapeutic system. Transdermal permeation of a drug involves the following steps:

1. Sorption by stratum corneum.
2. Penetration of drug through viable epidermice.
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 chemical properties. The rate of permeation across the skin is given by,

$$dQ/dt = P_s (C_d - C_r)$$

Where C_d 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 respectly. P_s is the overall permeability coefficient of the skin tissue to the penetrant. This permeability coefficient is given by the relationship.

$$P_s = k_s . D_{ss}/h_s$$

Where k_s is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermals therapeutic system on to the stratum cornium, D_{ss} is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness off skin tissues and h_s is the overall thickness of skin tissues. As K_s, D_{ss} and h_s are constant under given the permeability coefficient P_s for a skin penetrant can be considered to be constant.

From equation (1) it is clear that a concentrate of the drug permeation can be obtain only when $C_d >> C_r$ i.e. the drug concentration at the surface of the stratum corneum C_d is consistently and substantially greater than the drug concentration in the body Cr. The equation is

$$dQ/dt = P_s C_d$$

And the rate of skin permeation is constant provided the magnitude of C_d remains fairly constant trough out the course of skin permeation. For keeping C_d constant the drug should be release from the device at a rate R_ri.e. either constant or greater than the rate of skin uptake R_s

i.e.,

$R_r >> R_r$

Since

$R_r >> R_r$, the drug concentration on the skin surface C_d is maintained at level equal to or greater than the equilibrium solubility of the drug in the stratum cornium C_s i.e., $C_d >> C_s$. Therefore a maximum rate of skin permeation is obtained and is given by the equation:

$$(dQ/dt)_m = P_s C_s$$

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

Factors influencing Transdermal drug delivery[8]

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.

A. Biological factors

- ***Skin condition*** – Acids and alkalis; many solvents like chloroform, methanol damage the skin cells and promotes 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. Children are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug in TDDSs.
- ***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 to species, so affects the penetration.

B. Physicochemical factors

- ***Skin hydration*** – In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin.

Souse of humectants 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 pKa or pKb 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 *K*, partition coefficient 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. Because of partition coefficient domination, the effect of molecular size is not known.

Factors affecting permeability [19]

A. Physiological factors:

- Anatomic site of application on the body
- Skin condition and disease
- Age of the patient
- Skin metabolism
- Desquamation (peeling or flaking of the surface of the skin)
- Skin irritation and sensitization
- Race

B. Formulation factors

- Physical chemistry of transport
- Vehicles and membrane used
- Penetration enhancers used
- Method of application
- Device used

C. Physicochemical properties of enhancers

- Partition coefficient of 1 or gearter is required
- pH value should be moderate, the flux of ionizable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their Transdermal permeability
- Concentration of penetrant higher than solubility, excess solid drug functions as a reservoir and helps in maintaining constant drug concentration for prolonged time.

Technologies for developing Transdermal patches [16, 20]

The technologies can be classified in four basic approaches,

A. A Polymer membrane partition-controlled TDD systems:

In this type of systems, the drug reservoir is sandwiched between a drug impermeable backing laminate and a rate controlling polymeric membrane (Fig.11).

