An Updated Review On Transdermal Drug Delivery Systems

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Abstract:
Transdermal drug delivery systems (TDDS), also known as "patches," are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. 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. The TDDS review articles provide valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who is involved in TDDS. With the advancement in technology Pharma industries have trendified all its resources. Earlier we use convectional dosage form but now we use novel drug delivery system.

Keywords: Transdermal drug delivery systems (TDDS), Diffusion, First-generation TDS, Second-generation TDS, Polymer Matrix, Permeation enhancers,

INTRODUCTION:

Transdermal drug delivery system (TDDS) are defined as ,distinct dosage form which, when applied to the intact skin, deliver the drugs, through skin at a controlled rate to the systemic circulation. Although some Keywords: Transdermal drug delivery systems (TDDS), Diffusion, First-generation TDS, Second-generation TDS, Polymer Matrix, Permeation enhancers, Iontophoresis, Microneedlesdrugs have inherent side effects that cannot be eliminated in any dosage form, many drugs show unwanted behavior that is specifically associated with a particular route of administration. One recent effort at eliminating some of the problems of traditional dosage form is the development of transdermal delivery system. Topical application has also been used for centuries, predominantly in the treatment of localized skin disease. Local treatment requires only that the drug permeate through the outer layer of the skin to treat the diseased state, with the hope that this occurs with little or no systemic accumulation. Certainly, each dosage form has its unique in medicine, but some attributes of the transdermal delivery system provide distinct advantages over traditional methods.[1] The transfollicular pathway in which the drug travels through cells and across them is the shortest way that most likely provides relatively large for diffusion of a molecule. The intracellular pathway avoids the cell contents,but aqueous considerably more tortuous. The transfollicular pathway involves passage or diffusion of drug molecule through the hair shaft openings, which presumably are filled with sebum.This route offers substantially lower diffusional resistance to the most of the drugs that are generally not permitted fairly through other routes.[3] However the path length is relatively long and the density of hair follicles in human skin quite low. The transdermal permeation of most neutral molecules are recognized to be primarily a process of passive diffusion across the intact stratum corneum through the transfollicular region. The transdermal drug delivery systems have been designed as an alternative route for systemic drug delivery.The systemic drug administration through skin holds several advantages such as maintains constant drug level in blood, decrease of side effects, and improvement of bioavailability by circumvention of hepatic first pass metabolism and increase patient compliance. Now a days skin considered as a safe port for drug administration, to provide continuous drug release into systemic circulation.[2] The best mixture is approximately 50% of the drug being each hydrophilic and lipophilic. This is because lipid-soluble substances readily pass through the intercellular lipid bi-layer of the cell membrane whereas water-soluble drugs are able to pass limiting steps in transdermal drug delivery system. The only path of entry by sweat ducts and hair follicles, but they are considered, rather insignificants.

Global Sales among TDDS Products [3]

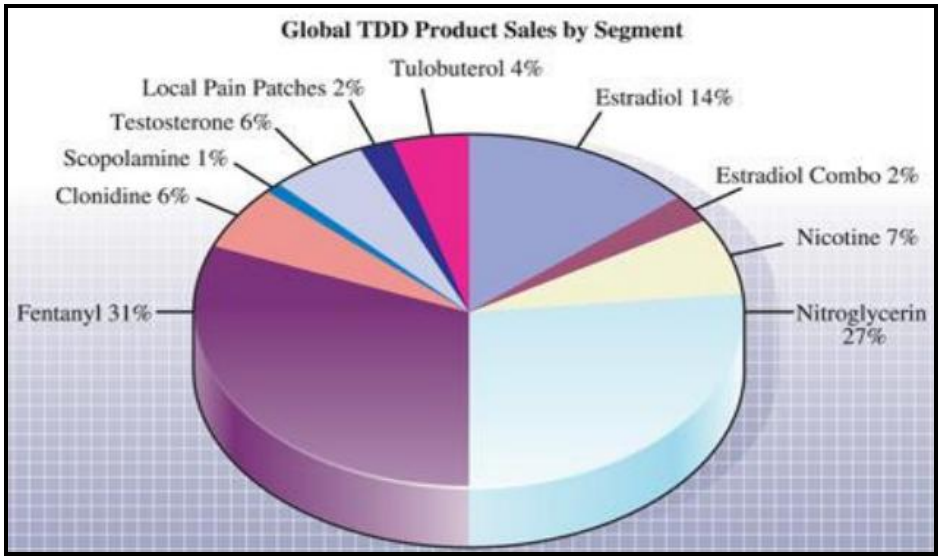

Fig. 1.1 Global sales among TDD products

1.1 Advantages: - [4]

- Avoidance of first pass metabolism of drugs.
- Reduced plasma concentration levels of drugs, with decreased side effects.
- Reduction of fluctuations in plasma levels of drugs, Utilization of drug candidates with short half-life and low therapeutic index.
- Easy elimination of drug delivery in case of toxicity.
- Reduction of dosing frequency.
- Self-administration is possible with these systems.
- Improved bioavailability.
- Minimize inter and intra patient variations.
- Improved patient compliance and comfort via non-invasive, painless and simple application.
- Reduce side effect due to optimization of the blood concentration time profile.
- Therapy can be quickly terminated by removal of the patch from the skin.
- Drug can be delivered over a long period of time.
- Elimination drug food interactions.

1.2 Disadvantages: - [5]

The drug must have desirable physicochemical properties for penetrate through skin

- High dose drug candidates are not suitable for TDDS.
- TDDS cannot deliver drugs in a pulsatile fashion.
- A molecular weight less than 500 Da is essential.
- Drugs in high concentration may cause skin irritation.
- Difficult to achieve high plasma drug concentration.
- May cause allergic reactions..
- High dose drug candidates are not suitable for TDDS.

