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## Review Article

### TRANSDERMAL PATCHES: A REVIEW ON NOVEL APPROACH FOR DRUG DELIVERY

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#### Abstract

Transdermal drug delivery represents one of the most rapidly advancing areas and established itself as an integral part of novel drug delivery systems. Today about 74% of drugs are taken orally and are found not to be as effective as desired. Drug delivery through the skin to achieve a systemic effect without producing any fluctuations in plasma concentration of the drug. Drugs that are given by transdermal route may enhance the potency as well as safety of drugs. A transdermal drug delivery device (pharmaceutical preparation of varying sizes, containing, one or more active ingredient), which provides an alternative route for administering medication defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation therefore system can improve the therapeutic efficacy and safety of the drugs. These devices allow for pharmaceuticals to be delivered across the skin barrier. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. Transdermal drug technology specialists are continuing to search for new methods that can effectively and painlessly deliver larger molecules in therapeutic quantities to overcome the difficulties associated with the oral route.

**Keywords:** transdermal delivery, plasma concentration, potency, therapeutic efficacy, adhesive, systemic circulation, active ingredient, self contained, controlled release.

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#### INTRODUCTION(1,2)

Drugs administered in the conventional dosage forms usually produce large range in fluctuations in plasma drug concentrations leading to undesirable toxicity or poor effectiveness. These factors as well as other factors such as repetitive dosing and unpredictable absorption, led to the concept of the controlled drug delivery system or therapeutic system. A dosage form that releases one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ is a controlled drug delivery system. The primary objectives of

controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing. The most common, form of delivery of drugs is the oral route. It has the notable advantage of easy administration, but also have significant drawbacks – namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and or frequent dosing, which can be both cost prohibitive and inconvenient. To

overcome these difficulties there was a need for the development of new drug delivery system; which can improve the therapeutic efficacy and safety of drugs by more precise spatial and temporal placement within the body thereby reducing both the size and number of doses.

Transdermal drug delivery system is defined as the topically administered medications in the form of patches which when applied to the skin deliver the drug, through the skin at a predetermined and controlled rate. The Transdermal device is a membrane-moderated system. The membrane in this system is a microporous polypropylene film. The drug reservoir is a solution of the drug in a mixture of mineral oil and polyisobutylene. This study release is maintained over a three-day period. Transdermal patches are delivered the drug through the skin in controlled and predetermined manner in order to increase the therapeutic efficacy of drug and reduced side effect of drug. Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver the drug via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time. For effective Transdermal drug delivery system, the drugs are easily able to penetrate the skin and easily reach the target site. TDDS increase the patient compliance and reduces the load as compared to oral route. FDA approved the first Transdermal system Transderm-SCOP in 1979, for the prevention of nausea and vomiting associated with ravel, particularly by sea. Nicotin patch was the very first transdermal patch in market of India.

Transdermal therapeutic systems are also defined as a self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at control rate to the systemic circulation. Transdermal formulation maintain drug concentration within the therapeutic window for prolong period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration. Transdermal drug delivery systems are topically administered medicaments. In the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate.

A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. Transdermal patches are flexible pharmaceutical preparation of varying sizes, containing, one or more active ingredients. They are intended to be applied to the unbroken skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers.

These devices allow for pharmaceuticals to be delivered across the skin barrier. Theoretically, transdermal patches works in a very simple way. A drug is applied in a relatively high dosage to the inside of patch, which is worn on the skin for an extended period of time. Though a diffusion process, the drug enters the bloodstream directly through the skin.

Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood; the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.

Recently, the use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven to be effectively delivered through the skin, typically cardiac drugs such as nitroglycerin and hormones such as estrogen. A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. The basic components of any transdermal delivery system include the drug(s) dissolved or dispersed in a reservoir or inert polymer matrix; an outer backing film of paper, plastic, or foil, and a pressure-sensitive adhesive that anchors the patch to the skin. The adhesive is covered by a release liner which needs to be peeled off before applying the patch to the skin. Drugs administered via skin patches include scopolamine, nicotine, estrogen, nitroglycerin, and lidocaine. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives, and eliminates pulsed entry into systemic circulation which often causes undesirable side effects.

#### IDEAL PROPERTIES OF TDDS

The ideal properties of Transdermal drug delivery system are;

- Optimum partition coefficient required for the therapeutic action of drug.
- Shelf life up to 2 years.
- Low melting point of the drug is desired which is less than 200°C.
- Patch size should be  $<40\text{cm}^2$ .
- The pH of the saturated solution should be between 5 to 9.

