

TRANSDERMAL DRUG DELIVERY SYSTEM: An Overview

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Dedicated

**To my parents for their unparallel blessing and inspirations
&
All my honorable teachers for their great contribution and guidance
in my life.**

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Summary of Study:

The human skin is a readily accessible surface for drug delivery. Skin of an average adult body covers a surface of approximately 2 m² and receives about one-third of the blood circulating through the body. Over the past decades, developing controlled drug delivery has become increasingly important in the pharmaceutical industry. Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy. Transdermal drugs are self-contained, discrete dosage form. It delivers a drug through intact skin at a controlled rate into the systemic circulation. Delivery rate is controlled by the skin or membrane in the delivery system. It is a sophisticated complex drug delivery system which is difficult to formulate. It requires specialized manufacturing process/equipment. The materials of construction, configuration and combination of the drug with the proper cosolvent, excipient, penetration enhancer, and membrane are carefully selected and matched to optimize adhesive properties and drug delivery requirements. Several transdermal products and applications include hormone replacement therapy, management of pain, angina pectoris, smoking cessation and neurological disorders such as Parkinson's disease. Formulated to deliver the drug at optimized rate into the systemic circulation should adhere to the skin for the expected duration should not cause any skin irritation and/or sensitization, enhancing bioavailability via bypassing first pass metabolism, minimizing pharmacokinetic peaks and troughs, improving tolerability and dosing increasing patient compliance in continuous delivery. This review article provides an overview of TDDS, its advantages over conventional dosage forms, Limitations, various components of Transdermal patches, types of Transdermal patches, methods of preparation and Ideal requirements for TDDS, regulatory issues over transdermal drug delivery, its physicochemical methods of evaluation, therapeutic uses and recent advances in transdermal drug delivery system.

1. INTRODUCTION:

For thousands of years, human civilizations have applied substances to the skin as cosmetic and medicinal agents. However, it was not until the twentieth century that the skin came to be used as a drug delivery route (Prausnitz and Langer, 2008).

Transdermal drug delivery system is also known as a transdermal patch or skin patch which deliver a specific dose of medication to the systemic circulation. It is a medicated adhesive patch. Morphological, biophysical and physicochemical properties of the skin are to be considered when therapeutic agents are delivered through the human skin for systemic effects (Patel and Kavitha, 2011). Transdermal patch of scopolamine is the first transdermal patch which is approved by FDA in 1981. Transdermal delivery systems of scopolamine is used for the prevention of motion sickness (TransdermScop, ALZA Corp.) and nitroglycerine for the prevention of angina pectoris associated with coronary artery disease (Transderm Nitro). Transdermal drug delivery products give therapeutic benefit to patients. Approximately 16 active ingredients and more than 35 Transdermal drug delivery products have been approved for use globally and for sale in the US respectively. In the year 2005 market of \$ 12.7 billion and in 2015 market of \$ 21.5 is found by statistics analysis that is expected to increase to \$31.5 billion in the year 2015 (Saroha *et al.*, 2011).

Patches applied to the skin eliminate the need for vascular access by syringe or the use of pumps and today there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, oestradiol, oxybutinin, scopolamine, and testosterone. There are also combination patches for contraception, as well as hormone replacement. Depending on the drug, the patches generally last from one to seven days (Dipen and Kavitha, 2012). Transdermal drug delivery systems (TDDS) are the topically applied “patches” designed to deliver a therapeutically effective dose of a drug across the patient’s skin at a controlled rate for the systemic effect (Mishra, 2002; Patel *et al.*, 2011). The major obstacle for the topical drug delivery is the low diffusion rate of drugs across the relatively impermeable, outermost skin layer, the stratum corneum (Bouwstra *et al.*, 2002). Besides, the intercellular lipid region, the major pathway for lipophilic drugs, has a diffusion path length of about 500nm which is much longer than the thickness of stratum corneum (20 mm) (Gaur *et al.*, 2009; Phillips and Michniak, 1995).

Table-1: Some marketed Transdermal Products.

PRODUCT	DRUG	MANUFACTURER	INDICATION
Alora	Estradiol	TheraTech/proctol and Gamble	Postmenstrual syndrome
Androderm	Testosterone	Theratech/GalxosmithKline	Hypogonadism in males
Catapres-TTS	Clonidine	ALZA/Boehinger Ingelheim	Hypertension
Climaderm	Estradiol	EthicalHoldings/Wyeth-Ayerest	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals/Berlex Labs	Postmenstrual syndrome
Deponit	Nitroglycerine	Schwarz pharma	Angina pectoris
Duragesic	Fentanyl	Alza/ Jansscn pharmaceutical	Moderate /severe pain
Estraderm	Estradiol	Alza/Novartis	Post menstrual syndrome
Fempatch	Estradiol	Parke-davis	Post menstrual syndrome
Habitraol	Nicotin	Novartis	Smoking cessation
Minitrann	Nitroglycerine	3M pharmaceuticals	Angina pectoris
Nicoderm	Nicotin	Alza/glaxo smithkline	Smoking cessation
Nitrodisc	Nitroglycerine	Roberts pharmaceuticals	Angina pectoris
Nitro-dur	Nitroglycerine	Key pharmaceuticals	Angina pectoris
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation
Testoderm TTS	Testosterone	Alza	Hypogonadism in males
Transderm	Scopolamine	Alza/Novartis	Motion sickness
Transderm	Nitroglycerine	Alza/Novartis	Angina pectoris

Despite the interests and the merits in this drug delivery system, only very few drug candidates have been approved for transdermal delivery. Besides skin toxicity of the drug or drug excipients, the major obstacle facing this route of delivery is the barrier nature of the skin which limits the number of molecules permeating it to only few that can meet certain criteria. Such molecules should possess appropriate physicochemical properties such as low melting point (<150 °C), low molecular weight (<500 D) and intermediate lipophilicity (log P= 1-3) as well as high potency (total daily dose < 10 mg). Only few drugs meet these criteria.

Consequently, several approaches have been established in an attempt to overcome the barrier properties and deliver most medicaments through the skin. They include both the chemical and physical enhancement strategies. The former strategy involving chemical methods include penetration enhancers, pro-drugs, colloidal formulations, and supersaturated systems. The latter strategy involves physical methods, including phonophoresis, electroporation etc. More researches in recent years have therefore been devoted towards investigating the effect of numerous chemical or physical or the combination of both enhancers on the skin permeability of most of the common drugs especially those drugs that already have problems at their present route of administration. Several percutaneous research strategies are available including in vivo and in vitro permeation studies (Uzor *et al.*, 2011).

2. ADVANTAGES AND DISADVANTAGES OF TDDS:

2.1. Advantages

First, there are biological advantages to delivering drugs through the skin:

- ✚ Transdermal delivery avoids the stomach environment where the drug can be degraded and rendered ineffective or where it can cause unpleasant gastrointestinal symptoms for the patient (Gordon, 2005).
- ✚ Transdermal delivery avoids the first pass effect where active drug molecules can be converted to inactive molecules or even to molecules responsible for side effects (Rios, 2007).
- ✚ Transdermal drug delivery provides steady plasma levels. When a patch is applied that lasts for 24 hours, or even 7 days, once steady state is reached the plasma levels remain constant because the rate of drug delivered from the patch is constant. When a drug is given four times a day, or even once a day, the drug levels rise after administration and then gradually fall until the next administration producing peaks and troughs throughout the course of therapy (Gordon, 2005).
- ✚ Unlike the limited controlled release from oral and intravenous routes, TDDS provides steady infusion of drug over an extended period of time, suitable for the drugs with short

biological half life requiring frequent dosing, leading to increased patient compliance and decreased inter and intra patient variability (Mishra, 2002; Patel *et al.*, 2012).

- ✚ Therapeutic failure or adverse effects frequently associated with intermittent dosing for the chronic diseases can be avoided (Magnusson *et al.*, 1997).
- ✚ Self administration and removal when required.
- ✚ Pain, inconvenience of injections can be overcome by this non- invasive and safe parenteral route of drug delivery (Gondaliya and Pundarikakshudu, 2003; Koteswar *et al.*, 1992).

Other advantages to delivering drugs through the skin include the fact that:

- ✚ Transdermal drug delivery systems, especially simple patches, are easy to use and noninvasive and patients like noninvasive therapies.
- ✚ Because they are easy to use, patches can increase compliance and reduce medical costs. There are many studies that show a patient's overall healthcare costs are reduced when pharmaceutical compliance is increased. In addition, there are specific studies that show that patient compliance increases and healthcare costs decrease when patches are prescribed.
- ✚ If a transdermal delivery system is used in place of a needle, then medical waste can also be decreased, again, decreasing healthcare costs (Gordon, 2005; Rios, 2007).