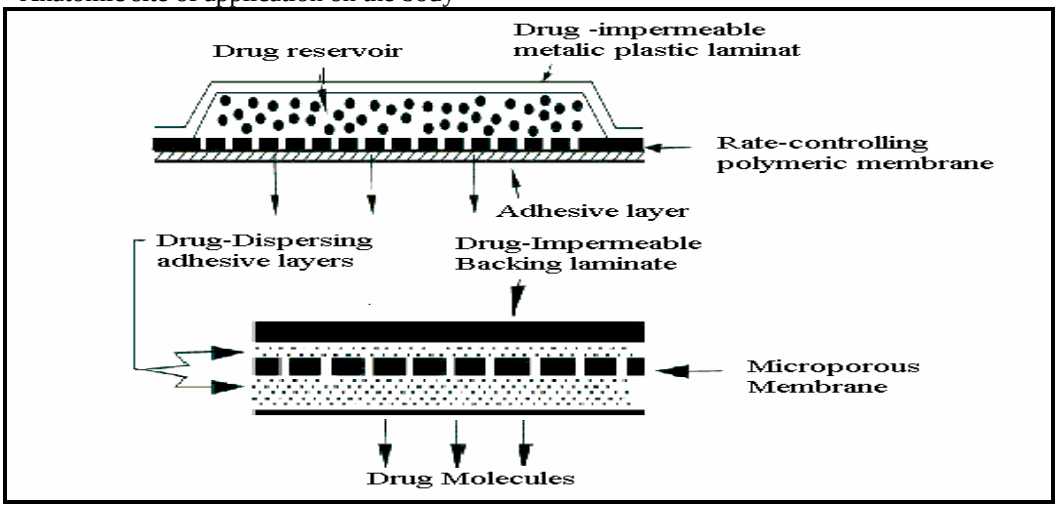


Fig 11: Cross Sectional View of Polymer Membrane Partition-Controlled TDD System

The drug is allowed to permeate only through the rate controlling membrane. The drug solids are homogeneously dispersed in a solid polymer matrix, suspended in an unleachable, viscous liquid medium e.g. silicone fluid, to form a paste like suspension, or dissolved in a releasable solvent e.g. alkyl alcohol, to form a clear drug solution. The rate controlling membrane can be either a micro porous or a nonporous polymeric membrane e.g. ethylene-vinyl acetate copolymer, with specific drug permeability. On the external surface of the polymeric membrane a thin layer of drug compatible, hypoallergenic pressure sensitive adhesive polymer e.g. silicone adhesive, may be applied to provide intimate contact of TDD system with the skin surface. Varying the composition of drug reservoir formulation and the permeability coefficient and thickness of rate controlling membrane can alter the drug release rate. E.g. Some FDA approved systems – Transderm-Nitro for angina pectoris, Transderm-Scop for motion sickness, Catapres-TTS system for hypertension. The intrinsic rate of drug release from this type of TDD system is defined by

$$\frac{dQ}{dt} = \frac{Cr}{\frac{1}{Pm} + \frac{1}{Pa}}$$

Where, *CR* is drug concentration in the reservoir compartment and Pa and Pm are the permeability coefficient of the adhesive layer and the rate controlling membrane. Pm is the sum of permeability coefficient simultaneous penetration across the pores and the polymeric material Pm and Pa, respectively, are defined as follows,

$$Pm = \frac{Km/rD}{hm}$$

$$Pa = \frac{Ka/mDa}{ha}$$

Km / r the partition coefficient for the interfacial partitioning of drug from the reservoir to the membrane,
Ka / m the partition coefficient for the interfacial partitioning of drug from membrane to adhesive
Da diffusion coefficient in rate controlling membrane
Dm diffusion coefficient in adhesive layer
ha thickness of rate controlling membrane
hm thickness of adhesive layer

B. Polymer matrix diffusion-controlled TDD systems:

In this system, the drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix, and then the medicated polymer formed is molded into medicated disks with defined surface area and thickness. This drug reservoir containing polymer disk is then mounted on occlusive base plate in a compartment fabricated from a drug-impermeable plastic backing. Instead of coating adhesive polymer directly on the surface of medicated disk, it is applied along the circumference of the patch to form a strip of adhesive rim surrounding the medicated disk. e.g. Nitro-Dur system and NTS system for angina pectoris. The rate of release from polymer matrix drug dispersion-type is,

$$\frac{dQ}{dt} = \frac{ACpDp\ 1/2}{2t}$$

Where, *Ld*is drug loading dose initially dispersed in polymer matrix
$C_P$is solubility of drug in polymer matrix
D_P is diffusivity of drug in polymer matrix

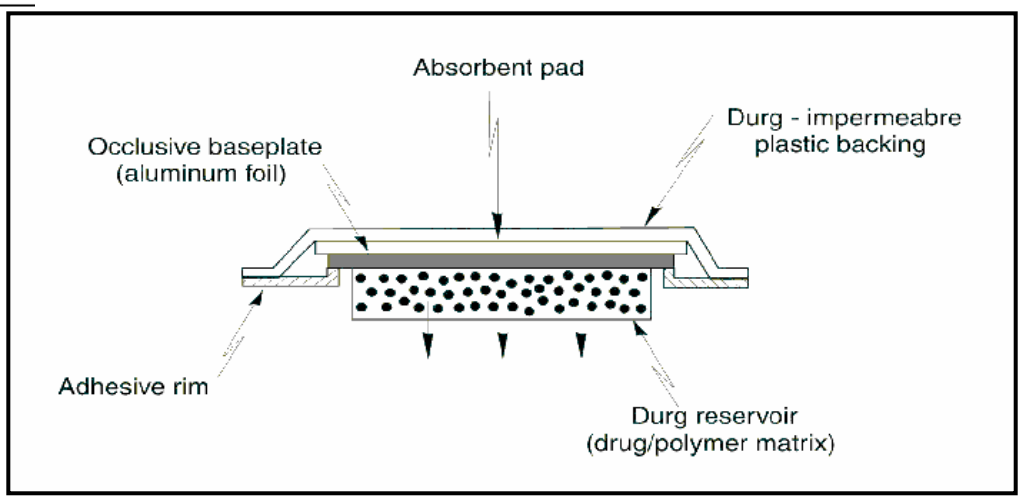


Fig 12: Cross-Sectional View Of Polymer Matrix Diffusion-controlled TDD Systems

Only drug is dissolved in polymer matrix can release, $C_P$is practically equal to C_R. alternately, the polymer matrix drug dispersion-type TDD system can be fabricated by directly dispersing drug in a pressure-sensitive adhesive polymer, e.g. poly acrylate, and then coating the drug-dispersed adhesive polymer by solvent casting or hot melt onto a flat sheet of a drug-impermeable backing laminate to form a single layer of drug reservoir. This yields a thinner patch. e.g. Minitran system, Nitro-Dur II system for angina pectoris.