#### ADVANTAGES OF TRANSDERMAL PATCHES( 2,3)

The advantages of transdermal delivery are obvious even delivery of a therapeutic level of drug is painless, the patient does not need to inject himself, there are no bulky delivery devices to manage or dangerous needles to dispose of, and there are few or no

gastrointestinal effects from the drug itself. Peak plasma levels of the drug are reduced, leading to decreased side effects. In addition, transdermal delivery is useful for those drugs that have a high first pass effect through the liver, have poor oral uptake, need frequent administration, or that interact with stomach acid. The first pass effect results in the destruction of a significant amount of the drug.

Drugs absorbed through the skin, however, enter the general circulation directly avoiding the liver, with less total drug absorption occurring

- ✓ Topical patches are a painless, non-invasive way to deliver substances directly into the body.
- ✓ Topical patches are a better way to deliver substances that are broken down by the stomach acids, not well-absorbed from the gut, or extensively degraded by the liver.
- ✓ Topical patches over a controlled, steady delivery of medication over long periods of time.
- ✓ Topical patches have fewer side effects than oral medications or supplements.
- ✓ Topical patches are easier to use and remember.
- ✓ Topical patches over an alternative to people who cannot, or prefer not to take medications or supplements orally.
- ✓ Topical patches are cost-effective.
- ✓ People prefer topical patches.
- ✓ Transdermal patch of nicotine, which releases nicotine in controlled doses to help with cessation of tobacco smoking.
- ✓ Nitroglycerine patches are also sometimes prescribed for the treatment of Angina.
- ✓ Clonidine, the antihypertensive drug and ketoprofen, the non-steroidal anti-inflammatory drug are also available in the form of transdermal patches.
- ✓ Transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant.
- ✓ Transdermal delivery agent for the Attention Deficit Hyperactivity Disorder (ADHD).

#### FUNDAMENTALS OF SKIN PERMEATION(4)

Transdermal permeation is based on passive diffusion. Before a topically applied drug can act either locally or systemically, it must penetrate the stratum corneum – the skin permeation barrier. In the initial transient diffusion stage drug molecules may penetrate the skin along the hair follicles or sweat ducts and then absorbed through the follicular epithelium through the intact stratum corneum becomes the primary pathway

for transdermal permeation. The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process, which involves

- Dissolution within and release from the formulation.
- Partitioning into the skin's outermost layer, the stratum corneum.
- Diffusion through the SC, principally via a lipidic intercellular pathway.
- Partitioning from the SC into the aqueous viable epidermis, diffusion through the viable epidermis and into the upper dermis, and uptake into the papillary dermis and into the microcirculation.

The phenomenon of percutaneous absorption can be visualized as a of series of steps in sequence, sorption of a molecule onto the surface layer of stratum corneum, diffusion through it and various layers of epidermis. Finally at the papillary layer of dermis, the molecule is taken up in to microcirculation for subsequent systemic distribution. The viable tissue layers and capillaries are relatively permeable and peripheral circulation is sufficiently rapid.

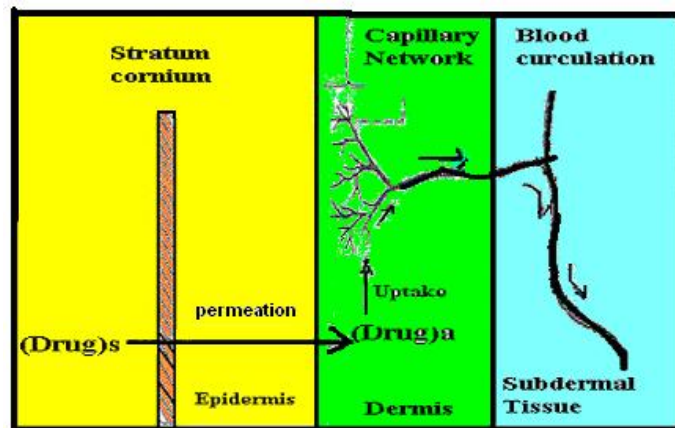


Figure no. 2: A multilayer skin model showing sequence of Transdermal permeation of drug for systemic delivery

#### FACTORS THAT INFLUENCE TRANSDERMAL DELIVERY(5,6,7)

1. Biological parameters
2. Physicochemical parameters

##### 1. Biological parameters:

**a) Skin Condition:** The skin is a tough barrier to penetration, but only if it is intact. Vesicants such as acid, alkalis injure barrier cells and there by promote penetration. In disease characterized by defective stratum corneum, percutaneous absorption increases.

**b) Blood flow:** Theoretically, changes in peripheral circulation, or blood flow through the dermis, could affect percutaneous absorption. Thus an increased blood flow could reduce time for which a penetrant remain in the dermis and also raise the concentration gradient across the skin.

**c) Regional skin sites:** Variation in cutaneous permeability around the body depends on the thickness and the nature of stratum corneum and the density of skin appendages. However rate of absorption at identical skin sites in different healthy volunteers varies.

**d) Skin metabolism:** It has been recently reviewed the role which the skin plays in metabolism of drugs and steroidal hormones. The topical bioavailability should account for not only skin permeation but also cutaneous drug metabolism.