1.3 Skin structure and function: - [6]

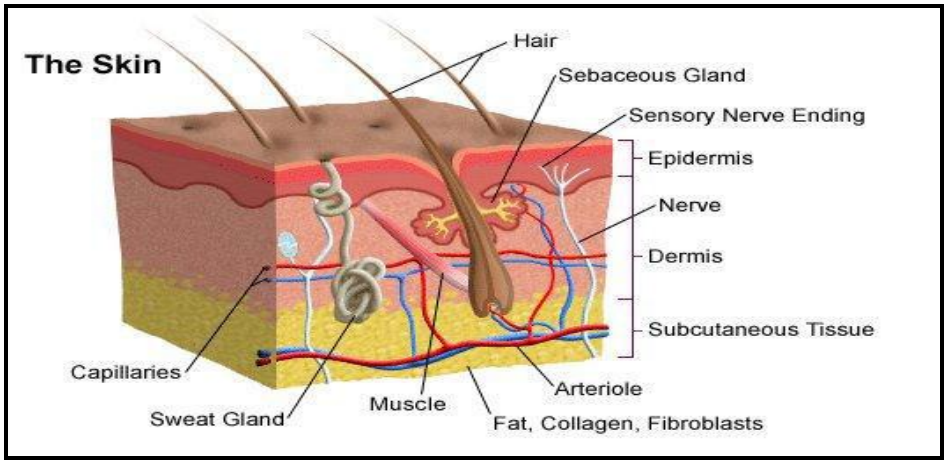

Fig. 1.2 Structure of Skin

The skin is the largest single organ in the body. An average human skin is known to contain, on an average 40-70 hair follicles and 200-250 sweat ducts per every square centimeter of the skin. These skin appendages, however actually occupy grossly only 0.1% of total stratum corneum surface henceforth the trans-appendageal route of percutaneous absorption has provided only a very limited contribution to the overall kinetic profile of transdermal permeation. Therefore, the transdermal permeation of most neutral molecule at steady can thus be considered as primarily diffusion through the intact stratum corneum in the interfollicular region. So, for fundamental understanding of TDD (Transdermal drug delivery), the structure should be understood fig: 1.2

1.4 Function of skin: - [7-8]

1. Protection: keratin in the tissue protects underlying tissues from microbes, abrasion, heat, and chemicals. It also protects from physical agent like dehydration, UV light.
2. Regulates body temperature: The skin contributes to thermoregulation, the homeostatic regulation of body temperature, in two ways: by liberating sweat at its surface and by adjusting the flow of blood in the dermis.
3. Absorption: Absorption of lipid soluble material like fat soluble vitamins A,D,E and K certain drugs, steroids, heavy metals, organic solvents, O_2 and CO_2.
4. Excretion: It has small role in the excretion; about 400ml of water evaporates through it daily. It also eliminates nitrogen containing wastes like ammonia, urea, and uric acid.
5. Cutaneous sensations: These include tactile sensation- touch, pressure, vibration, and tickling as well as thermal sensation and pain.
6. Synthesis of vitamin D: Synthesis of Vitamin D is done by activation of precursor molecule in the skin in presence of UV rays in sunlight.
7. Blood reservoir: The dermal vascular supply is extensive and can hold large volumes of blood.

1.5 Anatomy and Physiology of skin: -

Human skin comprises of three distinct but mutually dependent, tissues 2-5:
1. The stratified, vascular, cellular epidermis.
2. Underlying dermis of connective tissues and
3. Hypodermis.

1.5.1 Epidermis: -

The multilayered of epidermis varies in thickness, depending on cell size and number of cell layers of epidermis, ranging from 0.06 mm on the eyelids sole and 0.8 mm on palms. Skin has three layers:
Horney layer (Stratum corneum):
This is the outermost layer of skin also called as horney layer. It is approximately 10µm thick when dry, but swells to several times this thickness when fully hydrated. It has 10 to 30 layers of dead, keratinized cells called corneocytes.

Viable epidermis:

This is situated beneath the outermost layer and varies in thickness ranging from 0.06 mm on the eyelids sole upto 0.8 mm on the palms. Going inwards, it consists of various layers as stratum granulosum, stratum lucidum, stratum spinosum and the stratum basal. In the basal layer, mitosis divisions of the cells constantly reproduce 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. It is flexible but relatively impermeable. The stratum corneum is the principle barrier for penetration of drug. The structure of horney layer may be modeled as a wall-like structure

1.5.2. Dermis: -

The dermis, beneath the epidermis, contains tough connective tissue, hair follicles and sweat glands. Dermis is 3-5mm thick layer of skin and is composed of a matrix type. Connective tissue, which contains blood vessels , lymph vessels and nerves. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The cutaneous blood supply has essential function in regulation of body temperature. The blood supply thus keeps the dermal concentration of a permit very low and the resulting concentration difference across the epidermis provides the essential concentration gradient for transdermal permeation. It also provides nutrients and oxygen to the skin while removing toxins and waste products.

1.5.3. Hypodermis: - [9]

The deeper subcutaneous tissue (hypodermis) is made of fat and connective tissue. The hypodermis or subcutaneous fat tissue supports the epidermis and dermis layer. 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.

1.5.4 Sebaceous Glands: -
The sebaceous glands secrete sebum, an oily substance that helps keep skin from drying out. Most of the glands are located in the base of hair follicles.

1.5.5 Sweat Glands: -
When your body gets hot or is under stress, these glands produce sweat, which evaporates to cool you. Sweat glands are located all over the body but are especially abundant in your palms, soles, forehead, and underarms.

1.5.6 Hair Follicle: -
Every hair on your body grows from a live follicle with roots in the fatty layer called subcutaneous tissue.
1.5.7 Collagen: -
Collagen is the most abundant protein in the skin, making up 75% of your skin.

1.5.8 Elastin: -
When you hear the word elastin, think elastic. This protein is found with collagen in the dermis and is responsible for giving structure to your skin and organs. As with collagen, elastin is affected by time and the elements.

1.5.9 Keratin: -
Keratin is the strongest protein in your skin. It's also dominant in your hair and nails.

1.6 Drug permeation pathway: - [10]
Percutaneous absorption involves passive diffusion of the substances through the skin. A molecule may use two diffusional routes to penetrate normal intact skin, the appendageal route and the epidermal route

