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A Detailed Review on Preparative Methods and Applications of Transdermal Drug Delivery System

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ABSTRACT

Human skin comprises three distinct but mutually dependent tissues a) The stratified, vascular, cellular epidermis, b) the Underlying dermis of connective tissues and c) Hypodermis. In 1981, FDA approved the first TDDS device for commercial use which provides the controlled systemic absorption of the drug through the different layers of skin. Transdermal drug delivery systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation. Transdermal medication delivers a steady infusion of a drug over an extended period of time. Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug. The first transdermal treatment of Alzheimer's disease was done through the Rivastigmine patch. This review article focuses the on advantages, disadvantages, applications, basic components, preparative methods involved in the fabrication of transdermal patches.

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INTRODUCTION

Transdermal drug delivery systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation.[1]

In 1877 Fleischer declared that the skin is totally impermeable and this extreme view could not hold for long time. In 1957 Monash proved a superficially located barrier in the skin as an obstacle to the penetration. These pioneering works were followed by extensive research ultimately proving that the stratum corneum was the main barrier to percutaneous absorption and substances/drugs cannot easily penetrate through it due to its nature. Transdermal drug delivery system releases the drug by zero (or pseudo zero order) or by first order or both kinetics and which maintain the drug level for prolonged period for desired action.[2]

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. Some drugs must be combined with substances, such as alcohol, that increase their ability to penetrate the skin in order to be used in a skin patch.

In 1981, FDA approved the first TDDS device for commercial use which provides the controlled systemic absorption of the drug. More than 35 TDDS products are approved in 2002 which made a business of about $4.5 billion in 2008.In these devices different types of methods and mechanisms used to develop and enhance the driving force of drug diffusion; it is a thermodynamic activity or increase the skin penetration. In these technique scientists used different types of penetration enhancers, prodrugs etc. The first commercially available vapour patch to reduce smoking was approved in Europe in 2007. The first transdermal treatment of Alzheimer's disease was done through Rivastigmine patch.[3]

Advantages of Transdermal Drug Delivery Systems [4]

1) Transdermal medication delivers a steady infusion of a drug over an extended period. Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided.

2) Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastro-intestinal irritation, low absorption,

decomposition due to hepatic “first- pass” effect, formation of metabolites that cause side effects, short half - life necessitating frequent dosing, etc.

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

4) The simplified medication regimen leads to improved patient compliance and reduced inter & intra – patient variability.

5) At times the maintenance of the drug concentration within the diphase is not desired. Application and removal of transdermal patch produce the optimal sequence of pharmacological effect.

6) Self-administration is possible with these systems.

7) The drug input can be terminated at any point of time by removing transdermal patch.

Limitations of transdermal drug delivery systems :[5]

- Transdermal delivery is neither practical nor affordable when required to deliver large doses of drugs through skin
- Cannot administer drugs that require high blood levels
- Drug of drug formulation may cause irritation or sensitization
- Not practical, when the drug is extensively metabolized in the skin and when molecular size is great enough to prevent the molecules from diffusing through the skin.
- Not suitable for a drug, which doesn’t possess a favourable, o/w partition coefficient
- The barrier functions of the skin of changes from one site to another on the same person, from person to person and with age.

Popular Uses [6]

- The highest selling transdermal patch in the United States is the nicotine patch, which releases nicotine to decrease the tobacco smoking. The first commercially available vapor patch to decrease degree of smoking was approved in Europe in 2007.

- Two opioid medications used for intense pain are prescribed in patch form: Fentanyl (marketed as **Duragesic**) and Buprenorphine (marketed as **BuTrans)**.

- Estrogen patches are used to treat menopausal symptoms as well as post-menopausal osteoporosis. Other transdermal patches for delivery of certain hormones include the contraceptive patch (marketed as **Ortho Evra** or **Evra**) and testosterone patches for both men (**Androderm**) and women (**Intrinsa**).

- Nitro-glycerine patches are sometimes prescribed for the treatment of angina instead of sublingual pills.

- Transdermal scopolamine is commonly used for treatment of motion.

- Anti-hypertensive drug Clonidine is available in market in form of transdermal patch named as **Catapres-TTS.**

- A transdermal patch of the MAOI selegiline (brand name **Emsam**) was the first transdermal patch used as antidepressant approved for use in the U.S. in March 2006.

- A transdermal delivery patch (**Daytrana**) used for Attention (ADHD), drug used methylphenidate (other names **Ritalin** or **Concerta**), was approved for market sell by the FDA in April 2006.

- Vitamin B12 is also administered in the form of transdermal patch. Cyanocobalamin, stable form of vitamin B12 is used in the patch.

- An Alzheimer's treatment patch (market name **Exelon**) was commercially introduced in 2007. Drug used in it Rivastigmine.

Anatomy and physiology of skin [7]

Human skin comprises of three distinct but mutually dependent tissues.