**e) Species differences:** Mammalian skin differs widely in characteristics such as horny layer thickness, sweat gland and hair follicle densities, and pelt condition, the capillary blood supply and the sweating ability from species to species, so affect the permeation.

## 2. Physicochemical parameters:

**a) Hydration of skin:** When water saturates the skin; tissue swells, softens and wrinkles and its permeability increases markedly. In fact, hydration of stratum corneum is one of important factor in increasing the penetration rate of most substances that permeate the skin.

**b) Temperature:** The penetration rate of material through the human skin can change tenfold for large temperature variation, as the diffusion coefficient decreases as the temperature falls. Occlusive vehicles increase skin temperature by few degrees, but any consequent increased permeability is small compared to effect of hydration.

**c) Diffusion coefficient:** The diffusional speed of molecule depends mainly on state of matter in the medium. In gases and air, diffusion coefficients are large because the void space available to the molecules is large as compared to their size.

**d) Drug concentration:** The drug permeation usually follows the Fick's law. The flux of solute is proportional to the concentration gradient across the entire barrier phase.

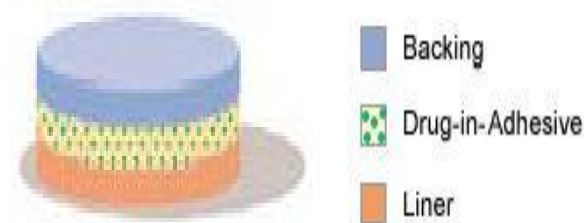
**e) Partition Coefficient:** Partition coefficient is important in establishing the flux of the drug through the stratum corneum. The balanced partition coefficient is required for drug permeation.

**f) Molecular size:** Absorption is apparently inversely related to molecular weight. Small molecule penetrates faster than large one.

## TYPES OF TRANSDERMAL PATCHES(7,8,9)

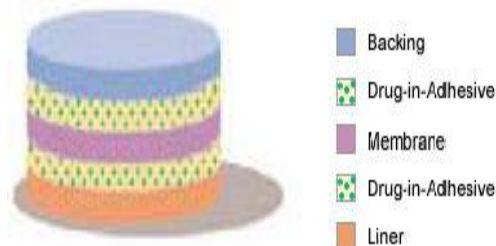
### a) Single layer drug in adhesive

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.



### b) Multi -layer drug in adhesive

This type is also similar to the single layer but it contains an 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.

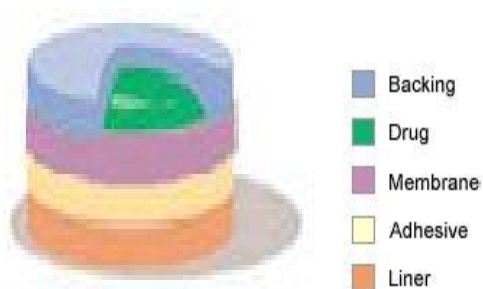


### c) Vapour patch

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 vapour patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

**d) 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.

**e) Matrix system****i. 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.

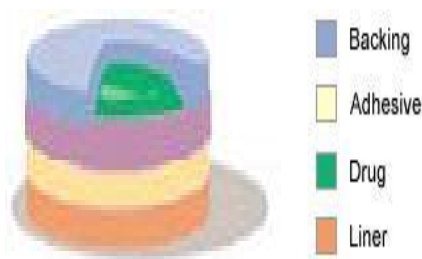
**ii. Matrix-dispersion system**

In this type the drug is dispersed homogeneously 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.

**f) Microreservoir system**

In this type the drug delivery system is a combination of reservoir and matrix-dispersion system. 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. This thermodynamically unstable dispersion is stabilized

quickly by immediately cross-linking the polymer in situ by using cross linking agents.

**COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM(10,11,12)**

The main components to a transdermal patch are:

**1. Release liner:** Release liner protects the patch during storage. The liner is removed prior to use.

**2. Drug reservoir:** It consists of drug particles dissolved or dispersed in the matrix. The drug reservoir is sandwiched between a drug-impermeable backing laminate and a rate controlling polymeric membrane.

**3. Adhesive:** Adhesive serves to adhere the components of the patch together along with adhering the patch to the skin. Patches generally consist of a porous membrane, a drug, an adhesive and a release-liner. The pressure-sensitive adhesives are based on natural or synthetic rubbers, polyacrylates or silicone. Many manufacturers prefer silicone adhesives because they are kind to the skin. They are also chemically stable, biologically inert, and transparent, retain adhesive properties in the presence of moisture, and have high permeability. The release liner, or peel-away strip, consists of paper, polystyrene, polyethylene, polyester or other polymeric films with a light coating of compounds such as silicones. Natural rubber and polyisobutylene were the earliest polymers used for formulating medical pressure sensitive adhesive (PSAs) due to their high peel strength, elongation, and ease of acceptance by skin tissue. However these are now largely replaced with modern, synthetic polymers as described below.