2.2. Disadvantages:

No drug delivery system is without its disadvantages. Some of the challenges of transdermal drug delivery include:

Only a narrow range of molecules can currently be delivered transdermally using available technologies. Only small, relatively lipophilic molecules can pass through the lipid bilayer "mortar" of the stratum corneum using traditional patch technology. As drug treatments become more and more complex, drug molecules are becoming larger and more complex as well and new technologies will be needed to deliver these drugs through the skin (Prausnitz and Langer, 2008). Figure-1 is representative of the types of molecules that can currently be delivered through the skin. All of these molecules are organic in nature and are considered lipid soluble. Even though

these molecules contain a few polar atoms such as oxygen and nitrogen, they are made primarily of carbon and hydrogen atoms that render them nonpolar. Nicotine is the smallest molecule represented with a molecular weight of only 162.24 g/mol. Although hormones or a molecule like fentanyl, with a molecular weight over 300 g/mol, are considered large organic molecules, they are still much smaller than even a small protein such as insulin.

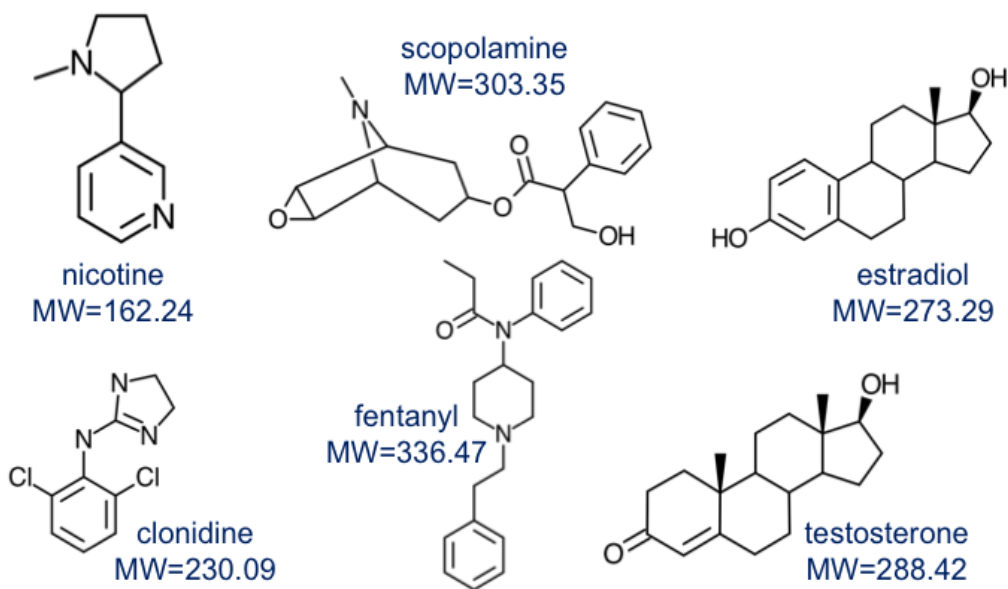


Figure-1: Low molecular weight, lipophilic organic drug molecules.

- ✚ Currently, only small quantities of drug can be delivered through the stratum corneum. Therefore, drugs that are given transdermally must be relatively potent so that they can be effective at low doses.
- ✚ **Patient trust** issues can also be a barrier to effective transdermal drug therapy. The general public might have been willing to accept a 3-day scopolamine patch when it was introduced in 1979 but it was quite a challenge in 1984 to convince doctors and patients alike that a clonidine patch would control blood pressure for seven days continuously. In more recent years, there have been accidental overdose deaths from fentanyl patches and questions have been raised about the safety of transdermal contraception. As new transdermal technologies are introduced, there will certainly be questions from patients and healthcare professionals about the safety and effectiveness of these new delivery systems.

3. ADVERSE EFFECTS:

In 2005, the FDA announced that they were investigating reports of death and other serious adverse events related to narcotic overdose in patients using Duragesic, the fentanyl transdermal patch for pain control. The Duragesic product label was subsequently updated to add safety information in June 2005. In 2008, two manufacturers of the Fentanyl patch, Alza Pharmaceuticals (a division of major medical manufacturer Johnson & Johnson) and Sandoz, subsequently issued a recall of their versions of the patch due to a manufacturing defect that allowed the gel containing the medication to leak out of its pouch too quickly, which could result in overdose and death. As of 2010, Sandoz no longer uses gel in its transdermal fentanyl patch; instead, Sandoz-branded fentanyl patches use a matrix/adhesive suspension where the medication is blended with the adhesive instead of held in a separate pouch with a porous membrane), similar to other fentanyl patch manufacturers such as Mylan and Janssen.

In 2007, Shire and Noven Pharmaceuticals, manufacturers of the Daytrana ADHD patch, announced a voluntary recall of several lots of the patch due to problems with separating the patch from its protective release liner. Since then, no further problems with either the patch or its protective packaging have been reported. In 2009, the FDA announced a public health advisory warning of the risk of burns during MRI scans from transdermal drug patches with metallic backings. Patients should be advised to remove any medicated patch prior to an MRI scan and replace it with a new patch after the scan is complete (Sakalle *et al.*, 2010). Skin burns have occurred with metal containing transdermal patches at the time of shock therapy from external as well as internal cardioverter defibrillators (ICD) (Patel *et al.*, 2012).

4. SKIN AND DRUG PERMEATION:

For understanding the concept of TDDS, it is important to review the structural and biochemical features of human skin and those characteristics which contribute to the barrier function and the rate of drug access into the body via skin.

4.1. Anatomically, the skin can be divided in to two layers:

- ✓ Epidermis and Dermis or corium

Some of the differences between epidermis and dermis layers of skin. The skin is one of the most extensive organs of the human body covering an area of about 2m² in an average human adult. This multilayered organ receives approximately one third of all blood circulating through the body (Guy *et al.*, 1987). Epidermis results from an active epithelial basal cell population and is approximately 150 micrometers thick. It is the outermost layer of the skin and the process of differentiation results in migration of cells from the basal layer towards skin surface (Flynn, 1985). Below this layer are the other layers of the epidermis - the stratum lucidum, stratum granulosum, stratum spinosum and stratum germinativum. Together, these other layers constitute the viable epidermis. Dermis is foundation of firm connective tissue upon which epidermis is laid and is of mesoderm origin. The dermis or corium consists of a dense felt work of connective tissue in which bundles of collagenous fibres predominate, mingled with a certain proportion of elastic tissue in superficial levels. Dermis contains fine plexuses of blood vessels, lymphatics and nerves, hair follicles, sweat glands and sebaceous glands (Gros and Clark, 1980).

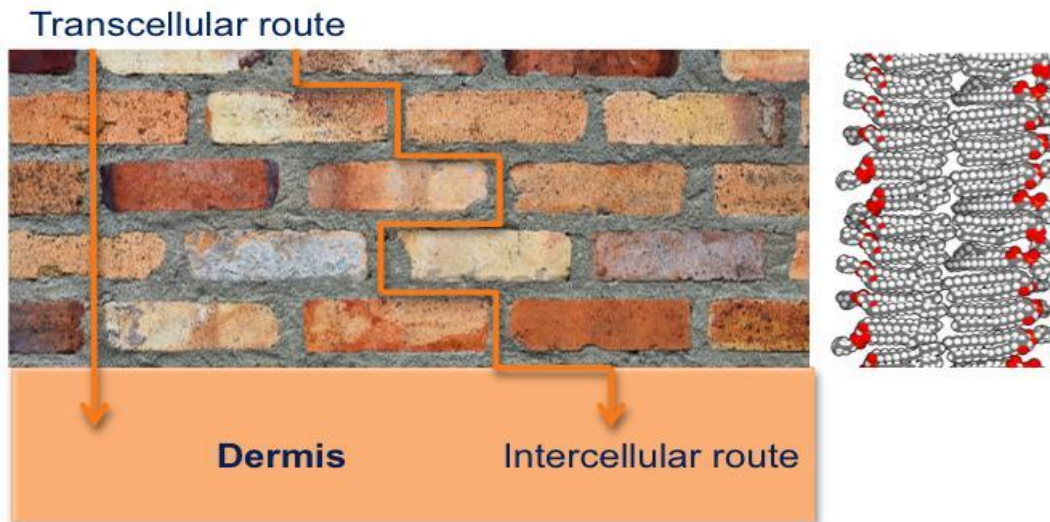


Figure -2: Brick and Mortar Structure with Lipid Bilayer.