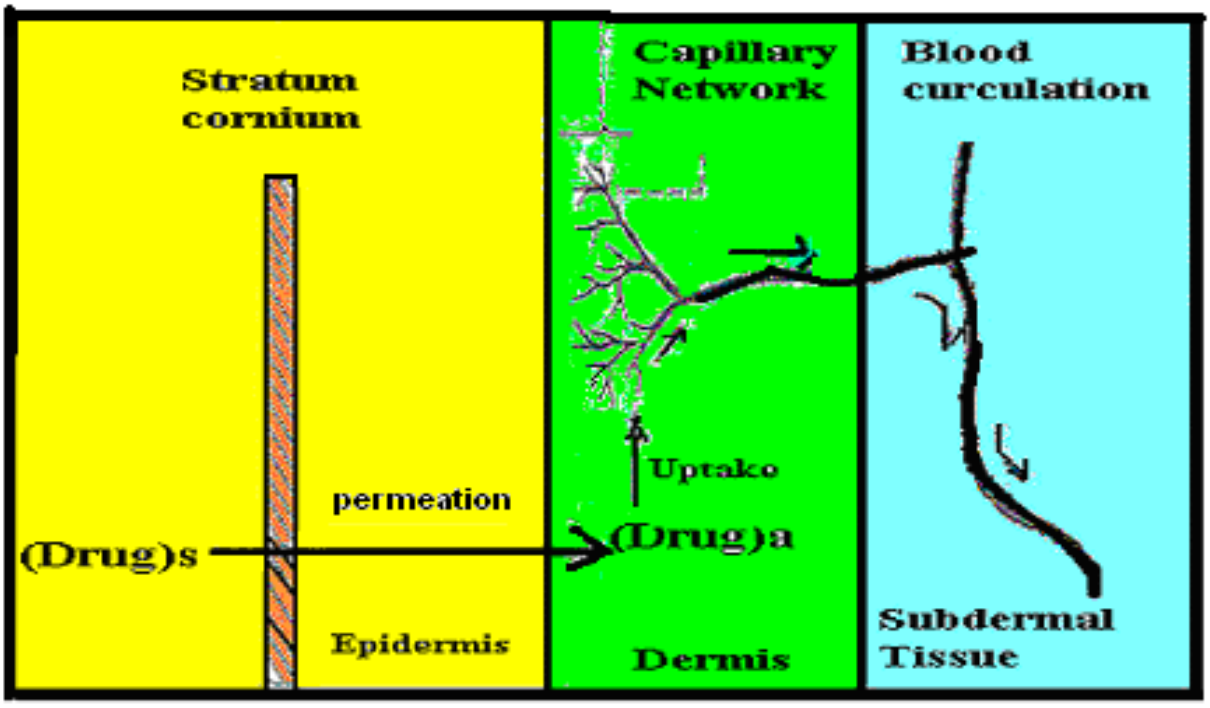

Fig. 1.3 Routes for drug permeation.

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 1.3)
A. Appendageal route (shunt route)
B. Epidermal
a. Transcellular.
b. Paracellular.

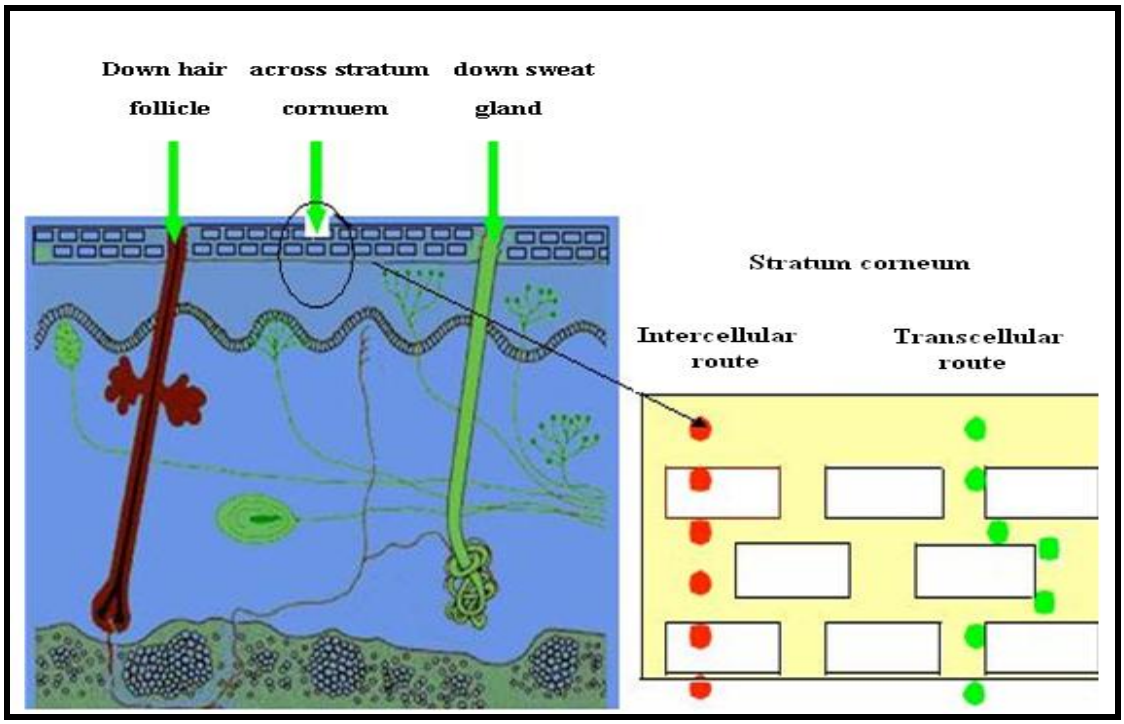

Fig.1.4 Drug permeation pathways across skin.

1.6.1 Appendageal route: -

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

1.6.2 Epidermal route: -

1.6.2.1 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.

1.6.2.2 Paracellular**: -**

Paracellular pathway means transport of molecules around or between the cells. Tight junctions or similar situations exist between the cells. The principle pathway taken by a permeant is decided mainly by the partition coefficient (logk). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophilic permeants penetrate the stratum corneum via the intercellular route. Most permeants penetrate the stratum corneum by both routes. However, the tortuous intercellular pathway is widely considered to provide the principle route and major barrier to the permeation of most the drugs.

1.7A Stratum Corneum as Skin Permeation barrier: - [11]

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. Permeation of drug molecule through skin.

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.

The skin contains a dead layer stratum corneum and viable layers, the viable tissue contains catechol-o-methyl transferase which metabolizes the drugs papillary layer of Dermis contains so many capillaries and it is highly probable that most molecules enter the micro circulation soon after leaving the epidermis. Thus the average total resistance time of a drug species in the dermal aqueous phase may be only a fraction of minute.

1.8 Factors Affecting Transdermal Permeability: - [12-13]

1.8.1 Biological Factors: -

Skin condition: The intact skin is a tough barrier but many agents like acids and alkalis; many solvents such as chloroform and methanol injure barrier cells thereby promote penetration. Diseased state alters the skin conditions of patient.

Skin age: The skin of young and the elderly is more permeable than adult tissue. Children are also more susceptible to

toxic effect of drugs and chemicals; partly because of their greater surface area thus skin age also affects the penetration of drug through TDDS.

Blood flow: The changes in the peripheral circulation could affect transdermal absorption. In clinically hyperaemic skin, any increase in absorption almost always arises because the disease damages the skin barrier.

Regional skin sites: Variations in cutaneous permeability around the body depend on the thickness and nature of the stratum corneum and the density of skin appendages. These factors affect significantly to the penetration.