A. Acrylic based adhesives, are widely used. These are used in varied applications due to their good adhesive qualities and low levels of allergenicity.

B. Silicone based adhesives are used in devices needing an inert and biocompatible adhesive.

C. Polyvinyl ether based adhesive are employed in moisture permeable skin patches.

**4. Membrane:** Membrane controls the release of the drug from the reservoir and multi-layer patches. It may



or may not be rate-controlling membrane. It should be flexible enough not to split or crack on bending or stretching. Some of rate-controlling membranes are polyethylene sheets, ethylene vinyl acetate copolymer, and cellulose acetate.

**5. Backing membrane:** Backing Membrane should be flexible and should provide a good bond to reservoir. It should be impermeable to the drug. Polymers like LDPE, LLDPE, MDPE and polyurethane are used in backing membrane. Membrane can be mono layer or multilayered.

**6. Other excipients:**

**A) Penetration enhancers:**

These are compounds, which promotes skin permeability by altering the skin as a barrier to the flux of a drug. Desirable properties of penetration enhancers are as follows.

- ✓ Pharmacologically inert.
- ✓ Nontoxic, nonirritating and nonallergic.
- ✓ Rapid onset of action, predictable and suitable duration of action for the drug used.
- ✓ Following removal of the enhancer, the stratum corneum should immediately and fully remove its normal barrier property.
- ✓ The barrier function of the skin should decrease in one direction only and flux of endogenous materials should not occur.
- ✓ Chemically and physically compatible with the delivery system.
- ✓ Readily incorporated in to the delivery system.
- ✓ Inexpensive and cosmetically acceptable.

**Examples:** Dimethyl sulfoxide (DMSO), N, N-Dimethylformamide (DMF), Pyrrolidones, Tetrahydrofurfuryl alcohol (THFA).

**B) Solvents:** Alcohols and ethanol, in particular have been proposed as effective permeation enhancer.

**Examples:** Acetamide and derivatives, acetone, Dimethyl acetamide, Diethyl acetamide, Ethanol.

**C) Surfactant:** These compounds are proposed to enhance substances polar transport, specific all hydrophilic drug. The ability of surfactant to alter the penetration is a function of polar head group and hydrocarbon chain length. Commonly used surfactants are.

**Anionic surfactants:** Dioctylsulthosuccinate, sodium lauryl sulfate, decodecylmethyl sulphoxaide.

**Nonionic surfactants:** Pluronic F-127, pluronic F-66.

**Bile salts:** Sodium taurocholate, sodium deoxycholate, sodium tauroglycocholate.

**MECHANISM OF ACTION OF TRANSDERMAL PATCHES(13,14,15)**

The application of the transdermal patch and the flow of the active drug constituent from the patch to the circulatory system via skin occur through various methods.

**1. Iontophoresis**

Iontophoresis passes a few milliamperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. Mainly used of pilocarpine delivery to induce sweating as part of cystic fibrosis diagnostic test. Iontophoretic delivery of lidocaine appears to be a promising approach for rapid onset of anesthesia.

**2. Electroporation**

Electroporation is a method of application of short, high-voltage electrical pulses to the skin. After electroporation, the permeability of the skin for diffusion of drugs is increased by 4 orders of magnitude. The electrical pulses are believed to form transient aqueous pores in the stratum corneum, through which drug transport occurs. It is safe and the electrical pulses can be administered painlessly using closely spaced electrodes to constrain the electric field within the nerve-free stratum corneum.

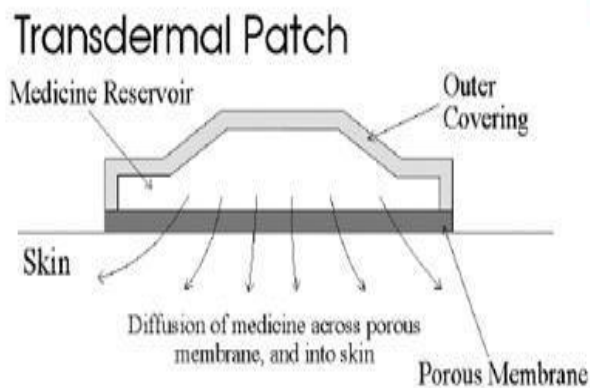


Fig 2: representing mechanism of drug release from transdermal patch

**3. Application by ultrasound**

Application of ultrasound, particularly low frequency ultrasound, has been shown to enhance transdermal

transport of various drugs including macromolecules. It is also known as sonophoresis. Katz et al. reported on the use of low-frequency sonophoresis for topical delivery of EMLA cream.