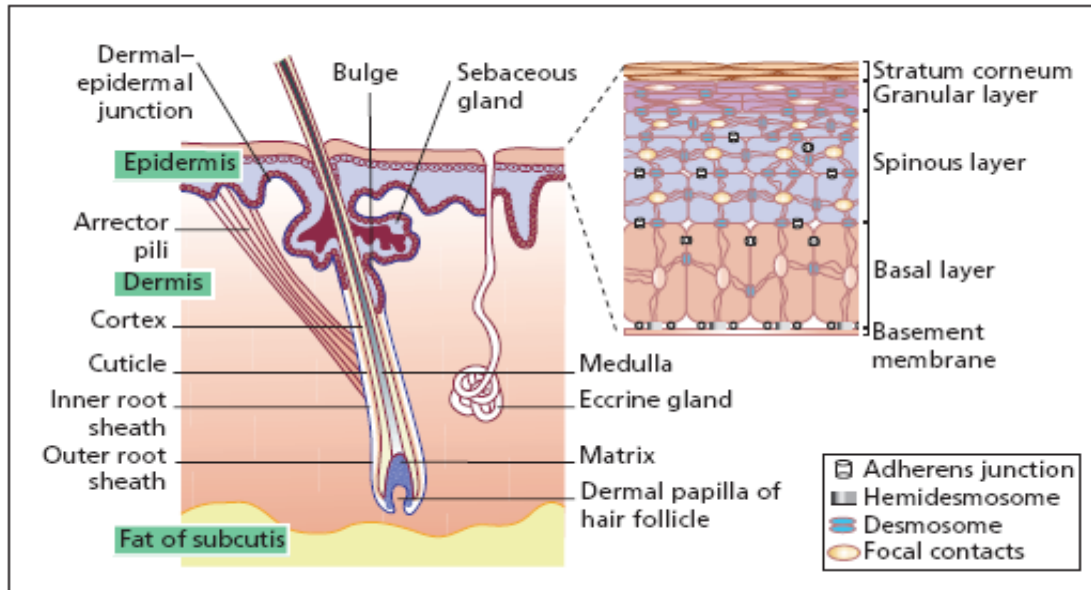


Figure-3: Schematic diagram of different layers of skin.

4.2. Drug penetration pathways:

There are critically three ways in which a drug molecule can cross the intact stratum corneum: via skin the appendages (shunt routes); through the intercellular the other layers of the epidermis the stratum lucilipiddomains; or by a transcellular route. A particular drug is likely to permeate by a combination of these routes, with the relative contributions of these pathways to the gross flux governed by the physicochemical properties of the molecule (Reinhold, 1989).

4.2.1. The appendageal route:

Skin appendages provide a continuous channel directly across the stratum corneum barrier. However, their influence on drug penetration is hindered by a number of factors. The surface area occupied by hair follicles and sweat ducts are small (typically 0.1% of skins surface area) therefore limiting the area available for direct contact of the applied drug formulation (Gandhi *et al.*, 2012).

4.2.2. Transcellular route:

Drugs entering the skin via the transcellular route pass through corneocytes. Corneocytes, containing highly hydrate keratin, provide an aqueous environment for which hydrophilic drugs

can pass. The diffusion pathway for a drug via the transcellular route requires a number of partitioning and diffusion steps (Gandhi *et al.*, 2012).

4.2.3. Intercellular route:

The intercellular pathway involves drug diffusing through the continuous lipid matrix. This route is a significant obstacle for two reasons. Recalling the 'bricks and mortar' model of the stratum corneum, the interdigitating nature of the corneocytes yields a tortuous pathway for intercellular drug permeation, which in contrast to the relatively direct path of the transcellular route. The intercellular domain is a region of alternating structured bilayers. Consequently, a drug must sequentially partition into, and diffuse through repeated aqueous and lipid domains. This route is generally accepted as the most common path for small uncharged molecules penetrating the skin (Gandhi *et al.*, 2012).

5. FACTORS INFLUENCING TRANSDERMAL DRUG:

The effective transdermal drug delivery can be formulated by considering three factors as Drug, Skin, and the vehicles. So the factors affecting can be divided into classes as biological factors and physicochemical factors.

5.1. Biological factors:

✓ Skin condition:

Acids and alkalis, many solvents like chloroform methanol damage the skin cells and promote penetration. Diseased state of patient alters the skin conditions. The intact skin is better barrier but the above mentioned conditions affect penetration.

✓ Skin age:

The young skin is more permeable than older. Children are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug in TDDS.

✓ Blood supply:

Changes in peripheral circulation can affect transdermal absorption.

✓ **Regional skin site:**

Thickness of skin, nature of stratum corneum, and density of appendages vary site to site. These factors affect significantly penetration.

✓ **Skin metabolism:**

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

✓ **Species differences:**

The skin thickness, density of appendages, and keratinization of skin vary species to species, so affects the penetration (Deshwal and Verma, 2012).

5.2. Physicochemical factors:

✓ **Skin hydration:**

In contact with water the permeability of skin increases significantly. Hydration is most important factor increasing the permeation of skin. So use of humectants is done in transdermal delivery.

✓ **Temperature and pH:**

The permeation of drug increase ten fold with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factors affecting drug penetration.

✓ **Diffusion coefficient:**

Penetration of drug depends on diffusion coefficient of drug. At a constant temperature the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.

✓ **Drug concentration:**

The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier.

✓ **Partition coefficient:**

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

✓ **Molecular size and shape:**

Drug absorption is inversely related to molecular weight; small molecules penetrate faster than large ones. Because of partition coefficient domination, the effect of molecular size is not known (Deshwal and Verma, 2012).

6. TYPES OF TRANSDERMAL PATCHES:

6.1. Single layer drug in adhesive:

In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and this type of layer is responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing. (Willams and Barry, 2004)

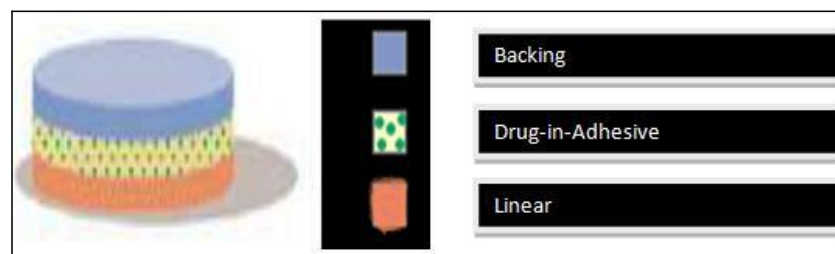


Figure-4: Single-layer drug-in-adhesive.

6.2. Multi -layer drug in adhesive:

This type is also similar to the single layer but it contains a immediate drug release layer which is different from other layer which will be a controlled release along with the adhesive layer. The

adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing (Pellet *et al.*, 2003).

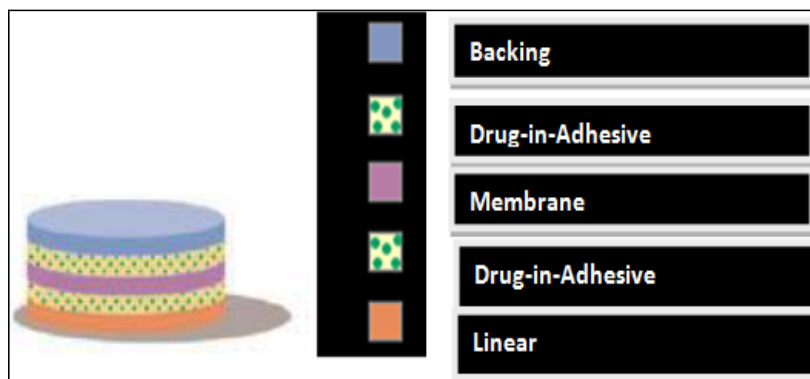


Figure- 5: Multi layer drug -in-adhesive.

6.3. Vapour patch:

In this type of patch the role of adhesive layer not only serves to adhere the various layers together but also serves market, commonly used for releasing of essential oils in decongestion. Various other types of vapor patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions (Pellet *et al.*, 2003).

6.4. Reservoir system:

In this system the drug reservoir is embedded between the two layers; an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug (Pellet *et al.*, 2003).

6.5. Matrix system:

✓ Drug-in-adhesive system:

In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting on an impervious

backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose (Brown and Jones, 2000).

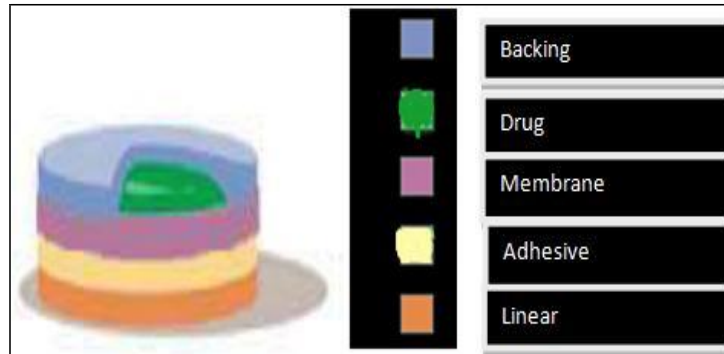


Figure- 6: Drug reservoir-in-adhesive.

✓ **Matrix-dispersion system**

In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim (Brown and Jones, 2000; Tsai *et al.*, 1998).