A) The stratified, vascular, cellular epidermis,

B) Underlying dermis of connective tissues and

C) Hypodermis

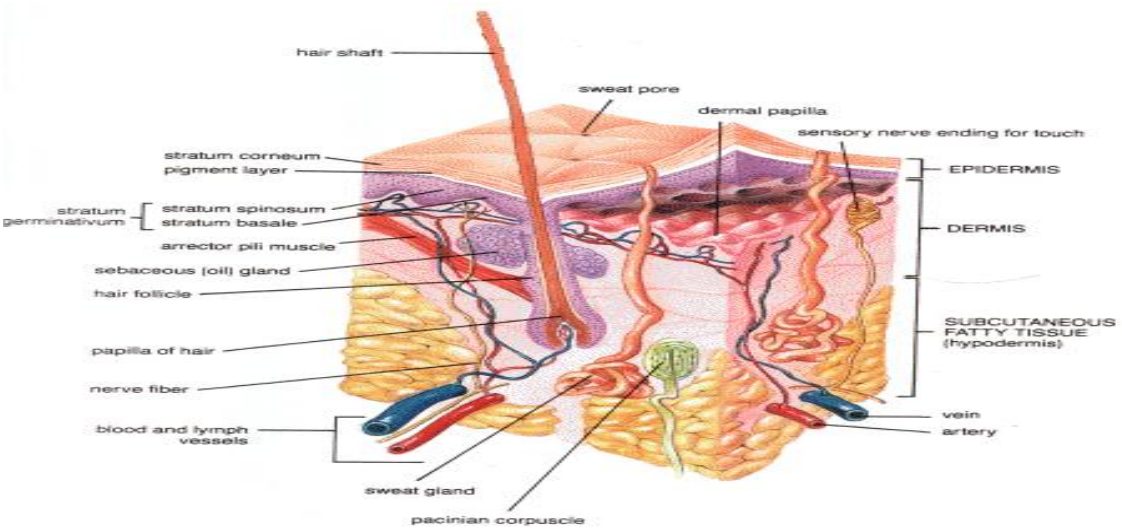

Figure 1: STRUCTURE OF SKIN

Epidermis:

The multi-layered epidermis varies in thickness, depending on cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. It consists outer stratum corneum and viable epidermis.

a) 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 dead, keratinized cells called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration of drug.

b) Viable epidermis

This is situated beneath the stratum corneum and varies in thickness from 0.06mm on the eyelids to 0.8mm on the palms. Going inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the stratum basale. In the basale layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horny cells from the skin surface.

c) 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 concentration gradient for transdermal permeation.

d) Hypodermis

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. 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.

A. ROUTE OF DRUG PENETRATION THROUGH HUMAN SKIN

When a molecule reaches intact skin, it contacts cellular debris, microorganisms, sebum and other materials. The diffusion then has three potential entry routes to the viable tissue, through the hair follicles with their associated sebaceous glands, via the sweat ducts or across the continuous stratum corneum between these appendages.

Electron photo-microscopic examination shows that intracellular region in stratum corneum is filled with lipid reach amorphous material. During cornification the lipid composition shifts from polar to neutral constituents. In the dry stratum corneum intracellular diffusion volume may be as high as 5% and least 1% of the fully hydrated stratum corneum. This intra-cellular volume is at least an order magnitude larger than that (approximate 0-2%) estimated for the intra-appendage pathway, thus, intracellular diffusion could be significant. Both the structured lipid environment between the cells and the hydrated protein, within a corneocytes plays major role in skin permeability, cell membranes are probably of only minor consequences **(Figure 2 & 3).**

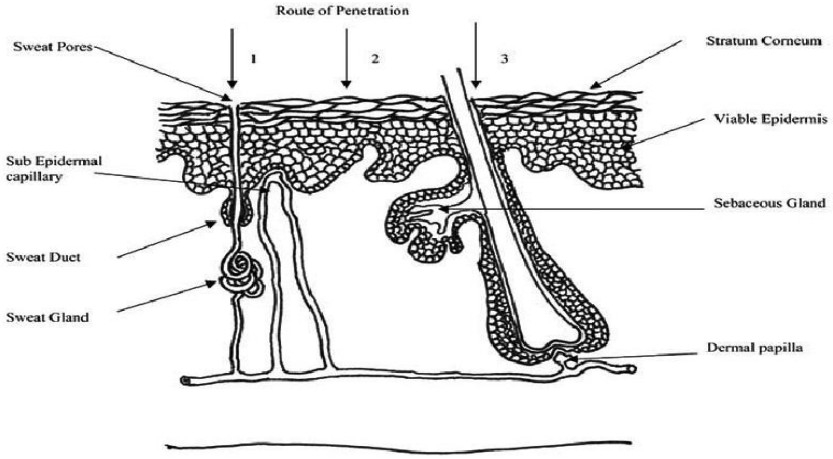

Figure 2: SIMPLIFIED REPRESENTATION OF SKIN SHOWING ROUTES OF PENETRATION

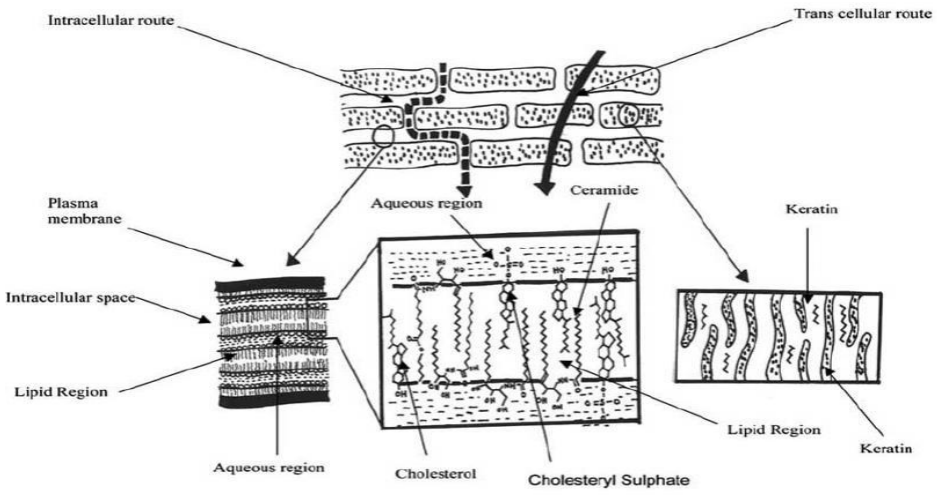

Figure 3: DIAGRAMMATIC REPRESENTATION OF THE STRATUM CORNEUM AND THE INTRA CELLULAR AND TRANS CELLULAR ROUTES OF PENETRATION

These figures illustrate two potential routes for drug permeation.