Skin metabolism: The skin metabolizes steroid hormones, chemical carcinogens and some drugs. Metabolism of skin determines efficacy of drug permeated through the skin.

Species differences: Skin thickness, sweat gland and hair follicle densities and melt condition affect the routes of penetration and the resistance to permeation.

1.8.2 Physicochemical factors: -

Skin hydration: In contact with water saturates the skin the tissue swells, softens and wrinkles results increases permeability. Hydration of the stratum corneum is one of the most important factors in increasing the penetration rate, so use of humectant is done in the transdermal therapeutics

Temperature and pH: The penetration rate of material through human skin can change tenfold for a large temperature variation, as the diffusion coefficient decreases as the temperature falls. Weak acids and bases dissociate to different degrees, depending on the pH and their pKa or pKb values. Thus, the proportion of unionized drug in the applied phase determines the effective concentration gradient, and this fraction depends on pH. Thus, temperature and pH are factors which affect the penetration of drug.

Diffusion coefficient: Penetration of drug depends upon the diffusion coefficient.

1.9 Basic Components of TDDS: - [14]

Transdermal patch may include the following components:

1. **Liner -** Protects the patch during storage.
2. **Drug -** Drug solution in direct contact with release liner.
3. **Adhesive -** Serves to adhere the components of the patch together along with the skin.
4. **Membrane -** Controls the release of the drug from the reservoir and multi-layer patches.
5. **Backing -** Protects the patch from the outer environment.
6. Other excipients like plasticizers and solvents.

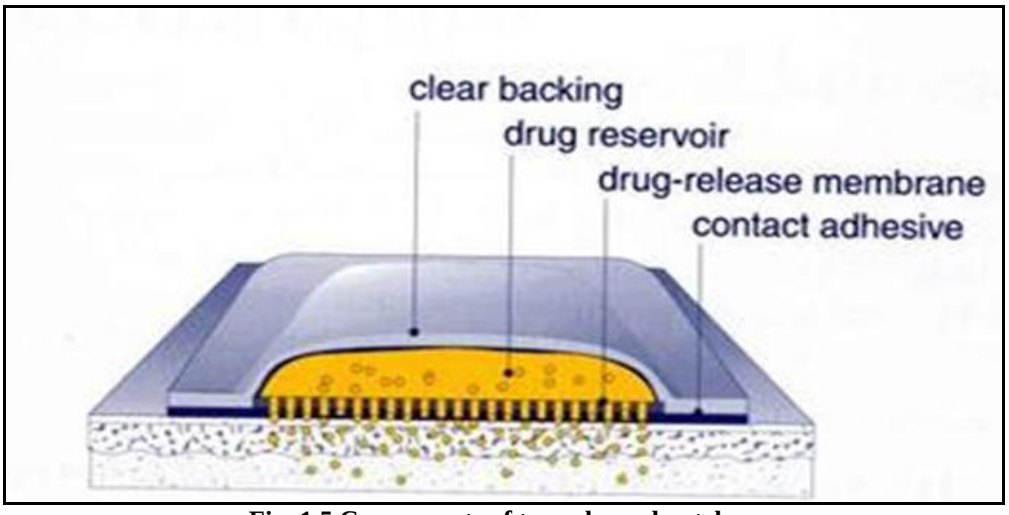

Fig. 1.5 Components of transdermal patches.

1.9.1 Polymer matrix / Drug reservoir: - [15]

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 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 polymer controls the release of the drug from the device.

Criteria for polymer to be used in a transdermal system: -

1. Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and get released through it.
2. The polymer should be stable, non-reactive with the drug, easily manufactured and fabricated into the desired product; and inexpensive.
3. The polymer and its degradation product must be non-toxic or non-antagonistic to the host.
4. The mechanical properties of the polymers should not deteriorate excessively when large amounts of agent are incorporated into it.
The polymers utilized for TDDS can be classified as: -
Natural Polymers: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan, starch etc.
Synthetic Elastomers: e.g. Hydrin rubber, poly-butadiene, poly-isobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butyl-rubber etc.

Synthetic Polymers: e.g. polyvinyl alcohol, polyvinyl-pyrrolidone, polyvinylchloride, polyethylene, polypropylene, poly-acrylate, poly-amide, poly-urea, poly-methyl methacrylate, epoxy etc.

1.9.2 Drug: -
The most important criteria for TDDS is that the drug possesses the right physicochemical and pharmacokinetic properties. Drug solution in direct contact with release liner.

Ideal properties for selection of drug: -
Following are some of the desirable properties of drug for transdermal delivery.

Physicochemical properties:
- Half-life should be short.
- Molecular weight should be <500 Dalton.
- The drug must non-irritant to skin and not produce allergy
- Oral bioavailability should be low.
- The pH of the saturated solution should be in between 5 to 9.
- Optimum partition coefficient is required for good therapeutic action
- Therapeutic index should be low
- Aqueous solubility >1mg/ml
- Low melting point of drug is desired.

Biological properties:
- The drug should be potent with daily dose <10-15 mg/day
- They should not get extensively metabolized in the skin.

1.9.3 Penetration Enhancer: - [16]
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. Sorption promotes act by interaction with intracellular lipids leading to distruption of their organization and increasing their fluidity. Some of them also interact with intercellular protein, keratin denaturation (azone and oleic acid) while others act by both mechanism (DMSO and propylene glycol). Another possible mechanism is by altering the skin hydration.

Ideal penetration enhancers should possess the following properties: -
- They should be non-toxic, non-irritating and non-allergic.
- They would ideally work rapidly; the activity and duration of effect should be both predictable and reproducible.
- They should have no pharmacological activity within the body.
- The penetration enhancers should work uni-directionally, i.e., they should allow therapeutic agents into the body while preventing the loss of endogenous materials from the body.
- When removed from the skin, barrier properties should return both rapidly and fully to normal.
- They should be cosmetically acceptable with an appropriate skin feel.
- Pharmacologically inert

These are the compounds which promote skin permeability by altering the skin as a barrier to the flux of desired penetrant. Methods of transdermal enhancement:
1. Physical

2. Biochemical
3. Super-saturation
4. Bio-convertable pro-drug
5. Chemical

Physical enhancement: -
Different physical approaches to increase percutaneous absorption have been utilized but the most important approaches are iontophoresis, ultrasound, electroporation and heat. These methods show most promising results in the percutaneous delivery of large molecular weight compounds but the major limitation is the input of energy to achieve their effects.