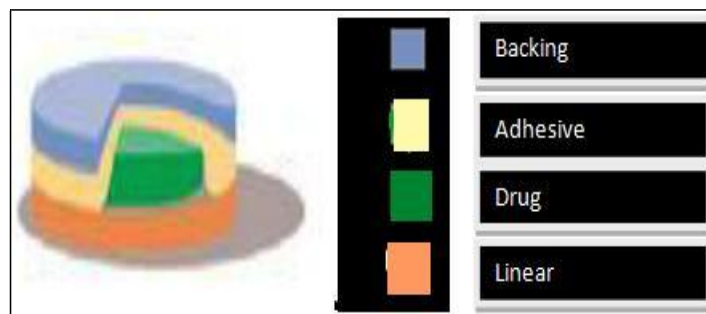


Figure- 7: Drug matrix-in-adhesive.

6.6. Microreservoir Controlled TDDS:

This drug delivery system is a combination of reservoir and matrix-dispersion systems. The drug reservoir is formed by first suspending the drug in an aqueous solution of water-soluble polymer

and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. The thermodynamically unstable dispersion is stabilized quickly by immediately cross linking the polymer in situ. A Transdermal system therapeutic system thus formed as a medicated disc Positioned at the center and surrounded by an adhesive rim (Patani and Chien, 1999).

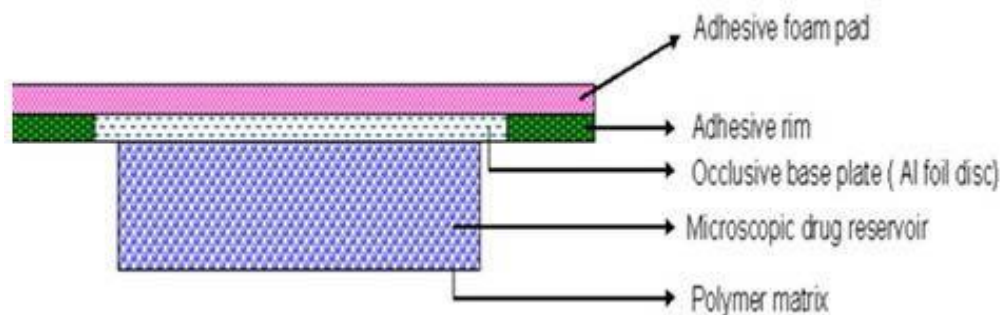


Figure-8: Microreservoir controlled TDDS.

Nitro-dur® System (Nitroglycerin) for once a day treatment of angina pectoris.

7. COMPOSITION OF TDDS:

- 7.1. Polymer matrix.
- 7.2. Drug.
- 7.3. Permeation enhancers.
- 7.4. Pressure sensitive adhesives (PSAs).
- 7.5. Backing membrane.
- 7.6. Release liner.
- 7.7. Other excipients (Hanumanaik *et al.*, 2012).

7.1. Polymer matrix / Drug reservoir:

Polymer matrix, prepared by the dispersion of a drug in a suitable polymer, controls the release of the drug from the device. Polymers used in TDDS should be stable, compatible and non-reactive with the drug and other components of the system, should provide effective release of the drug throughout the device. They should be easily fabricated to the desired product. Polymers and their degradation products must be non-toxic and non-antigenic to the host (Mishra, 2002).

The polymers used for TDDS can be classified as:

7.1.1. Natural polymers:

Hydroxypropyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (sodium CMC), cellulose acetate, methyl cellulose, ethyl cellulose, gelatin, chitosan, sodium carboxymethylguar, sodium alginate, polymerized rosin etc (Bagyalakshmi *et al.*, 2007; Kulkarni *et al.*, 2004; Satturwar *et al.*, 2005).

7.1.2. Synthetic polymers:


Polyvinyl alcohol, polyethylene, polyethylene glycol, polyvinylpyrrolidone, eudragits, ethylene vinyl acetate copolymer, ethyl vinyl acetate, silicon rubber etc (Satturwar *et al.*, 2005; Gondaliya and Pundarikakshudu, 2003; Schroeder *et al.*, 2007).

7.2. Drug:

Drugs, having the following properties, are selected for TDDS

7.2.1. Physicochemical properties:

The drug should have some degree of solubility in both oil and water (ideally greater than 1 mg/ml) The substance should have melting point less than 200 °F. Concentration gradient across the membrane is directly proportional to the log solubility of drug in the lipid phase of membrane, which in turn is directly proportional to the reciprocal of melting point (in degree absolute of the drug). In order to obtain the best candidates for TDD, an attempt should be made to keep the melting point as low as possible (Jayaswal and Sood, 1987).

 Substances having a molecular weight of less than 1000 units are suitable.

- ✦ A saturated aqueous solution of the drug should have a pH value between 5 and 9. Drugs highly acidic or alkaline in solution are not suitable for TDD; because they get ionized rapidly at physiological pH and ionized materials generally penetrate the skin poorly.
- ✦ Hydrogen bonding groups should be less than 2 (Finnin and Morgan, 1999).

7.2.2. Biological properties:

- ✦ Drug should be very potent, i.e., it should be effective in few mgs per day (ideally less than 25 mg/day)
- ✦ The drug should have short biological half life
- ✦ The drug should be non irritant and non allergic to human skin
- ✦ The drug should be stable when in contact with the skin
- ✦ The drug should not stimulate an immune reaction to the skin
- ✦ Tolerance to drug must not develop under near zero order release profile of transdermal delivery
- ✦ The drug should not get irreversibly bound in the subcutaneous tissue
- ✦ The drug should not get extensively metabolized in the skin (Mishra, 2002).

7.3. Permeation enhancers:

7.3.1. Chemical permeation enhancers:

They disrupt the highly ordered intercellular lipid bilayers of the stratum corneum by inserting amphiphilic molecules or by extracting lipids, reversibly decreasing the barrier resistance and allowing better permeation of the co-administered drugs (Prausnitz and Langer, 2008). An ideal enhancer should be inert, non-toxic, non-allergenic, non-irritating, work unidirectionally and compatible with the excipients and drugs. Their potency appears to be drug, skin and concentration dependent (Williams and Barry, 2004).

Some examples of permeants are ethanol (the most common permeation enhancer), essential oils or terpenes (cineole, carveol, menthone, citral, menthol, d-limonene), dimethyl sulfoxide, propylene glycol, N-methyl-2-pyrrolidone, ethyl pyrrolidone, polyethylene glycol 400, isopropyl myristate, myristic acid, succinic acid, laurocapram (azone), methyl laureate, lauric acid, sodium lauryl sulfate, non-ionic surfactant (spans, tweens), pluronic, oleic acid, diethylene glycol monoethyl ether, urea etc (Dubey *et al.*, 2010; Schroeder *et al.*, 2007; Kulkarni *et al.*, 2004; Gondaliya and Pundarikakshudu, 2003; Suwanpidokkul *et al.*, 2004; Chakkapan *et al.*, 1994; Williams and Barry, 2004).

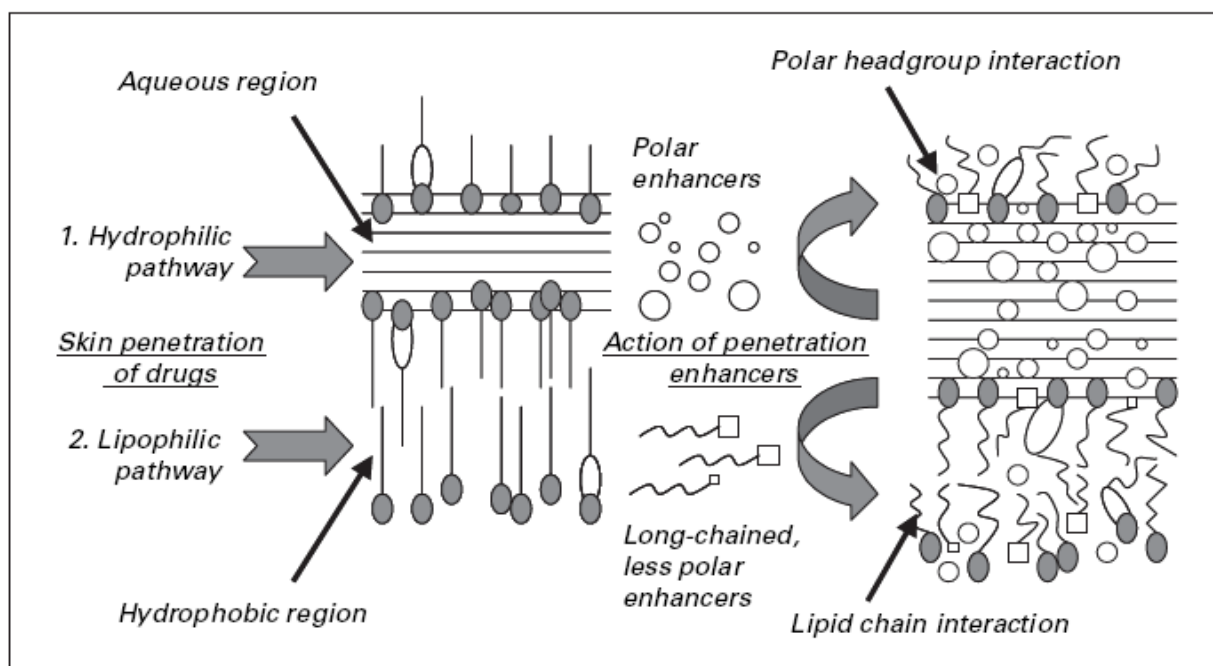


Figure- 9: Hydrophilic and lipophilic pathways of drug penetration and action mode of penetration enhancers.