C. Drug reservoir gradient-controlled TDD systems:

Polymer matrix drug dispersion-type TDD systems can be modified to have the drug loading level varied in an incremental manner, forming a gradient of drug reservoir along the diffusional path across the multi laminate adhesive layers. The drug release from this type of drug reservoir gradient-controlled TDD systems can be expressed by

$$\frac{dQ}{dt} = \frac{Ka/rDa}{ha} A(\text{ha})$$

In this system the thickness of diffusional path through which drug molecules diffuse increases with time, i.e. ha (t). The drug loading level in the multi laminate adhesive layer is designed to increase proportionally i.e. Ld (ha) so as to compensate time dependent increase n diffusional path as a result of drug depletion due to release. Thus, theoretically this should increase a more constant drug release profile. E.g. Deponit system containing nitroglycerine for angina pectoris.

D. Micro reservoir dissolution-controlled TDD systems:

A hybrid of reservoir- and matrix dispersion-type drug delivery systems, which contains dug reservoir formed by first suspending the drug solids in an aqueous solution of water-miscible drug solubulizer e.g. propylene glycol, then homogeneously dispersing the drug suspension, with controlled aqueous solubility, in a lipophilic polymer, by high shear mechanical force, to form thousands of unleachable microscopic drug reservoirs.

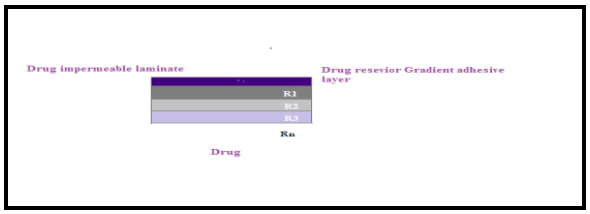


Fig13: Cross-Sectional View of A Drug Reservoir Gradient-Controlled TDD System

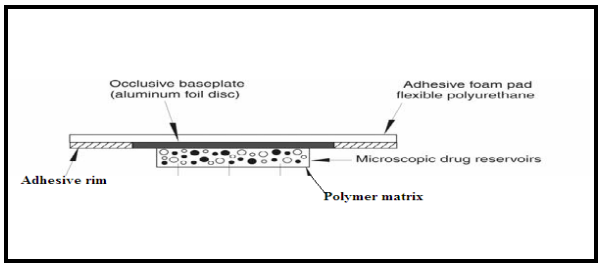


Fig14: Cross Sectional View of Micro Reservoir Dissolution-Controlled TDD Systems

Basic Components of Transdermal patches [8]

1. Polymer matrix / Drug reservoir
2. Drug
3. Permeation enhancers
4. Pressure sensitive adhesive (PSA)
5. Backing laminates
6. Release liner
7. Other excipients like plasticizers and solvents

1. Polymer matrix:

Polymers are the backbone of a Transdermal drug delivery system. Systems for Transdermal delivery are fabricated as multi layered polymeric laminates in which a drug reservoir or a drug polymer matrix is sandwiched between two polymeric layers: an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive 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 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, and 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 and chitosan *etc*.

• **Synthetic Elastomers:** e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene,butylrubber*etc*.

• **Synthetic Polymers:** e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate *etc*. The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxy propylmethylcellulose are used as matrix formers for TDDS. Other polymers like EVA, silicon rubber and polyurethane are used as rate controlling membrane.

2. Drug

The most important criteria for TDDS is that the drug possesses the right physicochemical and pharmacokinetic properties. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non- compliance due to frequent dosing. For example, drugs like rivastigmine for alzheimer's and Parkinson dementia, rotigotine for parkinson, methylphenidate for attention deficit hyperactive disorder and selegiline for depression are recently approved as TDDS.

Biopharmaceutical parameters in drug selection for transdermals patch [16]

- ✧ Dose should be low i.e.<20mg/day.
- ✧ Half life should be 10 h or less.
- ✧ Molecular weight should be <400 Da.
- ✧ Partition coefficient should be Log P (Octanol-water) between1.0 and 4.
- ✧ Skin permeability coefficient should be <0.5 X 10-3cm/h.
- ✧ Drug should be non irritating and non sensitizing to the skin.
- ✧ Oral bioavailability should be low.
- ✧ Therapeutic index should be low.