1. Inter cellular: between the cells and

2. Trans cellular: across lipid rich region.

At least for polar drugs, the Trans cellular route provides the main pathway during percutaneous absorption. Trans appendageal route usually cannot contribute appreciable to the steady state flux and fractional area available for absorption is small. This route may be

important for ions and large polar molecules, which cross-intact stratum corneum with difficulty.

PERCUTANEOUS ABSORPTION

Percutaneous absorption is defined as penetration of substances into various layers of skin and permeation across the skin into systemic circulations. The percutaneous absorption is a step-wise process and can be divided into three parts:

1. Penetration is the entry of a substance into a particular layer.

2. Permeation is the penetration from one layer into another, and is different both functionally and structurally from the first layer.

3. Absorption is the uptake of a substance into systemic circulation.

The stratum corneum is a wall-like structure with protein bricks and lipid mortar. The lipid matrix (Keratin phospholipid complex) of the stratum corneum plays a significant role in determining the permeability of substances across the skin. This is supported by the evidence from controlled stripping experiments, electron microscopy studies and also from the analysis of penetration and permeation data.[2]

Factors affecting permeability:

Physiological factors:

Stratum corneum layer of the skin

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.

Formulation factor:

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

Physicochemical properties of enhancers:

1 Partition coefficient of 1 or greater is required,

2 P_H value should be moderate, the flux of ionisable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability,

- Concentration of penetrate higher than solubility,

3 Excess solid drug functions as a reservoir and helps in maintaining constant drug concentration for prolonged time.

BIOPHARMACEUTICAL PARAMETERS IN DRUG SELECTION FOR TRANSDERMAL PATCH:

4 Dose should be low i.e.<20mg/day.

5 Half-life should be 10 h or less.

6 Molecular weight should be <400.

7 Partition coefficient should be Log p (octanol-water) betwee1.0 and 4.

8 Skin permeability coefficient should be <0.5 X 10^{-3} cm/h.

9 Drug should be non- irritating and non -sensitizing to the skin.

10 Oral bioavailability should be low.

11 Therapeutic index should be low.[3]

Basic Components of TDDS:

❖ Polymer matrix / Drug reservoir.

- ❖ Drug.
- ❖ Permeation enhancers.
- ❖ Pressure sensitive adhesive (PSA).
- ❖ Backing laminates.
- ❖ Release liner.
- ❖ Other excipients like plasticizers and solvent.

- **Polymer matrix / Drug reservoir:**

Polymers are the heart of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have good stability and compatibility with the drug and other components of the system and they should provide effective released of a drug throughout the device with safe status.

The polymers used for TDDS can be classified as:

Natural polymers:

E.g. Cellulose derivatives, Zein, Gelatine, Shellac, Waxes, Gums, Natural rubber and Chitosan *etc*.

Synthetic elastomers:

E.g. Polybutadiene, Hydrin rubber, Polyisobutylene, Silicon rubber, Nitrile, Acrylonitrile, Neoprene, Butyl rubber *etc*.

Synthetic polymers:

E.g. Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyuria, Polyvinyl pyrrolidone, Poly methyl methacrylate *etc*.

The polymer like polyethylene glycol, Eudragits, Ethyl cellulose, Polyvinyl pyrrolidone and Hydroxy-propyl methylcellulose are used as matrix type TDDS. The polymers like EVA silicon rubber and polyurethane are used as rate controlling TDDS.

➢ **Selection of drugs:**

The selection of drug for TDDS is based on physicochemical properties of drug Transdermal drug delivery system is much suitable for drug having.

a. Extensive first pass metabolism.

b. Narrow therapeutic window.

c. Short half-life which causes non-compliance due to frequent dosing.

d. Dose should be less (mg/day)

e. Low molecular weight (less than 500 Daltons).

f. Adequate solubility in oil and water (log P in the range of 1-3).

g. Low melting point (less than 200°C).

- **Permeation enhancers:**

These compounds are useful to increase permeability of stratum corneum by interacting with structural components of stratum corneum *i.e.*, proteins or lipids to attain higher therapeutic levels of the drug. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability.

Example:

Dimethyl sulfoxide, Propylene glycol, 2-Pyrrolidone, Isopropyl myristate, Laurocapram (Azone), Sodium lauryl sulfate, Sorbitan monolaurate, Pluronic, Cardamom oil, Caraway oil, Lemon oil, Menthol, d-limonene, Linoleic acid.

- **Pressure sensitive adhesives: (PSA)**

The pressure-sensitive adhesive (PSA) affixes the transdermal drug delivery system firmly to the skin. It should adhere with not more than applied finger pressure, be aggressively and permanently tacky and exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue. Adhesives must be skin compatible, causing minimal irritation or sensitization, and removable without inflicting physical trauma or leaving residue. In addition, they must be able to dissolve drug and excipient in quantities

sufficient for the desired pharmacological effect without losing their adhesive properties and skin tolerability.

PSAs used in commercially available transdermal systems includes,

a. polyacrylate,

b. polyisobutylene

c. polysiloxane

❖ **Polyacrylates:**

These types of adhesive are most widely used. In general, all acrylic adhesives are polar in character, allowing them to absorb moisture readily and to maintain adhesion to wet skin. They also dissolve most drugs well, enabling high drug loading of polyacrylate matrices.

❖ **Polyisobutylenes (PIBs):**

This characterized by a low solvent capacity for drugs. PIBs are often used in membrane-controlled systems where the initial burst of drug released from the adhesive layer should be limited. PIB-based adhesives are mixtures of high and low molecular weight polymers, which provide cohesion and tackiness, respectively. By adjusting the composition of the PIB formulation, cold flow and adhesiveness can be customized for each system.