7.3.2. Physical permeation enhancers:

Iontophoresis enhance and control drug penetration through the skin by applying low density electric current. Electroporation applies high voltage pulses across the skin for a fraction of second, creating new aqueous pathways in the stratum corneum for drug diffusion (Jadoul and Preat, 1997). Erbium: yttrium-aluminium-garnet (Er:YAG) laser applies single pulse of low energy to ablate the stratum corneum layers (Lee *et al.*, 2008). Ultrasound or micro needle

application breach the stratum corneum and create micro channels for the drug permeation (Lanke *et al.*, 2009).

7.3.3. Other permeation enhancers:

Ethanol liposomes, niosomes, protransferosome gel and prodrug approach are reported to increase permeability by increasing the drug solubilization and partitioning into the skin (Dubey *et al.*, 2010; El-Laithy *et al.*, 2011; Puglia *et al.*, 2006).

7.4. Pressure sensitive adhesives (PSAs):

PSAs affix TDDS firmly to the skin on applying light pressure. They should be skin-compatible, non-irritant, easily removable without leaving a residue or inflicting pain. They ensure intimate contact between the drug releasing area of TDDS and the skin surface which is critical for the controlled release of drug. Commercially available PSAs include polyacrylate, polyisobutylene and silicones (Murthy *et al.*, 2001; Dimas *et al.*, 2000; Ho and Dodou, 2007).

7.5. Backing membrane:

Backing materials must be flexible while possessing good tensile strength. Commonly used materials are polyolefins, polyesters, and 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 (Foco *et al.*, 2004; Paranjothy and Thampi, 1997).

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 backing materials are vinyl, polyester films, Polyester-polypropylene films, Polypropylene resin, Polyethylene resin, Polyurethylene, Co Tran 9722 film, Ethylene-vinyl acetate, Aluminized plastic laminate. (Foco *et al.*, 2004; Paranjothy and Thampi, 1997; Bhaskaran and Harsha, 2000; Aqil *et al.*, 2006; Dey *et al.*, 2007; Satturwar *et al.*, 2005).

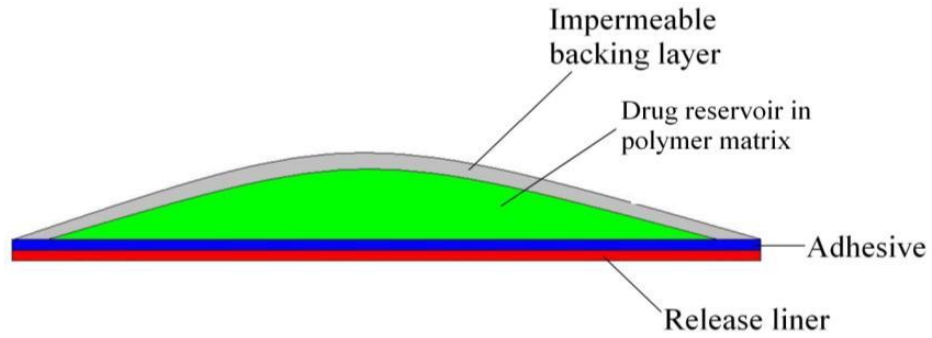


Figure- 10: Matrix diffusion controlled film.

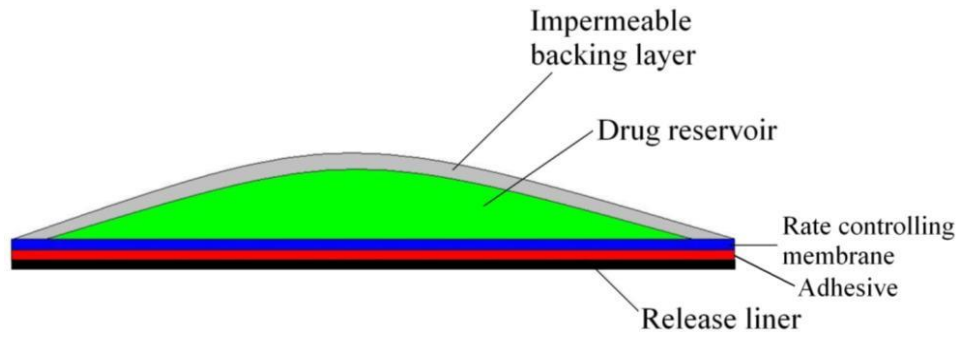


Figure- 11: Membrane permeation controlled film.

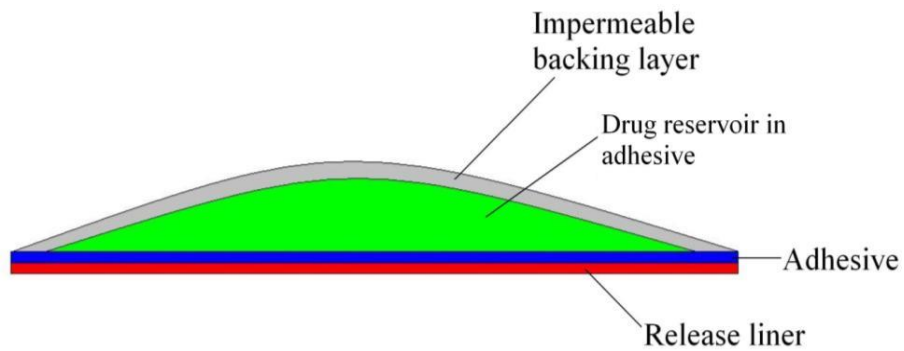


Figure-13: Adhesive diffusion controlled film.

7.6. Release Liner:

Release liner is a protective liner for the TDDS patch that is removed prior to the application on the skin. Typically, it consists of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer of silicon (Aqil *et al.*, 2006; Dimas *et al.*, 2000).

7.7. Other excipients:

Various solvents such as water, ethanol, isopropylmyristate, isopropyl alcohol, and dichloromethane are used alone or in combination to prepare the drug reservoir (Suwanpidokkul *et al.*, 2004; Bagyalakshmi *et al.*, 2007; Aqil *et al.*, 2006). Propylene glycol, ethanol are used as co solvents along with the permeation en-hancer (Magnusson *et al.*, 1997; Ruland *et al.*, 1994). Plasticizers like diethyl phthalate, dibutylphthalate, glycerol, triethyl citrate, polyethylene glycol 400, eudraflex and propylene glycol provide plasticity to the trans-dermal patch (Rajendran *et al.*, 1997; Dey *et al.*, 2007; Gondaliya and Pundarikakshudu, 2003; Aqil *et al.*, 2006; Panigrahi *et al.*, 2005; Bhaskaran and Harsha, 2000).

Table -2: Composition of some marketed transdermal therapeutic systems.

Product	Drug Reservoir	Backing	Membrane	Adhesive	Release Liner
Androderm (testosterone) TheraTech, Inc./Smith- Kline Beecham	Drug, alcohol, glyceryl monooleae, methyl laurate gelled with acrylic acid copolymer	Metallized polyester/ ethylene methacrylic acidcopolyer/ EVA	Polyethylen microporous membrane	Peripheral acrylic adhesive	Siliconecoated polyester
Estraderm (estradiol) Alza/Ciba Geigy	Drug and alcohol gelled with hydroxypropyl cellulose	Polyester, polyethylene composite	EVA copolymer with 5% vinyl acetate	Light mineral oil and PIB	Siliconized polyethylene terephthalate

Testoderm TTS (testosterone) Alza	Drug and alcohol gelled with HPC	Polyester/EVA copolymer	EVA copolymer	PIB	Silicone coated polyester
Transderm Nitro (nitroglycerin) Alza/Ciba-Geigy	Drug adsorbed on lactose, colloidal silica, and silicone oil	Flesh-colored polyfoil	EVA copolymer	Silicone adhesive	Fluorocarbon polyester film
Transderm Scop (scopolamine) Alza/Ciba-Geigy	Scopolamine, light mineral oil, and polyiso butylene	Aluminized polyester film	Microporous polypropylene	Mineral oil, polyiso-butylene	Siliconized polyester

8. IDEAL REQUIREMENTS FOR TDDS:

- ✚ Shelf life up to 2 years
- ✚ Small size patch (i.e., less than 40 cm²)
- ✚ Convenient dose frequency (i.e., once a day to once a week)
- ✚ Cosmetically acceptable (i.e., clear, white colour)
- ✚ Simple packaging (i.e., minimum number of pouches and steps required to apply the system)
- Adequate skin adhesion (i.e., no fall off during the dosing interval and easy removal without skin trauma)
- ✚ No residue i.e., cold flow, around the edge of the patch in storage or after application to skin or beneath the patch after removal)

- ✚ No unacceptable dermal reactions (i.e., contact dermatitis, skin sensitization, photo toxicity, photosensitization, erythema, itching, stinging, burning, etc.)
- ✚ Consistent biopharmaceutical performance (i.e., precision of the required pharmacokinetic and pharmacodynamic response between individuals and in the same individuals over time (Ghosh and Pfister , 1997).