3. Permeation enhancers

To increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug penetration enhancers interact with structural components of stratum corneum *i.e.*, proteins or lipids. The enhancement in absorption of oil soluble drugs is apparently due to the partial leaching of the epidermal lipids by the chemical enhancers, resulting in the improvement of the skin conditions for wetting and for transepidermal and transfollicular penetration. The miscibility and solution properties of the enhancers used could be responsible for the enhanced Transdermal permeation of water soluble drugs. Pharmaceutical scientists have made great efforts in Transdermal permeation studies using various enhancers for several drug moieties.

Classification of penetration enhancers [9]

- **Terpenes (essential oils):**e.g. Nerodilol, menthol, 1 8 cineol, limonene, carvone etc.
- **Pyrrolidones:** E.g. N-methyl-2-pyrrolidone (NMP), azoneetc.
- **Fatty acids and esters:** E.g. Oleic acid, linoleic acid, lauric acid, capric acid etc.
- **Sulfoxides and similar compounds:** E.g. Dimethyl sulfoxide (DMSO), N, N dimethyl Formamide Alcohols, Glycols,and Glycerides :E.g. Ethanol, Propylene glycol, Octyl alcohol etc.
- **Micellaneous Enhancers**: E.g. Phospholipids, Cyclodextrins, Amino acid derivatives, Enzymes etc.

The permeation of drugs across is also enhanced by physical means like pulsed DC iotophorosisi. it passes a few mill amperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier, sonophoresis i.e application of ultrasound, particularly low frequency ultrasound, has been shown to enhance Transdermal transport of various drugs including macromolecules., electro oration i.e application of short, high voltage electrical pulses to the skin for increasing the permeability of the skin for diffusion of drugs by 4 orders of magnitude, use of micro projections i.e Transdermal patches with microscopic projections called micro needles were used to facilitate Transdermal drug transport etc.

4. Pressure sensitive adhesive:

A PSA maintains an intimate contact between patch and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tacky, exert a strong holding force. For e.g. polyacrylates, polyisobutylene and silicon based adhesives. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. PSA should be physicochemically and biologically compatible and should not alter drug release. The PSA can be positioned on the face of the device(asin reservoir system) or in the back of the device and extending peripherally(as in case of matrix system).

5. Backing laminate

The primary function of the backing laminate is to provide support. Backing layer should be chemical resistant and excipient compatible because the prolonged contact between the backing layer and the excipients may cause the additives to leach out or may lead to diffusion of excipients, drug or penetration enhancer through the layer. They should a low moisture vapor transmission rate. Theymust have optimal elasticity, flexibility, and tensile strength. Examples of some backing materials are an aluminium vapor coated layer, a plastic film (polyethylene, polyvinyl chloride, polyester) anda heat seal layer.

6. Release liner:

During storage release liner prevents the loss of the drug that has migrated into the adhesive layer and contamination. It is therefore regarded as a part of the primary packaging material rather than apart of dosage form for delivering the drug. The release liner is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (*e.g.* polyethylene, polyvinylchloride) and a release coating layer made up of silicon. Other materials used for TDDS release liner includes polyester foil.

7. Other excipients:

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers

such as dibutylpthalate, triethylcitrate, polyethyleneglycol and propylene glycol are added to provide plasticity to the
Transdermal patch**.**

General clinical considerations in the use of TDDS [7]

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 locations is important to allow the skin to regain its normal permeability and to prevent skin irritation.

- TDDSs should be applied to clean, dry skin relatively free of hair and not oily, inflamed, irritated, broken, or callused. Wet or moist skin can accelerate drug permeation beyond ondansetron time. Oily skin can impair the adhesion of patch. Ifhair is present at the site, it should be carefully cut, not wet shaved, nor should adepilatory agent be used, 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.
- Cutting should not physically alter TDDSs, 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 the heel of hand for about 10 sec.

CONCLUSION:

A great deal of advancement has been done in this field of Transdermal Drug Delivery Framework particularly in transdermal patches. This framework intrigues a considerable measure of specialists because of expansive points of interest of Transdermal Drug Delivery Framework. To consolidate fresher drugs by means of this framework numerous new research are going ahead in the present day. Distinctive gadgets which help in expanding the rate of entrance and ingestion of the drug are additionally mulled over. Nonetheless, in the present days because of specific disservices like substantial measurements can't be given, huge drug atom can't be conveyed; aggravation of skin, the rate of retention of the drug is less and so on the utilization of Transdermal Drug Delivery is restricted. Anyhow, with the innovation of new drugs and new gadgets which can be joined by means of this framework, it utilized is expanding quickly as a part of the present time.

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