❖ **Silicone:**

These adhesives are characterized by low allergenicity. Similar to PIBs, silicones dissolve most drugs poorly and regulate tackiness and cohesion through polymer size. Molecular weight of silicones, however, can be hard to control during storage of drug-adhesive formulations, since drugs containing amine groups can catalyze further polymerization in silicone adhesives retaining residual silanol groups. To address this problem, special silicones have been developed that are rendered resistant to amine-catalyzed condensation through end-capping of silanol functional groups.

Hot Melt Pressure Sensitive Adhesives (HMPSA)

This type pressure sensitive adhesive are melt to a viscosity suitable for coating, but when they are cooled they generally stay in a flow less state. They are thermoplastic in nature. HMPSA are having two compounded.

1. Compounded HMPSA is

- Ethylene vinyl acetate copolymers,
- Paraffin waxes,
- Low density polypropylene,
- Styrene-butadiene copolymers,
- Ethylene-ethylacrylate copolymers.

2. Uncompounded HMPSA is

1. Polyesters,
2. Polyamides,
3. Polyurethanes.

- **Backing laminate:**

Backing materials must be flexible while possessing good tensile strength. Commonly Used materials are

1. Polyolefin,
2. Polyesters,
3. Elastomers in clear, pigmented, or metallized form.

Elastomeric materials such as low-density polyethylene conform more readily to skin movement and provide better adhesion than less compliant materials such as polyester. Backing materials should also have low water vapour transmission rates to promote increased skin hydration and, thus, greater skin permeability. In systems containing drug within a liquid or gel, the backing material must be heat-sealable to allow fluid-tight packaging of the drug reservoir using a process known as form-fill-seal. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapour transmission rate.

Examples of some are backing materials:

- ❖ vinyl, polyester films,
- ❖ Polyester-polypropylene films,
- ❖ Polypropylene resin,
- ❖ Polyethylene resin,
- ❖ Polyurethylene,
- ❖ Co Tran 9722 film,
- ❖ Ethylene-vinyl acetate,
- ❖ Aluminized plastic laminate.

- **Release Liners:**

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water. Typically, release liner is composed of a base layer which may be non-occlusive (*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 metallised laminates.[8]

Other excipients: ***[9]***

Solvents:

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

Plasticizers:

In transdermal systems, plasticizers are used to improve the brittleness of the polymer and to provide flexibility. They are generally non-volatile organic liquids or solids with low melting temperature and when added to polymers, they cause changes in definite physical and mechanical characteristics of the material. Upon addition of plasticizer, flexibilities of polymer macromolecules or macromolecular segments increase as a result of loosening of tightness of intermolecular forces. Many of polymers used in pharmaceutical formulations are brittle and require the addition of plasticizer into the formulation.

The plasticizers with lower molecular weight have more molecules per unit weight compared to the plasticizers with higher molecular weight. These molecules can more easily penetrate between the polymer chains of the film forming agent and can interact with specific functional groups of the polymer. By adding plasticizer to a polymeric material, elongation at break, toughness and flexibility are expected to increase; on the other hand tensile stress, hardness, electrostatic chargeability, and glass transition temperature are expected to decrease.

Table 01: Plasticizers used in transdermal films

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

VARIOUS METHODS FOR PREPARATION TDDS:

a. Asymmetric TPX membrane method:

A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive.

b. Circular Teflon mould method:

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butyl phthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular Teflon mould. The moulds are to be placed on a levelled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored for another 24 hrs at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. The type films are to be evaluated within one week of their preparation.

c. Mercury substrate method:

In this method drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10-15 minutes to produce a homogenous dispersion and poured in to a levelled mercury surface, covered with inverted funnel to control solvent evaporation.

d. By using IPM membranes method:

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

e. By using EVAC membrane method:

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

f. Aluminium backed adhesive film method:

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

g. Preparation of TDDS by using Proliposomes:

The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at 60-70°c temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to 20-30°C. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C, after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders proliposomes) are placed in a desiccators overnight and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.

h. By using free film method:

Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass Petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the Petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in desiccators until use. Free films of different thickness can be prepared by changing the volume of the polymer solution. [8]

Technologies for developing transdermal drug delivery systems: [7]

The technologies can be classified in four basic approaches:

1. Polymer membrane partition-controlled TDD systems:
2. Polymer matrix diffusion-controlled TDD systems
3. Drug reservoir gradient-controlled TDD systems
4. Micro reservoir dissolution-controlled TDD systems

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.

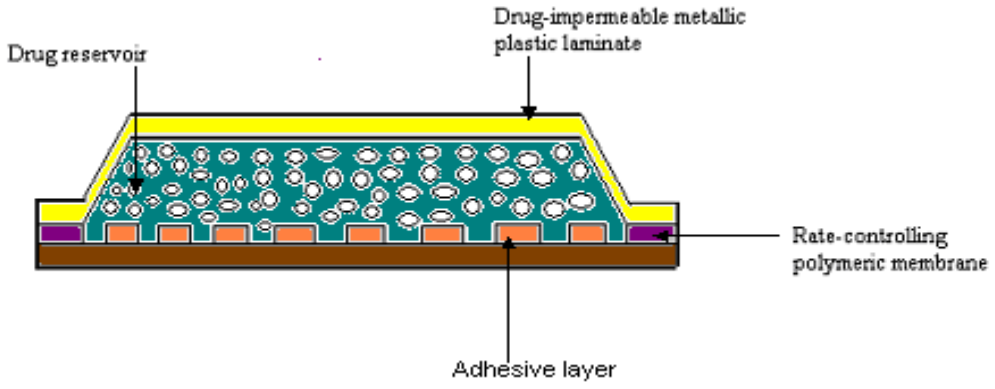

Figure 4: CROSS-SECTIONAL VIEW OF POLYMER MEMBRANE PERMEATION-CONTROLLED TDDSYSTEMS

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 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** formation sickness**, Catapres-TTS** system for hypertension.