9. EVALUATION PARAMETERS:

The evaluation methods for transdermal dosage form can be classified into following type

- ✓ Physicochemical evaluation
- ✓ In vitro evaluation
- ✓ In vivo evaluation
- ✓ Stability studies (Divyesh *et al.*, 2011; Snigdha *et al.*, 2011).

9.1. Physicochemical evaluation:

✓ **Interaction Studies:**

Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters (Singh *et al.*, 1993).

✓ **Thickness of the Patch:**

The thickness of the drug loaded patch is measured in different points by using a digital micro-

meter and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

✓ **Weight Uniformity:**

The prepared patches are to be dried at 60°C for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

✓ **Folding Endurance:**

A strip of specific area is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

✓ **Percentage Moisture Content:**

The prepared films are to be weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

Percentage moisture content = $[(\text{Initial weight} - \text{Final weight}) / \text{Final weight}] \times 100$

✓ **Percentage Moisture Uptake:**

The weighed films are to be kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.

Percentage moisture uptake = $[(\text{Final weight} - \text{Initial weight}) / \text{initial weight}] \times 100$

✓ **Water Vapour Permeability (WVP) Evaluation:**

Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula: **WVP=W/A**

Where, **WVP** is expressed in gm/m per 24hrs,

W is the amount of vapour permeated through the patch expressed in gm/24hrs and **A** is the surface area of the exposure samples expressed in m².

✓ **Drug Content:**

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug content with the suitable method (UV or HPLC technique). Each value represents average of three different samples (Rhaghuram *et al.*, 2003).

✓ **Content Uniformity Test:**

10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test (Aggarwal and Dhawan, 2009).

✓ **Uniformity of Dosage Unit Test:**

An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was analysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculate (Shaila *et al.*, 2006).

✓ **Polariscope Examination:**

This test is to be performed to examine the drug crystals from patch by polariscope. A specific surface area of the piece is to be kept on the object slide and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch

✓ **Shear Adhesion Test:**

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of cross linking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength (Aarti *et al.*, 1995).

✓ **Adhesive Studies:**

- **Tack Properties:** It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer (Aarti *et al.*, 1995).
- **Thumb Tack Test:** It is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected.
- **Peel Adhesion Test:** In this test, a length of tape is adhered to a surface and then the tape is removed by lifting away from the surface in a specified manner. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. The results are reported as the force required for a given width of tape. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180° angle, and the force required for tape removed is measured (Aarti *et al.*, 1995).

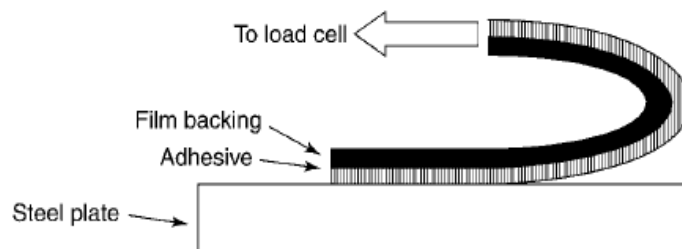


Figure- 14: Peel Adhesion test.

- **Flatness Test:** Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness. $\% \text{ constriction} = \frac{I1 - I2}{I1} \times 100$

Where, I1 = Initial length of each strip. I2 = final length of each strip.

- **Rolling Ball Tack Test:** This test measures the softness of a polymer that relates to tack. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch (Lec *et al.*, 1991).

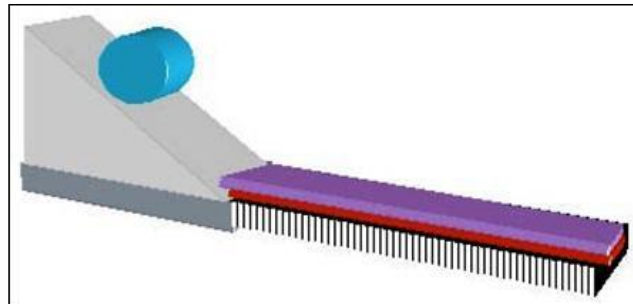


Figure- 15: Rolling ball tack test.

- **Quick stick (peel-tack) Test:** In this test, the tape is pulled away from the substrate at 90°C at a speed of 12 inches/min. The peel force required breaking the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

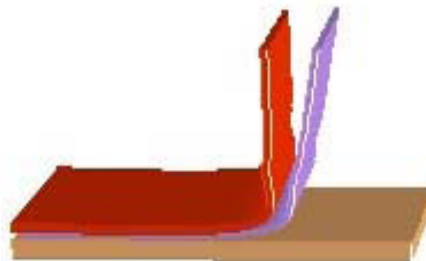


Figure- 16: Quick stick (peel-tack) tests.

- Probe Tack Test:** The Experimental technique known as probe tack is designed to test the adhesive properties of film for very short contact times. In this test, a flat- ended cylindrical probe is brought in contact with the adhesive film which is deposited on a rigid substrate. The probe is then maintained in contact under a controlled pressure for a certain contact time. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams (Karande *et al.*, 2005).

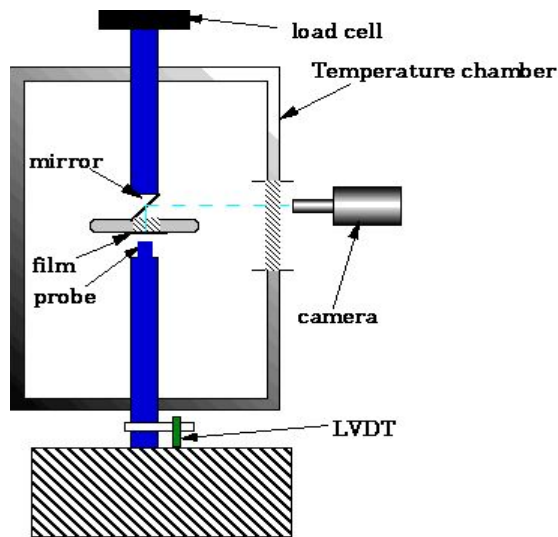


Figure- 17: Probe Tack test.

- Percentage Elongation Break Test:** The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula.

$$\text{Elongation percentage} = \frac{L1-L2}{L2} \times 100$$

Where, **L1** is the final length of each strip and **L2** is the initial length of each strip.

- Shear strength properties or creep resistance:** Shear strength is the measurement of the cohesive strength of an adhesive polymer i.e., device should not slip on application determined by measuring the time it takes to pull an adhesive coated tape off a stainless plate. The test performed with an apparatus which was fabricated according to PSTC-7 (pressure sensitive tape council) specification (Karande *et al.*, 2005).

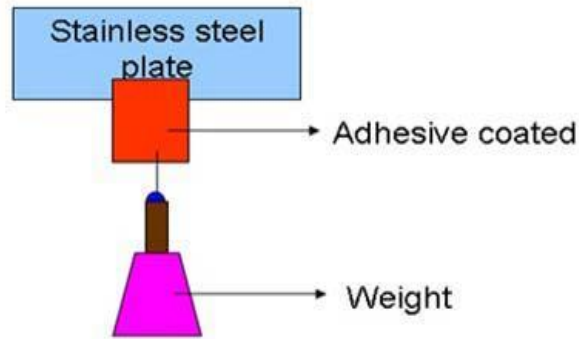


Figure- 18: Shear strength properties or creep resistance.

9.2. In Vitro Evaluation:

✓ In vitro drug release studies:

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to $32 \pm 0.5^\circ\text{C}$. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5 ml aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated (Singh *et al.*, 1993).

✓ In vitro skin permeation studies:

An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at $32 \pm 0.5^\circ\text{C}$ using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with

the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or H LC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated mg cm² vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load mg cm (Singh *et al.*, 1993).

✚ **Horizontal-type skin permeation system:** This has been widely used for the evaluation of drug permeation across skin. The cell is divided in receptor and donor compartments with a low solution volume (3.5ml) for each compartment and a small membrane area (0.64cm²). They are continuously stirred by matched set of star-head magnets, which are rotated at a speed of 600rpm. The system is controlled by thermo stated water through a water jacket surrounding the two compartments (Patel *et al.*, 2012).

✚ **Franz diffusion cell:** The cell is composed of two compartments: donor and receptor. The receptor compartment has a volume of 5-12ml and effective surface area of 1-5 cm². The diffusion buffer is continuously stirred at 600rpm by a magnetic bar. The temperature in the bulk of the solution is maintained by circulating thermostated water through a water jacket that surrounds the receptor compartment (Patel *et al.*, 2012).