#### 4. Use of microscopic projection

Transdermal patches with microscopic projections called microneedles were used to facilitate transdermal drug transport. Needles ranging from approximately 10-100  $\mu\text{m}$  in length are arranged in arrays. When pressed into the skin, the arrays make microscopic punctures that are large enough to deliver macromolecules, but small enough that the patient does not feel the penetration or pain. The drug is surface coated on the microneedles to aid in rapid absorption. They are used in development of cutaneous vaccines for tetanus and influenza. Various other methods are also used for the application of the transdermal patches like thermal poration, magnetophoresis, and photomechanical waves. However, these methods are in their early stage of development and required further detail studying.

#### METHODS OF PREPARATION OF TRANSDERMAL PATCHES(15,16,17,18)

Transdermal drug delivery patches can be prepared by various methods:

##### 1. Mercury Substrate Method:

In this method required amount of drug is dissolved in predetermined amount of polymer solution along with plasticizer. The above solution is to be stirred for some time to produce a homogenous dispersion and it is kept aside until air bubbles removed completely and then poured in to a glass ring which is placed over the mercury surface in a glass petridish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the petridish. The dried films are to be stored in desiccators.

##### 2. 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. Plasticizer added into drug polymer solution. The total contents are to be stirred and then poured into a circular teflon mould. And rate of solvent vaporization controlled with placing inverted glass funnel on teflon mould. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored in desiccators.

##### 3. Glass Substrate Method:

The polymeric solutions are kept a side for swelling then required quantity of plasticizer and drug solution are added and stirred for 10 min. Further, it is set-a side for some time to exclude any entrapped air and is then poured in a clean and dry anumbra petriplate. The rate of solvent evaporation is controlled by inverting a glass funnel over the petriplate. After over night, the dried films are taken out and stored in desiccators.

##### 4. 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.

##### 5. By Using EVAC Membranes 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.

##### 6. 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 aluminum former is lined with aluminum foil and the ends blanked off with tightly fitting cork blocks.

**FORMULATION TECHNIQUES OF TRANSDERMAL PATCHES**(19,20,21)

- (1) Membrane permeation – controlled system
- (2)

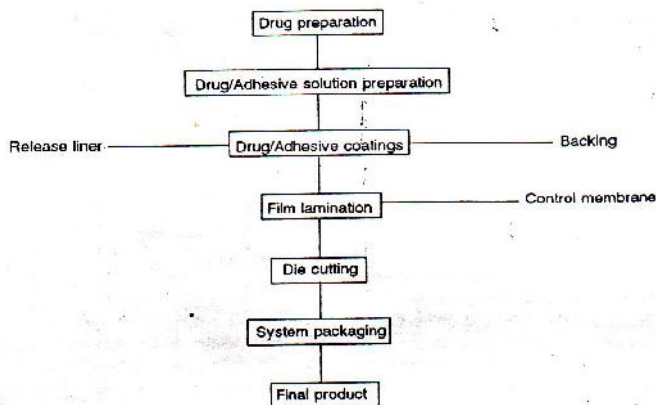


Fig.5: Multilaminar transdermal dosage from manufacturing process flow diagram

**(2) Adhesive dispersion type system**

The manufacturing process these systems can be divided into following parts.

**(I) Preparation of individual matrix solution**

Raw material [Polymer, tackifier, softening agent] is dissolved in an organic solvent to obtain a standard or stock soln. The matrix solution then prepared from the stock solution by mixing it with ingredients specified by the formulation. The active ingredient and other non-soluble additives are added.

**(II) Coating the individual matrix layers**

The individual layers are made by coating the solution (above). On the smooth paper or film web and removing the solvent by drying using coating machine. This machine consists of two units (A) the coating unit (B) drying unit.

**(A) Coating unit**

The solvent based formulations are coated onto the appropriate web. Depending on the viscosity, solid contents, flow ability and surface tension of the matrix solution.

**(B) Drying Unit**

Closed to the environment and is directly connected to the drying unit to avoid solvent and this active agent evaporation. The solvent is evaporated from the adhesive mass by running the coated web through a

drying channel using a transport system like cranked shaft, conveyor belt.

**(I) Building the multilayer laminate**

Lamination is used to build up the multilayer matrix system. Here two matrix layers, each adhering to one side of the web are laminated. Then a carrier material of this two layer laminate is removed and a third layer, with the laminated side to the laminated side of the two layer laminate is pressed. This procedure is repeated until the final laminate is complete.

**(II) Separating unit of the multilayer laminate**

The bulk product is slit longitudinally and the individual unit is punched out from the narrow rolls so obtained. Precision of the operations is of paramount importance here hence it affects the release rate of the active ingredient. Then the liner is applied with the necessary release aids to the system.

**(III) Packaging**

Primary packaging is done using sealed, four cornered while secondary packaging in cardboard boxes precedes shipment.