The intrinsic rate of drug release from this type of TDD system is defined by

$$\frac{dQ}{dt} = \left(\frac{K_{m/r} K_{a/m} D_a D_m}{K_{m/r} D_m h_a + K_{a/m} D_a h_m} \right) C_R$$

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.

B) Polymer matrix diffusion-controlled TDD systems:

In this system, the drug reservoir is formed by homogeneously dispersing the drug solids in 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.

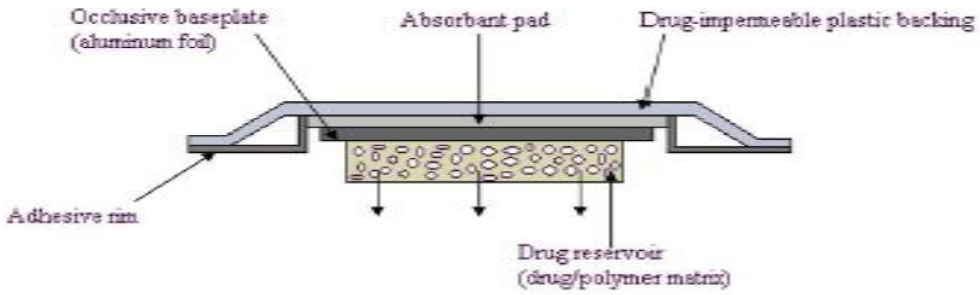

Figure 5: CROSS-SECTIONAL VIEW OF POLYMER MATRIX DIFFUSION-CONTROLLED TDD SYSTEMS.

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

$$\frac{dQ}{dt} = \left(\frac{L_d C_P D_P}{2t} \right)^{1/2}$$

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, CP is practically equal to CR.

Alternately, the polymer matrix drug dispersion type TDDS can be fabricated by directly dispersing drug in a pressure-sensitive adhesive polymer e.g. polyacrylate and then coating the drug-dispersed adhesive polymer by solvent casting or hot melt onto a flat sheet of 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.

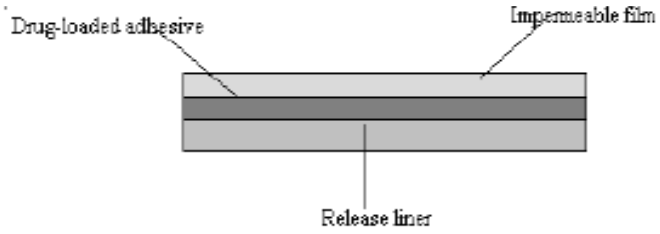

Figure 6: CROSS SECTIONAL VIEW OF AN ADHESIVE POLYMER DRUG DISPERSION-TYPE TDD SYSTEM SHOWING VARIOUS MAJOR STRUCTURE COMPONENTS.

C) Drug reservoir gradient-controlled TDD systems:

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

$$\frac{dQ}{dt} = \left[\frac{KF_{a/r}\,D_a}{h_a(t)}\right] L_d(h_a)$$

In this system, the thickness of diffusion path through which drug molecules diffuse increases with time i.e. ha (t). The drug loading level in the multilaminate adhesive layer is designed to increase proportionally i.e. $\mathbf{L_d}$ (ha) so as to compensate time dependent increase in diffusion 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 nitro glycerine for angina pectoris.

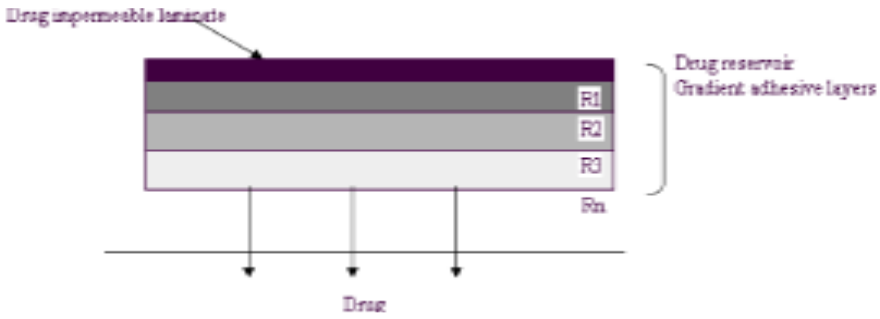

Figure 7: CROSS-SECTIONAL VIEW OF A DRUG RESERVOIR GRADIENT-CONTROLLED TDDS.

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 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.

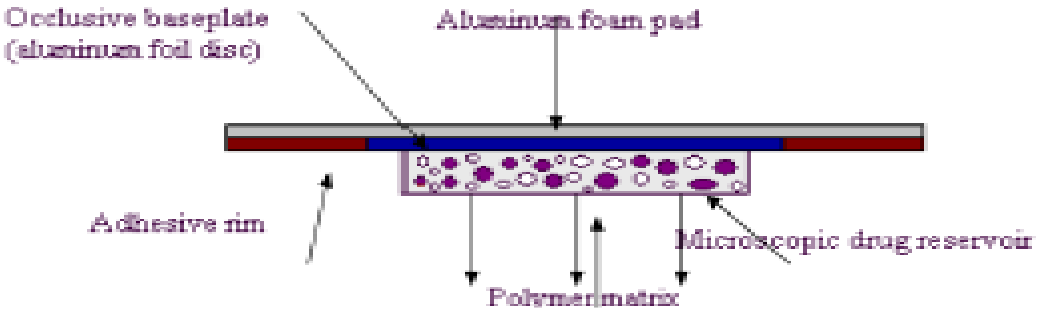

Figure 8: CROSS-SECTIONAL VIEW OF MICRORESERVOIR DISSOLUTION-CONTROLLED TDD SYSTEMS

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 centre of an adhesive pad. E.g **Nitrodisc** system for angina pectoris. The rate of drug release from this system is defined by

$$\frac{dQ}{dt} = \frac{D_p D_s A K_p}{D_p h_d + D_s h_p A K_p} \left(B S_p \frac{K F_{d/r} D_l S_l (1-B)}{h_l} \left[\frac{1}{K_l} - \frac{1}{K_m} \right] \right)$$