✚ **Flow-through diffusion cell:** Flow through diffusion cells have the advantage that they can be used when the drug has lower solubility in the receptor compartment. This cell can be fully automated and connected directly to HPLC. They have large capacity donor chamber to aloe appropriate loading of the applied compound and a low volume (0.3ml) receiving chamber that ensures rapid removal of penetrant at relatively low pumping rates (Patel *et al.*, 2012).

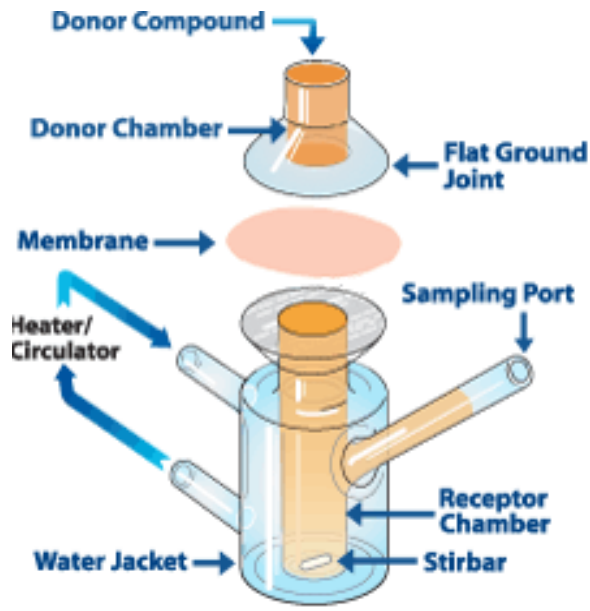


Figure- 19: Cell Franz diffusion apparatus.

9.3. In Vivo Evaluation Studies:

✓ **In vivo Evaluation:**

In vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using:

- ✓ **Animal models**
- ✓ **Human volunteers**
- ✓ **Biophysical models**
- **Animal models:** Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted lead us to a conclusion that hairless animals are preferred over hairy animals in both in vitro and in vivo experiments. Rhesus monkey is one of the most reliable models for in vivo evaluation of transdermal drug delivery in man (Aggarwal and Dhawan, 2009).

- **Human models:** The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug (Aggarwal and Dhawan, 2009).
- **Biophysical Models:** Models based on steady-state mass balance equation, solution of Fick's second law of diffusion for the device, stratum corneum and viable epidermis, as well as linear kinetics have been described in the literature. It can be concluded that many techniques for in-vivo evaluation of transdermal systems have been put forward there is scope for further refinement. Some of the unresolved issues include the barrier function of the skin with age, skin metabolism, in-vivo functioning of penetration enhancers etc (Aggarwal and Dhawan, 2009).

✓ **Skin Irritation study:**

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm²) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury (Shaila *et al.*, 2006).

9.4. Stability studies:

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°C and 75±5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content (Singh *et al.*, 1993).

10. THERAPEUTIC APPLICATIONS OF TDDS:

- ✦ Hisetal, used in the treatment of multiple sclerosis may be formulated in TDDS using oleic acid as permeation enhancer to achieve sufficient drug delivery (Ruland *et al.*, 1994).
- ✦ Diclofenac sodium, celecoxib used as Non- Steroidal Anti Inflammatory Drugs (NSAIDs), formulated in TDDS may overcome the gastric lesions associated with oral dosing (Rana *et al.*, 1999; Yener *et al.*, 2003).
- ✦ Drugs used for long term dosing in the chronic diseases like captopril, verapamil, terbutaline sulphate, pinacidil, propranolol which have a short biological half life, considerable first pass metabolism may be formulated as TDDS to achieve prolonged steady state plasma concentration (Koteshwar *et al.*, 1992; Paranjothy and Thampi, 1997; Kulkarni *et al.*, 2004; Aqil *et al.*, 2006; Dey *et al.*, 2007).
- ✦ Hydrophilic polymers like polyvinylpyrrolidone may provide faster drug release whereas hydrophobic polymers like ethyl cellulose can provide prolonged drug delivery (Dey *et al.*, 2007).
- ✦ Gel formulation with lipid disperse system of betahistine has potential for the development of an efficient controlled release transdermal system (Ogiso *et al.*, 1994).
- ✦ Enhancer and co-solvent may synergistically enhance the delivery of peptides like thyrotropin releasing hormone across the human skin (Magnusson *et al.*, 1997).
- ✦ Prazosin Hydrochloride in membrane controlled TDDS may deliver the drug enough to maintain the minimum effective concentration and can avoid hypotension associated with high initial oral dosing (Rajendran *et al.*, 1997).
- ✦ TDDS of indomethacin in polyvinylpyrrolidone polymer (acting as antinucleating agent) may provide better anti-inflammatory activity and lower ulcer indices compared to oral administration (Rao and Diwan, 1998).

- ✦ Diclofenac sodium, existing in anionic form at skin pH may be formulated as ion-pairs with oppositely charged enhancers to enhance the transdermal delivery compared to non-ion paired forms (Rana *et al.*, 1999).
- ✦ Iontophoresis may increase the permeation rate of hydrophilic atenolol to a greater extent than permeation enhancer and overcome incomplete absorption in the gastrointestinal (GI) tract (Bhaskaran *et al.*, 2000).
- ✦ Nimesulide in sodium alginate transdermal gel may provide better analgesic and anti-inflammatory activity and avoid the adverse effects associated with long term treatment with high oral dosing (Pandey *et al.*, 2000).
- ✦ Terbutaline sulphate, being diamagnetic, may be incorporated in the magnetic TDDS to experience driving force to escape from the applied magnetic field and enhance diffusion across the skin (Murthy *et al.*, 2001).
- ✦ Bupropion Hydrochloride, an antidepressant drug may be converted to free base to increase the lipophilicity and transdermal delivery and avoid the release of fatal metabolites associated with oral dosing (Gondaliya and Pundarikakshudu, 2003).
- ✦ Zidovudine, an anti-Human Immuno Deficiency Virus (anti-HIV) drug, formulated in TDDS may overcome toxic effects associated with frequent higher oral dose (Suwanpidokkul *et al.*, 2004).
- ✦ Levonorgestrel, a potent contraceptive agent, formulated as transdermal protransferosome gel may provide enhanced, prolonged and controlled delivery and overcome the GI disturbances, weight gain, irregular bleeding, headache etc. associated with oral dosing (Jain *et al.*, 2005).
- ✦ Polymerized rosin may be used to design the matrix type TDDS of Diltiazem Hydrochloride to prolong the drug release and avoid the variable and extensive first pass metabolism on oral dose (Satturwar *et al.*, 2005).

- ✚ Ester prodrug of ketorolac may provide enhanced permeation whereas nanostructured lipid carrier can act as controlled release system and avoid the gastric ulceration and renal failure associated with frequent long term oral dosing (Puglia *et al.*, 2006).

11. RECENT TECHNIQUES FOR ENHANCING TRANSDERMAL DRUG DELIVERY:

11.1. Structure-Based Enhancement Techniques:

✓ 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 microneedles 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 fibers are located into deeper region of the skin. Moreover distance to be travelled by drug will decrease (Kapoor *et al.*, 2011).

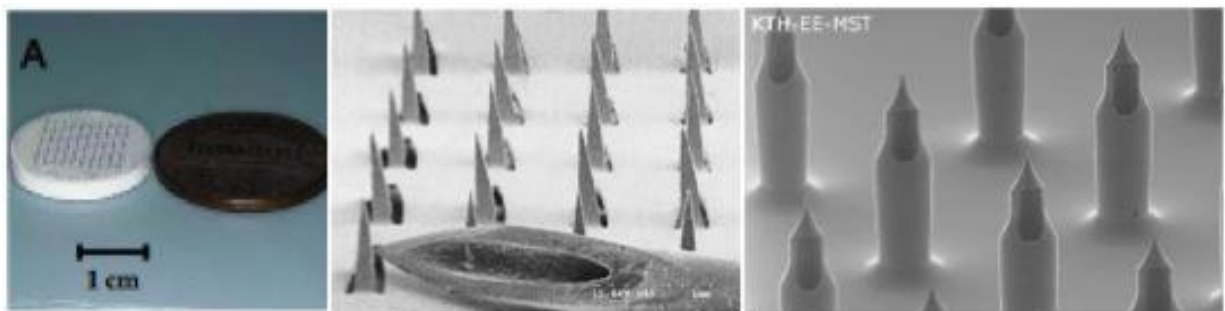


Figure- 20: Design of micro needle delivery device.

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

- ✚ **Poke with patch approach:** Involves piercing into the skin followed by application of the drug patch at the site of treatment.
- ✚ **Coat and poke approach:** Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.
- ✚ **Biodegradable microneedles:** Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin.
- ✚ **Hollow microneedles:** Involves injecting the drug through the needle with a hollow bore (Kapoor *et al.*, 2011; Ritesh and Anil, 2007).