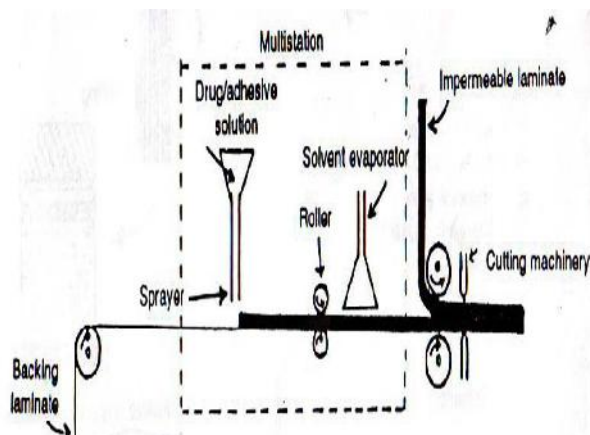


Fig. 6: The process and equipment involved in the manufacture of an adhesive dispersion system

**(3) Matrix diffusion controlled system**

The drug is dispersed in an insoluble matrix of rigid non swellable hydrophobic material. Materials used for rigid matrix are insoluble plastics such as PVC and fatty and materials like stearic and beeswax. With the plastic materials the drug is generally kneaded with the solution of Polyvinyl chloride in an organic solvent and granulated waxy matrix is prepared by dispersing the drug in molten fat followed by congealing.



The granules are then compressed into tablets. Swellable matrix systems are popular for sustaining the release of highly water soluble drug. The material for such matrices are generally hydrophilic gums and may be of natural origin (guar gum, tragacanth) semi synthetic (HPMC, CMC) or synthetic (poly cryamides). The drug and the gum are granulated together with a solvent such as alcohol and compressed into tablets. The release of drug from such initially dehydrated hydro gels involves simultaneous absorption of water and desorption of drug via a swelling controlled diffusion mechanism. The gum swells and the drug diffuses out of it the swollen mass devoid of drug appears transport.

#### (4) Microsealed dissolution-Controlled system or Encapsulation

The drug particles are coated or encapsulated by one of the several micro encapsulation techniques with slowly dissolving materials like cellulose, PEGs, polymethacrylates, waxes. The resulting pellets may be filled as such in hard gelatin capsule. The dissolution role of coat depends upon the solubility and thickness of the coating which may range from 1 to 200 microns.

### TECHNOLOGIES FOR DRUG DEVELOPING TRANSDERMAL DRUG DELIVERY SYSTEMS(22,23,24,25)

The technologies can be classified in four basic approaches.

#### 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 no. 6 shows cross-sectional view of polymer membrane permeation-controlled TDD system.

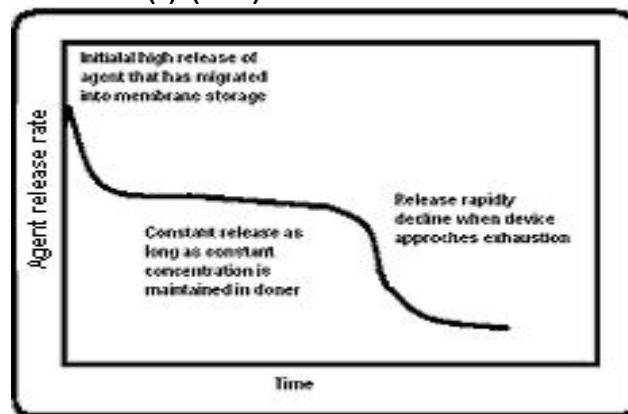
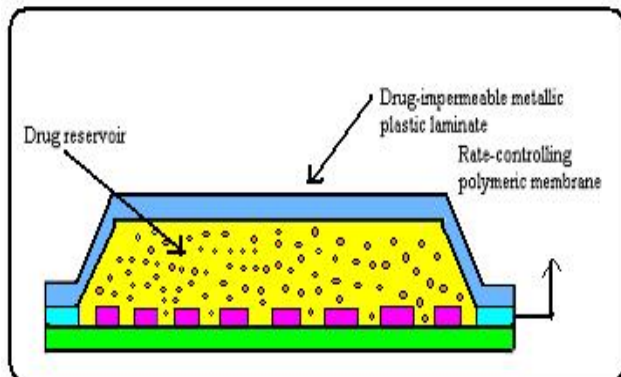
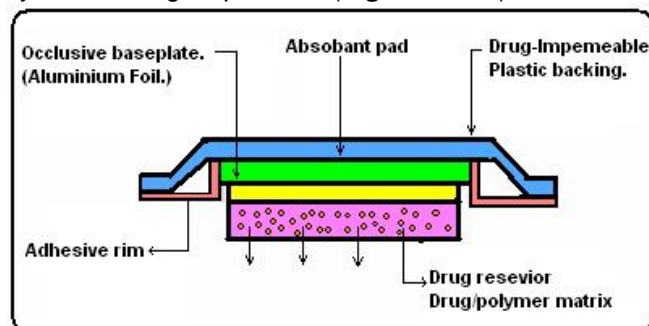


Figure no. 6: Cross-sectional views of polymer membrane permeation-controlled TDD systems and release rate obtained.