GENERATION OF TRANSDERMAL DRUG DELIVERY SYSTEMS:

First-Generation Transdermal Delivery Systems:

The first generation of transdermal delivery systems is responsible for most of the transdermal patches that have thus far been in clinical use. Significant advances in patch technology, and public acceptance, have enabled the recent surge in first-generation transdermal patches reaching the market. However, this surge will taper off as drugs with suitable properties for such systems are depleted. First-generation delivery candidates must be low-molecular weight, lipophilic and efficacious at low doses. Usually, their transdermal delivery should be more attractive than oral delivery due to low oral bioavailability, the need or desire for less frequent dosing or steady delivery profiles, or other factors.

The first-generation approach to transdermal delivery is limited primarily by the barrier posed by skin's outermost layer called stratum corneum, which is 10 to 20 μm thick. Underneath this layer is the viable epidermis, which measures 50 to 100 μm and is a vascular. Deeper still is the dermis, which is 1–2 mm thick and contains a rich capillary bed for systemic drug absorption just below the dermal–epidermal junction. Closer examination of the stratum corneum barrier reveals a brick and mortar structure, where the bricks represent non-living corneocyte cells composed primarily of cross-linked keratin and the intercellular mortar is a mixture of lipids organized largely in bilayers. Drug transport across the stratum corneum typically involves diffusion through the intercellular lipids via a path that winds tortuously around corneocytes, where hydrophilic molecules travel through the lipid head group regions and lipophilic molecules travel through the lipid tails. This transport pathway is highly constrained by the structural and solubility requirements for solution and diffusion within stratum corneum lipid bilayers.

A variation on the traditional transdermal patch of first-generation delivery systems involves no patch at all, but applies a metered liquid spray, gel or other topical formulation to the skin that, upon evaporation or absorption, can drive small lipophilic drugs into the stratum corneum, which in turn serves as the drug reservoir for extended release into the viable epidermis over hours. For example, testosterone gels have been in use for several years and a transdermal spray has been recently approved for estradiol delivery.

Second-Generation Transdermal Delivery Systems:

The second generation of transdermal delivery systems recognizes that skin permeability enhancement is needed to expand the scope of transdermal drugs.

The ideal enhancer should

i. Increase skin permeability by reversibly disrupting stratum corneum structure,

ii. Provide an added driving force for transport into the skin and

iii. Avoid injury to deeper, living tissues.

However, enhancement methods developed in this generation, such as conventional chemical enhancers, iontophoresis and non-cavitational ultrasound, have struggled with the balance between achieving increased delivery across stratum corneum, while protecting deeper tissues from damage. As a result, this second generation of delivery systems has advanced clinical practice primarily by improving small molecule delivery for localized, dermatological, cosmetic and some systemic applications, but has made little impact on delivery of macromolecules.

Third-Generation Transdermal Delivery Systems

The third generation of transdermal delivery systems is poised to make significant impact on drug delivery because it targets its effects to the stratum corneum. This targeting enables stronger disruption of the stratum corneum barrier, and thereby more effective transdermal delivery, while still protecting deeper tissues. In this way, novel chemical enhancers, electroporation, cavitational ultrasound and more recently microneedles, thermal ablation and microdermabrasion (Arora, Prausnitz and Mitragotri) have been shown to deliver macromolecules, including therapeutic proteins and vaccines, across the skin in human clinical trials. These advances were made possible in part by the emergence of technologies to localize effects to the stratum corneum combined with recognition that the safety afforded by localization should make these more aggressive approaches medically acceptable.[10]

Recent Techniques for Enhancing TDDS/optimization Techniques.[11]

A. Structure-Based Enhancement Techniques:

1. **Micro fabricated Microneedles:**

Microneedles are recently used techniques for transdermal drug delivery designed to form a physical pathway through the upper epidermis to enhance skin permeability. Micro-fabricated micro needles are devices which are hybrids of the hypodermic needle and transdermal patch in this technology needles of micron dimension are inserted in to skin surface. It damages or produces pores only in SC portion so one does not feel any pain since nerve fibres are located into deeper region of the skin. Moreover distance to be travelled by drug will decrease.

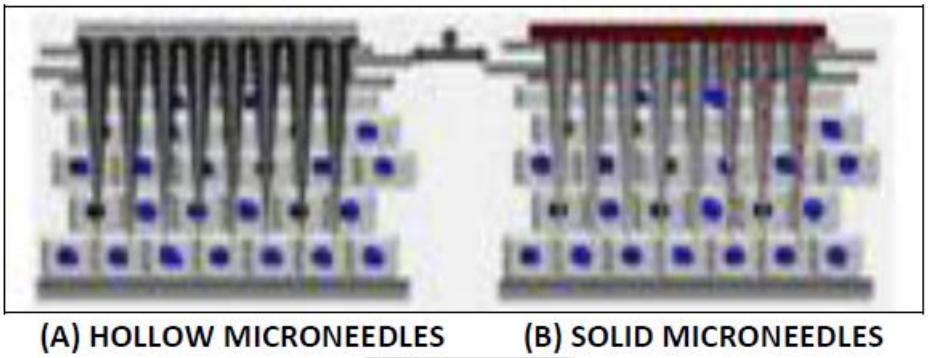

Figure 9: DESIGN OF MICRONEEDLE DELIVERY DEVICES (A) HOLLOW MICRONEEDLES (B) SOLID MICRONEEDLES

Microneedles are tiny and very sleek devices that are manufactured by the silicon etching technology and micro-electromechanical system manufacturing (**MEMS**) technique. There are number of delivery approaches that have been employed to use the micro needles for TDDS. These include;

a. **Poke with patch approach:** Involves piercing into the skin followed by application of the drug patch at the site of treatment.

b. **Coat and poke approach:** Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.

c. **Biodegradable microneedles:** Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin.

d. **Hollow microneedles:** Involves injecting the drug through the needle with a hollow bore.