✓ **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 8 cm² 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 peptidic hormones, and vaccines. With this new system; patients can receive drugs for 12 weeks (Ahad *et al.*, 2010; Ritesh and Anil, 2007). Three types of Macroflux have been designed. They include,

- ✚ **Dry-Coated Macro flux system:** This is used for short period delivery that consists microprojection array coated with medicament that adhered to a elastic polymer adhesive backing.
- ✚ **D-TRANS Macro flux system:** This is also for short duration administration that consists of a microprojection array combined with reservoir of drug.

✚ **E-TRANS Macro flux system:** This is for on demand delivery that involves a microprojection array combined with an electrotransport system (Ahad *et al.*, 2010; Ritesh and Anil, 2007).

✓ **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:

- ✚ It improves delivery potential without skin irritation due to its non-occlusive nature.
- ✚ Increased acceptability Dose flexibility
- ✚ Simple manufacture (Gaur *et al.*, 2009; Kapoor *et al.*, 2011).

11.2. Electrically-Based Enhancement Techniques:

✓ **Iontophoresis:**

In iontophoretic delivery devices, Drug is placed on the skin under the active electrode, and a current ($< 0.5\text{mA}$) 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 (Kapoor *et al.*, 2011; Ritesh and Anil, 2007).

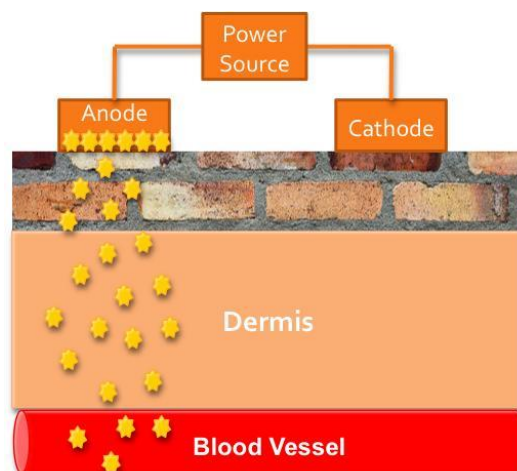


Figure- 21: Electrophoresis.

✓ **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 (Kapoor *et al.*, 2011; Ritesh and Anil, 2007; Gaur *et al.*, 2009).

✓ **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 (Naik *et al.*, 2009).

✓ **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 (Ahad *et al.*, 2010).

✓ **Electro-Osmosis:**

If a charged porous membrane is subjected to a voltage difference, a bulk fluid or volumes flow, called electro osmosis (Soni *et al.*, 2009; Ahad *et al.*, 2010).


11.3. Velocity Based Enhancement Techniques:

✓ **Needle-Free Injections:**

 Intraject


 Implaject

 Jet Syringe

 Iject

 Mini-ject

 Cross jet

 Jet Syringe (Arunachalam *et al.*, 2010; Ritesh and Anil, 2007).

✓ **Powderject Device:**

The powderject system fires solid particles (20-100 μm) through stratum corneum into lower skin layers, using a supersonic shock wave of helium gas (Gaur *et al.*, 2009).

11.4. Other Enhancement Techniques:

✓ **Liposomes:**

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 (Kapoor *et al.*, 2011; Ritesh and Anil, 2007; Soni *et al.*, 2009; Ahad *et al.*, 2010).

✓ **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 (Kapoor *et al.*, 2011; Soni *et al.*, 2009).

✓ **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 (Ritesh and Anil, 2007; Soni *et al.*, 2009).

✓ **Medicated Tattoos:**

Med-Tats is 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 (Ahad *et al.*, 2010; Snigdha *et al.*, 2011).

✓ **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 (Kapoor *et al.*, 2011; Soni *et al.*, 2009).

✓ **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 (Kapoor *et al.*, 2011; Snigdha *et al.*, 2011).

✓ **Magnetophoresis:**

The effect of magnetic field on diffusion flux of drug substance was found to enhance with increasing applied strength (Snigdha *et al.*, 2011).

13. RECENT ADVANCEMENT IN TDDS:

✓ Mucha *et al.* (2013) carried out a research on controlled delivery kinetics of Ibuprofen in transdermal patch. They used chitosan (CS) based materials in a form of composite with poly

(lactic acid) (PLA) granules; films and freeze-dried scaffolds also with blended form with hydroxypropylcellulose (HPC). And excellent adhesion of biopolymer matrices to PLA microspheres or hydroxyapatite (HAp) particles was proven. The order drug (ibuprofen (IBU)) release kinetics from obtained films is stated (Mucha *et al.*, 2013).

- ✓ Vitorino *et al.* (2013) carried out a research on delivering co-encapsulation of drugs as transdermal patch. In this work, a comprehensive study for the co-encapsulation of drugs with a differential lipophilicity, olanzapine and simvastatin, and their transdermal delivery in a formulation containing nanostructured lipid carriers (NLC) is presented. They found that the external medium in the NLC dispersion strongly influences permeation. He also seen that the use of NLC determines a synergistic effect with selected permeation enhancers, thus promoting marked flux enhancement ratios (48 and 21, respectively for olanzapine and simvastatin) relative to the drugs in solution. The developed formulations can be considered non-irritant (Vitorino *et al.*, 2013).
- ✓ Shi *et al.* (2013) carried out a research based on drug loaded nanofibers to improve the performances of transdermal patches. They used electrospin ibuprofen (IBU)-loaded composite nanofibers for their research. Cellulose acetate/poly(vinyl pyrrolidone) (CA/PVP) blends were used to fabricate uniform nanofibers. Investigations on the physicochemical properties of CA/PVP solutions indicated that the addition of appropriate PVP improved the electrospinnability of original CA solutions. Detections on the physical states of IBU in medicated CA/PVP nanofibers suggested that IBU was uniformly distributed in nanofibers in an amorphous state. Furthermore, CA/PVP nanofibers exhibited a high water vapor permeability, which could render an improved breathability to transdermal patches. They concluded that, the electrospun drug-loaded CA/PVP nanofibers exhibited great potentials to improve the thermodynamic stability and breathability of transdermal patches, which could be used to develop new types of transdermal drug delivery system (TDDS) (Shi *et al.*, 2013).
- ✓ Gaur *et al.* (2013) carried out a research on developing Diclofenac sodium loaded solid lipid nanoparticles (SLNs). They used guggul lipid as major lipid component and analyzed for physical parameters, permeation profile, and anti-inflammatory activity. The SLNs were prepared using melt-emulsion sonication/low temperature-solidification method and characterized for physical parameters, in vitro drug release, and accelerated stability studies,

and formulated into gel. Respective gels were compared with a commercial emulgel (CEG) and plain carbopol gel containing drug (CG) for ex vivo and in vivo drug permeation and anti-inflammatory activity. The SLNs were stable with optimum physical parameters. They found that physicochemical properties of major lipid component govern the properties of SLN. SLN made up of guggul lipid showed good physical properties with acceptable stability. Furthermore, it showed a controlled drug release profile along with a promising permeation profile (Gaur *et al.*, 2013).

- ✓ Donnelly *et al.* (2012) carried out a research on developing Hydrogel-Forming Microneedle Arrays. They used crosslinked polymers to produce unique microneedle arrays. Crosslinked polymers rapidly take up skin interstitial fluid upon skin insertion to form continuous, unblockable, hydrogel conduits from attached patch-type drug reservoirs to the dermal microcirculation. They found, such microneedles, which can be fabricated in a wide range of patch sizes and microneedle geometries, can be easily sterilized, resist hole closure while in place, and are removed completely intact from the skin. They established that, this technology has the potential to overcome the limitations of conventional microneedle designs and greatly increase the range of the type of drug that is deliverable transdermally, with ensuing benefits for industry, healthcare providers and, ultimately, patients (Donnelly *et al.*, 2012).
- ✓ Zhang *et al.* (2011) reported that Genetronics Inc (San Diego, California) have developed a prototype electroporation transdermal device. This device has been tested with various compounds with a view to achieving gene delivery, improving drug delivery and aiding the application of cosmetics (Zhang *et al.*, 2011).

14. CONCLUSION:

During the past decade, the number of drugs formulated in the patches has hardly increased, and there has been little change in the composition of the patch systems. Modifications have been mostly limited to refinements of the materials used. The reason is the only a limited number of drugs fit the molecular weight, and potency requirements for transdermal absorption. A rich area of research in recent 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.

However, subjective and objective analysis of these devices is required to make sure both scientific, regulatory and consumer needs are met. The devices in development are more costly and complicated compared to conventional transdermal patch therapies. In addition, effects of the device on the skin must be reversible, since any permanent damage to the SC will result in the loss of its barrier properties and hence its function as a protective organ. Regulatory bodies will also require data to substantiate the safety of the device on the skin for either short or long term use. Thus, for any of these novel drug delivery technologies to succeed and compete with those already on the market, their safety, efficacy, portability, user-friendliness, cost-effectiveness and potential market has to be addressed.

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