The drug molecules are released through the rate controlling membrane. In the drug reservoir component, drug is suspended in viscous fluid that forms paste like suspension. The rate of drug release from this type of TDDS depends on polymer composition, permeability coefficient and thickness of rate controlling membrane. The rate controlling membrane can be either a microporous or a nonporous polymeric membrane. e.g. ethylene-vinyl acetate copolymer, with specific drug permeability e.g. Some US FDA approved systems are Transderm-Nitro for angina pectoris, Transderm-Scop as an antiemetic.

#### B. Polymer matrix diffusion-controlled TDD systems:

Polymer matrix diffusion-controlled TDD systems formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix, and then the medicated polymer is molded into medicated disks with defined surface area and thickness. This drug reservoir containing polymer disk is then mounted on occlusive base plate in a compartment fabricated from a drug-impermeable plastic backing. Instead of coating adhesive polymer directly on the surface of medicated disk, it is applied along the circumference of the patch to form a strip of adhesive rim surrounding the medicated disk. e.g. Nitro-Dur system and NTS system for angina pectoris. (Figure no. 7.)



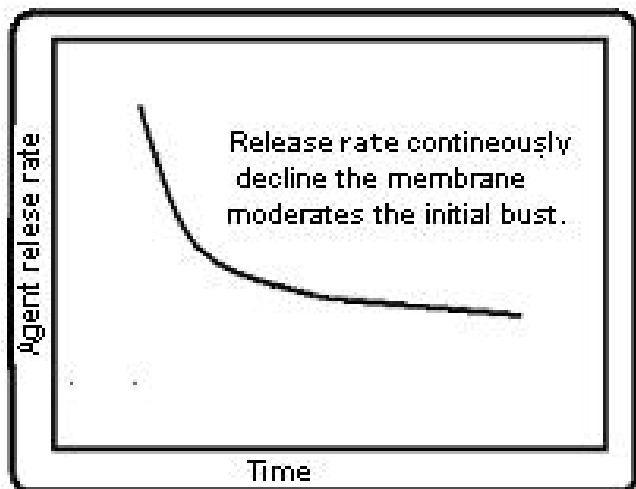


Figure no. 7: Cross-sectional view of polymer matrix diffusion-controlled TDD

**Systems and release rate obtained.**

Alternately, the polymer matrix drug dispersion-type TDD system 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. As compare to reservoir-membrane system, matrix systems have advantages of low cost, ease of fabrication and less risk of dose dumping which is mainly resulted from the damage of membrane.

**C. Drug reservoir gradient-controlled TDD systems:**

Polymer matrix drug dispersion-type TDD systems can be modified to have the drug loading level varied in an incremental manner, forming a gradient of drug reservoir along the diffusional path across the multilaminare adhesive layers.

In this system the thickness of diffusional path through which drug molecules diffuse increases with time. The drug loading level in the multilaminare adhesive layer is also designed to increase proportionally so as to compensate time dependent increase in diffusional path as a result of drug depletion due to release. Thus, theoretically this should yield a more constant drug release profile.e.g. Nitroglycerine TDS for angina pectoris. This type of system is depicted in Figure no. 8.

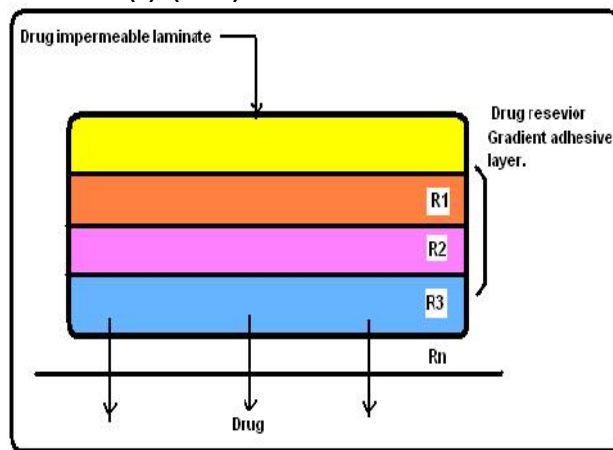


Figure no. 8:Cross-sectional view of a drug reservoir gradient-controlled TDD System.

**D. Microreservoir dissolution-controlled TDD systems:**

This type of delivery systems has some essential features i.e. hybrid of reservoir- and matrix dispersion-type In this approach drug reservoir is formed by first suspending the drug solids in an aqueous solution of water-miscible drug solubilizer. e.g. propylene glycol, then the drug suspension is homogeneously dispersed with lipophilic polymer, by high shear mechanical force, to form thousands of unleachable microscopic drug reservoirs.e.g. Nitrodisk system for angina pectoris. Figure no. 9.