Biochemical enhancers: -
These types of enhancers reduce barrier properties of the skin either by inhibiting enzymes responsible for synthesis of stratum corneum lipid or by promoting metabolism of existing skin lipids that are responsible for barrier function.

Super-saturation: -
The maximum skin penetration rate is obtained when a drug is at its highest thermodynamic activity as is the case in a supersaturated solution. Supersaturated solution can occur due to evaporation of solvent or by mixing of co-solvents. Increase in drug flux of five to ten fold have been reported from supersaturated solution of number of drugs e.g. The flux of oestradiol from an 18 times saturation system was increased 18 fold across human membrane.
T
hrough bio-convertible pro-drug: -
Pro-drug may be designed to obtain an optimal partition coefficient for entering the skin barrier. After absorption and diffusion to the viable tissues, enzymes convert the pro-drug to the active species. Many steroids have designed in this way. The intrinsic poor permeability of 5-fluorouracil, a polar drug with reasonable skin permeability was increased up to 25 times by forming N-acyl derivatives. The pro-drug approach has also been investigated for increasing skin permeability of non-steroidal anti-inflammatory drugs, naltrexone, nalbuphine, buprenorphine, b-blockers and other drugs.

Mechanism of chemical penetration enhancement: - [17]
Penetration enhancers may act by one or more of three main mechanisms:
1. Disruption of the highly ordered structure of stratum corneum lipid. e.g. Azone, DMSO, alcohols, fatty acids and terpenes etc.
2. Interaction with intercellular protein.
e.g. DMSO (dimethyl sulphoxide), urea, surfactants etc.
3. Improved partition of the drug, co-enhancer or solvent into the stratum corneum.
e.g. Ethanol, propylene glycol etc.
The enhancer can act by altering one of three pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The fatty acid enhancers increased the fluidity of the lipid protein portion of the stratum corneum. Some enhancers act on both polar and non polar pathway by altering the multi-laminate pathway for penetration. Enhancers can increase the drug diffusivity through skin proteins. The type of enhancer employed has a significant impact on the design and development of the product. A useful way to consider factors affecting drug permeation. Rate through the stratum corneum is via the simple equation given below for steady state flux. If we plot the cumulative mass of diffusant m, passing per unit area through the membrane , at long some chemical penetration enhancers time the graph approaches linearity and its slope its yield the steady flux dm/dt.
$dm/dt = D\ Co\ K\ /h$
Where,
C_o is the constant concentration of drug in donor solution, K is the partition coefficient of the solute between the membrane and the bathing solution, D is the diffusion coefficient and h is thickness of membrane.
From the above equation, we conclude that the ideal properties of a molecule that would penetrate stratum corneum, well these are low molecular mass, preferably less than 600Da, when D tends to be high. Adequate solubility in oil and water so that membrane concentration gradient may be high. High but balanced (optimal) K (if too large, may inhibit clearance by viable tissue) Low melting point, correlating with good solubility as predicted by ideal solubility. The mechanism of these sorption promoters to some extent is also related to octanol/water partition co-efficient. Recently, lipid-protein partition theory has been formulated to describe the potential mechanism of action of sorption promoters.

Water: -
It is the most natural penetration enhancer. Hydration state of stratum corneum is important for determining the penetration enhancement of given drug. By increasing the hydration of the stratum corneum transdermal flux of a variety of drugs also increases. One long-standing approach to improve transdermal and topical delivery of medicaments is to use water. In general, increased tissue hydration appears to increase transdermal delivery of both hydrophilic and lipophilic permeants. Clearly free water within the tissue could alter the solubility of a permeant in the stratum corneum and hence could modify partitioning from the permeant vehicle into the membrane.

Sulfoxides: - [18]

Dimethyl sulphoxides (DMSO) is one of the earliest and most widely studied penetration enhancers. DMSO works rapidly as a penetration enhancer - spillage of the material onto the skin can be tasted in the mouth within a second. Although DMSO is an excellent accelerant, it does create problems. The effect of the enhancer is concentration-dependent and generally co-solvents containing > 60% DMSO is needed for optimum enhancement efficacy. It has been postulated that DMSO denatures the intercellular structural proteins of the stratum corneum, or promotes lipid fluidity by disruption of the ordered structure of the lipid chains. In addition, DMSO may alter the physical structure of the skin by elimination of lipid, lipoprotein and nucleoprotein structures of the stratum corneum.

Azone: -

Azone enhances the skin transport of a wide variety of drugs including steroids, antibiotics and antiviral agents. Azone is most effective at low concentrations, being employed typically between 0.1% and 5%, often between 1% and 3%. Azone probably exerts its penetration enhancing effects through interactions with the lipid domains of the stratum corneum. Enhancer partitions into the bilayer lipids to disrupt their packing arrangement. Thus, Azone molecules may exist dispersed within the barrier lipids or in separate domains within the bilayers.

Pyrrolidones: -

The pyrrolidones partition well into human stratum corneum within the tissue and they may act by altering the solvent nature of the membrane. Pyrrolidones have been used to generate reservoirs within the skin membrane. Such a reservoir effect offers a potential for sustained release of a permeant from the stratum corneum over extended time periods. e.g. N-methyl-2-pyrrolidone (NMP), 2-pyrrolidone (2P).

Fatty acids: -

A large number of fatty acids and their esters have been used as permeation enhancers most popular of which is oleic acid. A general trend has been seen that unsaturated fatty acids are more effective in enhancing percutaneous absorption of drugs than their saturated counterparts. Studies suggested that drug solubilization in the vehicle, increased partitioning, increased solvent penetration and barrier disruption each can contribute to enhanced skin permeation rates in the presence of fatty acids. Moreover, oleic acid proved to be the best enhancer among azone. Oleic acid in PG was markedly successful in increasing the permeation rate of 5-FU and estradiol through human skin.

Essential oils, terpenes and terpenoids: -

Essential oils and terpenes are volatile, fragrant substances that are naturally occurring in many flowers and plants. These agents have been used for many years as flavouring agents as an ingredient in medicines. Terpenes are promising, clinically acceptable enhancers because of their low systemic toxicity, high enhancement activity and low cutaneous irritation at low concentrations (1–5%). The most popular terpene in current pharmaceutical applications is menthol. Terpenes have been shown to increase the percutaneous permeation parameters for a large number of model drugs, including both lipophilic and hydrophilic compounds. The effect of terpenes on the barrier properties of the skin has been attributed to their ability to affect the intercellular packing of the stratum corneum lipids. E.g. Eucalyptus oil, pippermint oil

Alcohols, fatty alcohols and glycols:-

Ethanol is commonly used in many transdermal formulations and is often the solvent of choice for use in patches. Further, permeation of ethanol into the stratum corneum can alter the solubility properties of the tissue with a consequent improvement for drug partitioning into the membrane. Fatty alcohols (or alkanols) may also have penetration enhancing activity. PG is widely used as a vehicle for penetration enhancers and shows synergistic action when used with, for example, oleic acid. However, PG has also been used as a penetration enhancer in its own right. Permeation of the solvent through the tissue could alter thermodynamic activity of the drug in the vehicle which would in turn modify the driving force for diffusion, solvent may partition into the tissue facilitating uptake of the drug into skin and there may be some minor disturbance to intercellular lipid packing within the stratum corneum bilayers.