2. **Macroflux*:***

This system incorporates a titanium microprojection array that creates superficial pathway through the skin barrier layer. The main component of the microprojection patch is a titanium disk affixed to a polymeric adhesive back. The titanium disk is 8cm2 and consists of an array of microscopic, titanium, tooth-like microprojections that are coated with medicinal substances. There are as many as 300 microprojections per cm with the length of individual micro projection less than 200μm. They penetrate just the 10μm to 25μm-thin layer of dead cells of the *stratum corneum*, in which they create 'holes' – microchannels – large enough to permit the transport of large molecules to the physiologically active deeper layers of the epidermis. The titanium microprojections are too small to cause pain. This technology offers a needle-free and painless transdermal drug delivery of large-molecular-weight compounds such as insulin, several peptide hormones, and vaccines. With this new system; patients can receive drugs for 12 weeks.

Three types of Macro flux have been designed. They include,

- **Dry-Coated Macro flux system**:

This is used for short period delivery that consists micro projection array coated with medicament that adhered to an elastic polymer adhesive backing.

- **D-TRANS Macro flux system**:

This is also for short duration administration that consists of a micro projection array combined with reservoir of drug.

- **E-TRANS Macro flux system:**

This is for on demand delivery that involves a micro projection array combined with an electro transport system.

3. **Metered-Dose Transdermal Spray (MDTS)**:

It is a liquid preparation in the form of solution that are used topically which is made up of a vehicle that is volatile come non-volatile in nature, which consists the completely dissolved medicament in solution. The use of MDTS reaches the sustained level and better permeation of the drug via skin.

The MDTS has the following potential advantages:

a) It improves delivery potential without skin irritation due to its non-occlusive nature.

b) Increased acceptability.

c) Dose flexibility

d) Simple manufacture

B. Electrically-Based Enhancement Techniques:

1. **Iontophoresis:**

In iontophoretic delivery devices, Drug is placed on the skin under the active electrode, and a current (< 0.5mA) passed between the two electrodes effectively repelling drug away from the active electrode and into the skin. Pilocarpine delivery can be taken as example to induce sweat in the diagnosis of cystic fibrosis and Iontophoretic delivery of lidocaine is considered to be a nice approach for rapid onset of anaesthesia.

2. **Ultrasound:**

The application of ultrasound of a suitable frequency significantly enhances the transdermal transport of drugs by means of skin system not larger than wrist watch-a phenomenon referred to as phonophoresis or sonophoresis. It is a combination of ultrasound therapy with topical drug therapy to achieve therapeutic drug concentrations at selected sites in the skin. In this technique, the drug is mixed with a coupling agent usually a gel but sometimes a cream or ointment is used which transfers ultrasonic energy from the device to the skin through this coupling agent. This involves rupturing the lipids present in stratum cornea, which allows the medicament to permeate via biological barrier. It employs ultrasound waves ranging from 20 kHz to 10 MHz with intensities of up to 3Wcm-2 have been applied to mitigate the stratum corneum barrier property.

3. **Photomechanical Waves:**

The mechanism of photochemical wave was found to act by producing changes in the lacunar system which results in the formation of transient channels through the *stratum corneum* by permeabilization mechanism.

4. **Electroporation:**

In this method, aqueous pores are generated in the lipid bilayers by the application of short electrical pulses of approx. 100-1000 volt/cm. It may combine with Iontophoresis to enhance the permeation of peptide.

5. **Electro-Osmosis:**

If a charged porous membrane is subjected to a voltage difference, a bulk fluid or volumes flow, called electro osmosis.

Velocity Based Enhancement Techniques:

1. Needle-Free Injections

a)Intraject ,b) Implaject ,c)Jet Syringe , d) Iject, e) Mini-jet, f) Cross jet

2. Powderject Device:

The powderject system fires solid particles (20-100 mm) through *stratum corneum* into lower skin layers, using a supersonic shock wave of helium gas.

Other Enhancement Techniques:

1. Liposome:

Liposomes are colloidal particles formed as concentric bimolecular layers that are capable of encapsulating drugs. They are lipid vesicles that fully enclose an aqueous volume. Liposomes acts by penetrating the epidermis, carrying the drug into skin.

2. Transferosomes:

Transferosomes are modified liposomes i.e. they are liposomes with edge activators (sodium cholate). Transferosomes by passes the cutaneous capillary bed because they are too large to enter the blood vessels locally and reach subcutaneous tissue. Transferosome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug.

3. Skin Abrasion:

The abrasion technique involves the direct removal or disruption of the upper layers of the skin to facilitate the permeation of topically applied medicaments. In general, one approach is

adopted to create micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules are generally known as Microscissuining.

4. Medicated Tattoos:

Med-Tats are a modification of temporary tattoo which contains an active drug substance for transdermal delivery. This technique is useful in the administration of drug in those children who are not able to take traditional dosage forms.

5. Laser Radiation:

This method involves direct and controlled exposure of a laser beam to the skin which results in the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs.

6. Super saturation:

Thermodynamic activity of drug can be increased by employing supersaturated systems. In this method, when saturated formulation is used, the thermodynamic activity of the drug in the vehicle is increased above unity, thus enhancing the permeability of topically applied formulations. Skin permeation was directly related to the degree of saturation and was independent of the absolute concentration of the drug.