Surfactants: -

Typically composed of a lipophilic alkyl or aryl fatty chain, together with a hydrophilic head group, surfactants are often described in terms of the nature of the hydrophilic moiety. Anionic surfactants include sodium lauryl sulphate (SLS), cationic surfactants include cetyl-trimethyl ammonium bromide, the non-oxynol surfactants are non-ionic surfactants and zwitter-ionic surfactants include dodecyl betaine. Anionic and cationic surfactants have potential to damage human skin; SLS is a powerful irritant and increase the trans-epidermal water loss in human volunteer's *In-vivo* and both anionic and cationic surfactants swell the stratum corneum and interact with intercellular keratin. Nonionic surfactants tend to be widely regarded as safe. Surfactants generally have low chronic toxicity and most have been shown to enhance the flux of materials permeating through biological membranes.

Urea: -

Urea promotes transdermal permeation by facilitating hydration of the stratum corneum and by the formation of

hydrophilic diffusion channels within the barrier. Cyclic urea permeation enhancers are biodegradable and nontoxic molecules consisting of a polar parent moiety and a long-chain alkyl ester group. As a result, enhancement mechanism may be a consequence of both hydrophilic activity and lipid disruption mechanism.

Lipids: -
Phospholipids have been successfully used as permeation enhancers in the form of vesicles, microemulsions and micellar systems. They do not have an appreciable effect when interacting with the stratum corneum as individual molecules. They fuse with the lipid bilayers of the stratum corneum there by enhancing partitioning of encapsulated drug as well as disruption of the ordered bilayer structure.

Cyclodextrins: -
They are biocompatible substances that can form inclusion complexes with lipophilic drugs so that their solubility will increase mainly in aqueous solutions. They alone were determined to be less effective so used in combination with fatty acids and propylene glycol e.g. β – Cyclodextrin.

Oxazolidinones: -
It is a new class of chemical agents which have the potential for use in many cosmetic and personal care product formulations. The structural features of these permeation enhancers are closely related to sphingosine and ceramide lipids which are naturally found in the upper skin layers e.g. 4-decyloxazolidin-2-one.

1.9.4 Pressure sensitive adhesive: - [19]
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 tachy, and exert a strong holding force. For e.g Poly-acrylates, poly-isobutylene 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 (as in reservoir system) or in the back of the device and extending peripherally as in case of matrix system.

1.9.5 Backing laminate: - [20]
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 remove out or may lead to diffusion of excipients, drug or penetration enhancer through the layer. They should a low moisture vapor transmission rate. They must have optimal elasticity, flexibility, and tensile strength. Examples of some backing materials are an aluminum coated layer, a plastic film (polyethylene, polyvinyl chloride, polyester) and a heat seal layer.

1.9.6 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 a part 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 or Teflon. Other materials used for TDDS release liner include polyester foil and metalized laminate.

1.9.7 Other excipients: -
Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as di-butyl-pthalate, tri-ethyl-citrate, poly-ethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch**.**

1.10 Types of Transdermal Drug delivery systems: - [21]
There are four types of transdermal patches: -
(I) Single–layer drug in–adhesive: -
The adhesive layer of this system also contains the drug. In this type patches the adhesive layer not only serves to adhere the various layer together, along with 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.

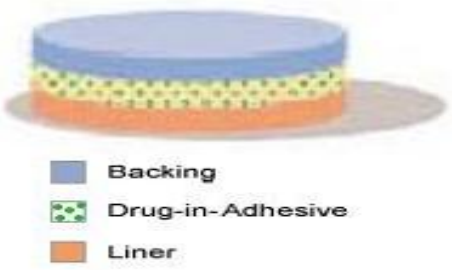

Fig 1.6 Single–layer drug in–adhesive.

(II) Multi-layer drug in adhesive: -

The multi-layer drug in adhesive is similar to the single layer system in that both adhesive layers are also responsible for the releasing of the drug. But it 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.

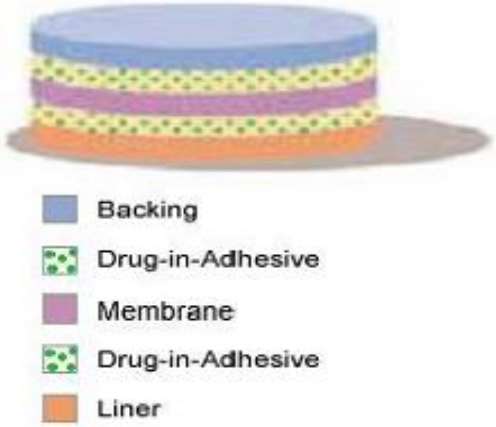

Fig 1.7 Multi– layer drug in–adhesive.

(III) Drug reservoir-in-adhesive: -

Transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the backing layer. In this type of system the rate of release is zero order.

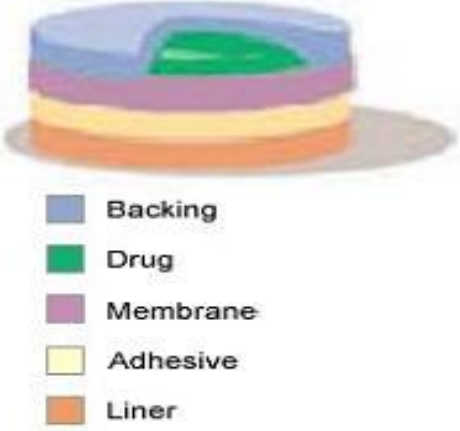

Fig 1.8 Drug reservoir-in-adhesive.

(IV) Drug Matrix-in-adhesive: -

This matrix system has a drug layer of semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it.

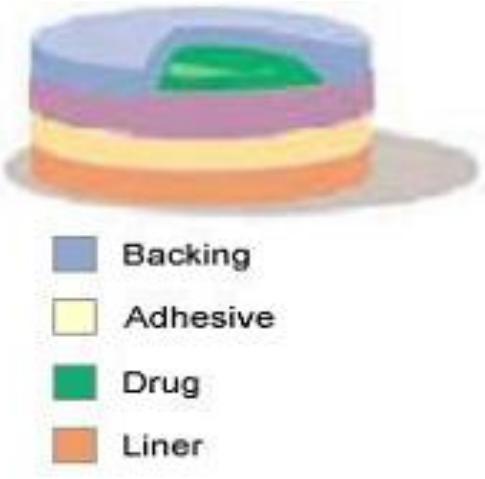

Fig 1.9 Drug Matrix-in-adhesive.

1.11 Approaches or Technologies used in Development of Transdermal Patch: - [22]
The technologies can be classified in four basic approaches:

1.11.1 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.

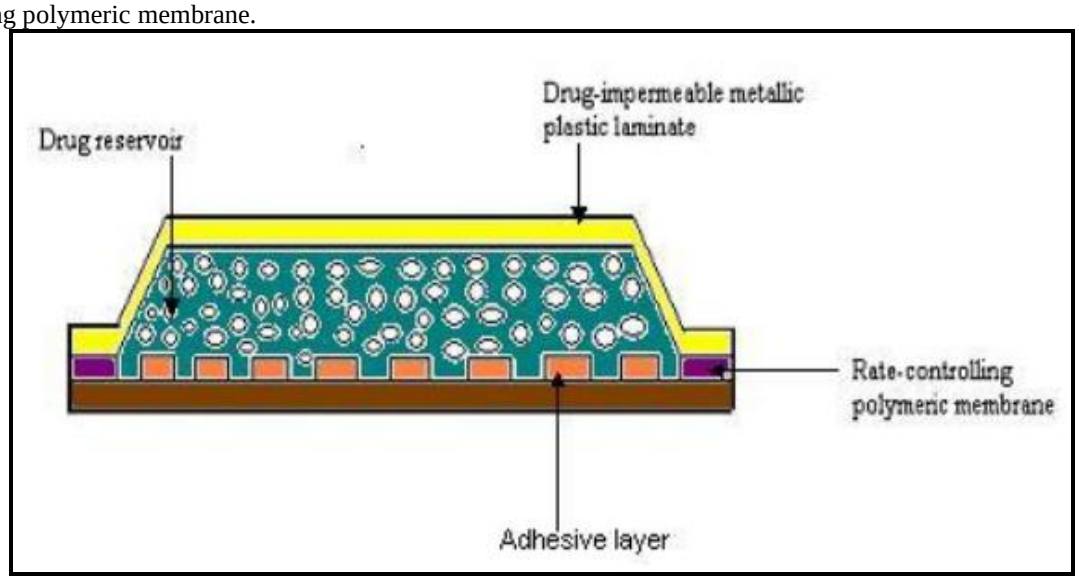

Fig. 1.10 Cross-sectional view of polymer membrane permeation-controlled TDD systems.

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 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 TDDS with the skin surface.
Varying the composition of drug reservoir formulation, 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

$$\frac{dQ}{dt} = \left[\frac{Km/r\ Ka/m\ Da\ Dm}{Km/r\ Dm\ ha + Ka/m\ Da\ hm}\right] C_R$$

Where, C_R is drug concentration in reservoir compartment.
$K_{M/R}$ the partition coefficient for the interfacial partitioning of drug from the reservoir to the membrane.
$K_{A/M}$ the partition coefficient for the interfacial partitioning of drug from membrane to adhesive.
D_A diffusion coefficient in rate controlling membrane.

D_M diffusion coefficient in adhesive layer.
h_A thickness of rate controlling membrane.
H_M thickness of adhesive layer.

1.11.2 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.

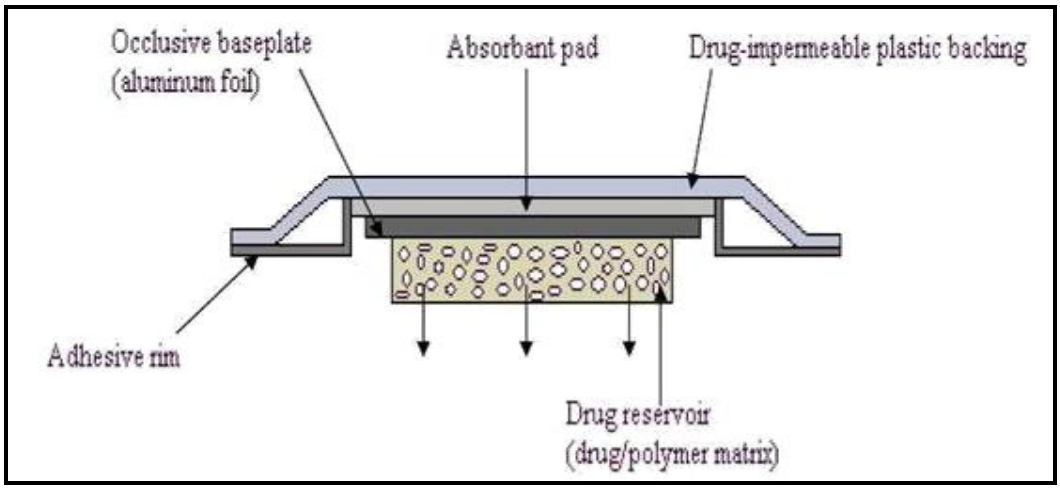

Fig. 1.11 Cross-sectional view of polymer matrix diffusion-controlled TDD systems.

The rate of release from polymer matrix drug dispersion-type is

$$\frac{dQ}{dt} = [LdCpDp/2t]^{1/2}$$

Where, L_D 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.
Only drug dissolved in polymer matrix can diffuse, C_P is practically equal to C_R.

1.11.3 Drug reservoir gradient-controlled TDD systems: -

Polymer matrix drug dispersion-type TDDS can be modified to have the drug loading level varied in an increased manner, forming a gradient of drug reservoir along the diffusional path across the multi-laminate adhesive layers.