7. Magnetophoresis:

The effect of magnetic field on diffusion flux of drug substance was found to enhance with increasing applied strength.

Transdermal Market [12]

More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients are approved for use in TDD products globally 43. **Table 2** gives detail information of the different drugs which are administered by this route and the common names by which they are marketed it also gives the conditions for which the individual system is use.

Table 02: TRANSDERMAL MARKET

PRODUCT NAME	DRUG	MANUFACTURE	INDICATION
Alora	Estradiol	TheraTech/proctol and Gamble	Postmenstrual syndrome
Androderm	Testosterone	TheraTech/ GlaxosmithKline	Hypogonadism in males
Catapres-TTS	Clonidine	ALZA/Boehinger Ingelheim	Hypertension
Climaderm	Estradiol	Ethical Holdings/Wyeth-Ayerest	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals/Berlex Labs	Postmenstrual syndrome
CombiPatch	Estradiol/Noret hindrone	Noven, Inc./Aventis	Hormone replacement therapy
Deponit	Nitroglycerine	Schwarz-Pharma	Angina pectoris
Duragesic	Fentanyl	Alza/ Janssen pharmaceutical	Moderate /severe pain
Estraderm	Estradiol	Alza/Novartis	Post menstrual syndrome
Fematrix	Estragon	Ethical holdings/solvay healthcare LTD	Post menstrual syndrome
Fempatch	Estradiol	Parke-davis	Post menstrual syndrome
Habitraol	Nicotin	Novartis	Smoking cessation
Minitran	Nitroglycerine	3M pharmaceuticals	Angina pectoris
Nicoderm	Nicotin	Alza/glaxosmithkline	Smoking cessation
Nicotrol	Nicotin	Cygnus inc./Mc Neil Consumer products Ltd.	Smoking cessation
Nitrodisc	Nitroglycerine	Roberts pharmaceuticals	Angina pectoris
Nitro-dur	Nitroglycerine	Key pharmaceuticals	Angina pectoris
Nuvelle TS	Estrogen/ Progesterone	Ethical holding/ Schering	Hormone replacement therapy
Ortho-Evara	Norelgestromin/ Estradiol	Ortho/Mc Neil pharmaceuticals	Birth control
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation
Testoderm TTS	Testosterone	Alza	Hypogonadism in males
Transderm Scop	Scopolamine	Alza/Novartis	Motion sickness
Transderm nitro	Nitroglycerine	Alza/Novartis	Angina pectoris

Recent trends in TDDS:

Fentanyl and nitro-glycerine are the drugs most popularly marketed using transdermal patches Drug in adhesive technology has become the preferred system for passive transdermal delivery; two areas of formulation research are focused on adhesives and excipients. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch.

A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier (primarily the stratum corneum) or increasing the energy of the drug molecules. These so-called “active” transdermal technologies include iontophoresis (which uses low voltage electrical current to drive charged drugs through the skin), electroporation (which uses short electrical pulses of high voltage to create transient aqueous pores in the skin), sonophoresis (which uses low frequency ultrasonic energy to disrupt the stratum corneum), and thermal energy (which uses heat to make the skin more permeable and to increase the energy of drug molecules). Even magnetic energy, coined magnetophoresis, has been investigated as a means to increase drug flux across the skin.

Table 03: CURRENTLY APPROVED USFDA DRUGS FOR TDDS

YEAR	GENERIC (BRAND) NAMES	INDICATION
1979	Scopolamine (Transderm Scop®)	Motion sickness
1984	Clonidine (Catapres TTS®)	Hypertension
1986	Estradiol (Estraderm®)	Menopausal symptoms
1990	Fentanyl (Duragesic®)	Chronic pain
1991	Nicotine (Nicoderm®, Habitrol®, Prostep®)	Smoking cessation
1993	Testosterone (Androderm®)	Testosterone deficiency
1995	Lidocaine/epinephrine *(*Iontocaine®*)*	Local dermal analgesia
1998	Estradiol/norethindrone (Combipatch®)	Menopausal symptoms
1999	Lidocaine (Lidoderm®)	Post-herpetic neuralgia pain
2001	Ethinyl estradiol/norelgestromin (OrthoEvra®)	Contraception
2003	Estradiol/levonorgestrel (Climara Pro®)	Menopause
2003	Oxybutynin (Oxytrol®)	Overactive bladder
2004	Lidocaine/ultrasound *(*SonoPrep®*)*	Local dermal anaesthesia
2005	Lidocaine/tetracaine (Synera®)	Local dermal analgesia
2006	Fentanyl/iontophoresis *(*Ionsys®*)*	Acute postoperative pain
2006	Methylphenidate (Daytrana®)	ADHD
2006	Selegiline (Emsam®)	Depression
2007	Rotigotine (Neupro®)	Parkinson's disease
2007	Rivastigmine (Exelon®)	Dementia
2008	Granisetron (Sancuso®)	Chemo-induced emesis
2009	Oxybutynin *(*Gelnique®*)*	Overactive bladder
2010	Buprenorphine (Butrans®)	Chronic pain

Future Scope:

The future scope of the TDDS includes:

i. An insulin patch

ii. Sufentanil patch for chronic cancer pain

iii. Varenicline patch for smoking cessation and a high-dose nicotine patch for fast metabolizers

iv. Estrogen and testosterone patches for post-menopausal women

v. Selegiline patch for depression in the elderly and cocaine addiction

vi. Clonidine transdermal for the treatment of delerium in trauma patients

vii. Dexamethasone iontophoretic delivery for the treatment of tennis elbow

viii. An iontophoretic sumatriptan patch for migraine treatment, and

ix. Transdermal glyceryl trinitrate for acute stroke therapy, to name a few

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