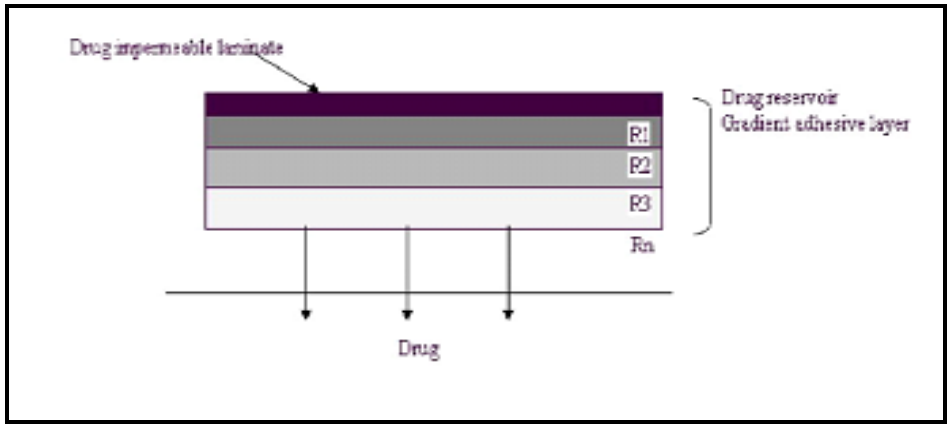

Fig. 1.12 Cross-sectional view of a drug reservoir gradient-controlled TDD system.

The drug release from this type of drug reservoir gradient- controlled TDDS can be expressed by:

dQ/dt = (ACpDp/2t)1/2

Where,
A–Initial drug loading dose dispersed in the polymer matrix.
Cp and Dp – are solubility and diffusivity of the drug in the polymer.

Thus, therotically this should increase a more constant drug release profile. E.g. Depot system containing nitroglycerine for angina pectoris.

1.11.4 Micro-reservoir dissolution-controlled TDD systems: -

A hybrid of reservoir and matrix dispersion-type drug delivery systems, which contains drug reservoir formed by first suspending the drug solids in an aqueous solution of water-miscible drug solubilizer 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.

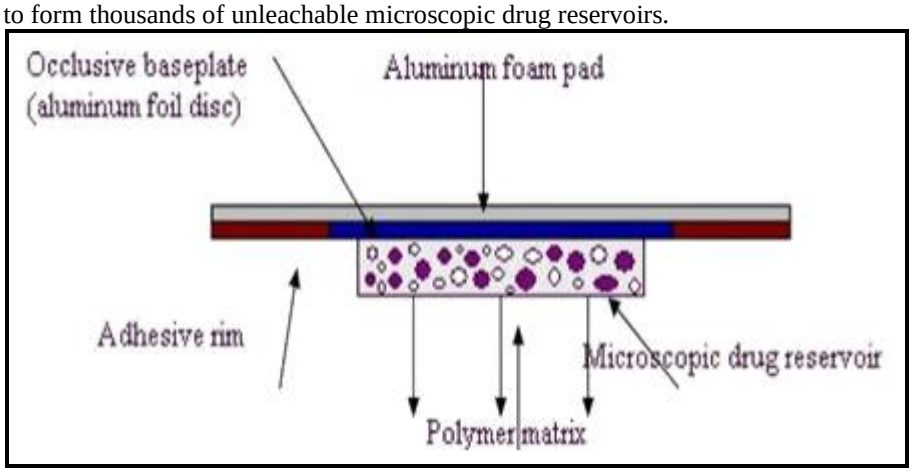

Fig. 1.13 Cross-sectional view of Micro-reservoir dissolution-controlled TDD systems.

This thermodynamically unstable system is quickly stabilized by immediately cross-linking the polymer chains in situ, which produces a medicated polymer disk with a constant surface area and a fixed thickness. Medicated disk is mounted at the center of an adhesive pad.e.g. Nitrodisk system for angina pectoris.

The rate of drug release from this system is defined by:

$$\frac{dQ}{dt} = \frac{DpDs\alpha Kp}{Dp\delta d + Ds\delta p\alpha k}[\beta S_p - D_1 S_1(1-\beta)/\delta_1\{1/K_1+1/K_m\}]$$

Where,

Kl, Km and KP - are partition coefficients for the interfacial partitioning of drug in the liquid compartment and the polymeric matrix.

Dl, DP and DS- drug diffusivities in the liquid compartment, polymer coating membrane and elution solution.

Sl and SP – Solubilities of the drug in the liquid compartment and polymer matrix.

δl, δP and δd– thicknesses of the liquid layer, polymer coating membrane and hydrodynamic diffusion layer.

β – Is the ratio of the drug concentration at the inner edge of the interfacial barrier over the drug solubility in the polymer layer.

1.12 Techniques for Enhancement of Skin Permeation: - [23-24]

Technologies used to modify the barrier properties of the stratum corneum can be divided into passive/chemical or active/physical methodologies. Passive methods include the influencing of drug and vehicle interactions and optimization of formulation, in order to modify the stratum corneum structure.

Transdermal drug delivery technologies:	
Active Method:	**Passive Method:**
A. Thermal ablation: Laser	**A.** Optimization of formulation
B. Electrical: Iontophoresis	vesicles e.g liposomes
C. Mechanical :Microneedle	**B.** Chemical enhancers
D.Other: Jet injector	**C.** Eutectic Systems
	D. Prodrug

Table. 1.2 Approaches for enhancing drug transport across the skin.

Active Method: -

1.12.1. Controlled Heat Aided Drug Delivery (CHADD) System

1.12.2. Laser radiation

Mechanical: -

1.12.3 Micro-needle array: -

A number of delivery strategies have been employed to use the micro-needles for transdermal drug delivery. These include

1. Poke with patch approach
2. Coat and poke approach
3. Biodegradable micro-needles
4. Hollow micro-needles
5. Dip and scrape

Other: -

1.12.4 Ultrasound (phonophoresis, sonophoresis)

Passive Method: -

1.12.5 Electroporation

1.12.6 Iontophoresis

1.12.7 Liposomes and other vesicles

1.12.8 Chemical penetration enhancers

1.12.9 Eutectic systems

1.12.10 Pro-drugs for dermal delivery

1.12.11High velocity particles

1.12.12 Skin abrasion

1.12.13 Medicated tattoos

1.12.14 Magnetophoresis

Table.1.1 Some Marketed formulations of TDDS. [25]

Therapeutic agent	Marketed name (Company)
Clonidine	Catapres-TTS (BoehringerIngelheim)
Estradiol	Vivelle (Novartis)
Fentanyl	Duragesic (Janssen)
Nicotine	Prosstep (Lederie)
Testosterone	Testoderm (Alza)
Nicotine	Habitrol (Novartis Consumer)
Nitro-glycerine	Transderm-Nitro (Novartis)
Nicotine	Nicoderm CQ (Smithkline consumer)
Scopolamine	Transderm-Scop(Novartis Consumer)

Conclusion : This article provide an valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who are involved in TDDS. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS a realistic practical application as the next generation of drug delivery system.

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