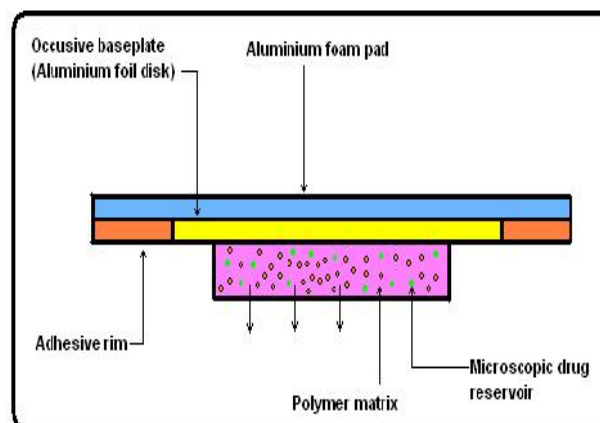


Figure no. 9:Cross-sectional view of a drug microreservoir dissolution-controlled TDD system.

**EVALUATION OF TRANSDERMAL PATCHES(26-34)**

The evaluation of transdermal patches is done to assess the quality and reproducibility. Various evaluation tests includes

**(A) Physical evaluation****(i) Drug content uniformity**

It is determined by taking specific no. of patches and completely dissolving then in specific media. Resulting solution is filtered out through membrane filter. The samples so obtained is analyzed by HPLC or U.V. spectrophotometer.

**(ii) Determination of surface pH**

Specific number of patches are kept in contact with distilled water and excess water is drained and pH noted by pH meter.

**(iii) Holding endurance**

It is calculated by cutting the patch in specific size by using sharp blade. Folding endurance was determined by repeatedly following a small strip of the patch at the same place till it broke. The no. of time the patch could be folded at the same place without breaking gave the value of folding endurance.

**(iv) Thickness of patches**

The thickness of transdermal patches is measured using micrometer screw gauge.

**(v) Weight of patches**

Specific number of patches of each formulation are weighed individually in digital balance and calculated standard deviation.

**(vi) Moisture content**

The prepared patches are cut into strips of specific size. The strips are then weighed individually and kept in a dessicator containing activated silica at 300C for 12 hours. The films are reweighed individually until a constant weight is obtained.

**Percentage (%) of moisture content** =  $\frac{\text{Loss in wt.}}{\text{Initial wt.}} \times 100$

**(vii) Water absorption studies**

Transdermal films are into strips of specific size. A strip is weighed and kept in a dessicator at 400 C for 24 hours, removed and exposed to 75% RH (Containing saturated solution of sodium chloride) at room temperature weight is taken until a constant weight is obtained.

**Water absorption capacity** =  $\frac{\text{Increase in weight}}{\text{Initial weight}} \times 100$

**(viii) Drug carrier Interaction**

Thin layer chromatography (TLC) or HPLC method is used for the drug carrier interaction studies.

**(ix) Tack properties**

Tack is the ability of a polymer to adhere to a substrate with little contact pressure. It is depends on the molecular weight and composition of polymer. Test of tack includes.

**(a) Thumb tack test**

This is a subjective test in which evaluation is done by pressing the thumb briefly into the adhesive.

**(b) Rolling ball tack test**

This test involves measurement of the distance that a stainless steel ball travels along an upward – facing adhesive. The less tacky the adhesive the for they will travel.

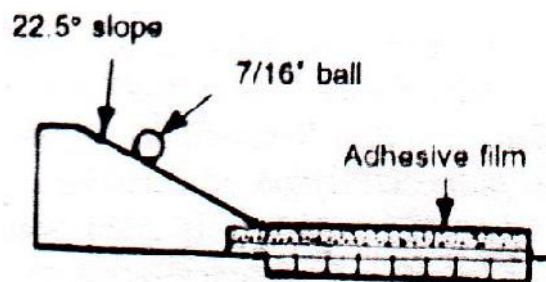


Fig. 7: Rolling ball tack test for adhesive evaluation

**(c) Quick stick (Peel-tack) test**

The Peel force required to break the bond between on adhesive and substrate is measured by pulling the force away from the substrate at 90o at a speed of 12inch/min.

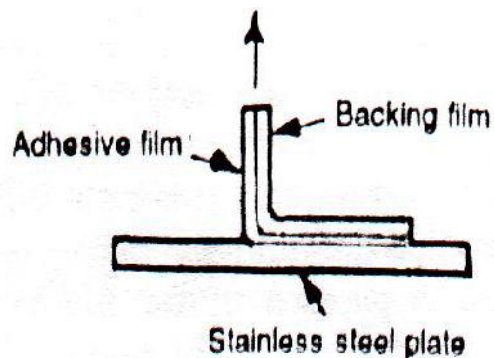
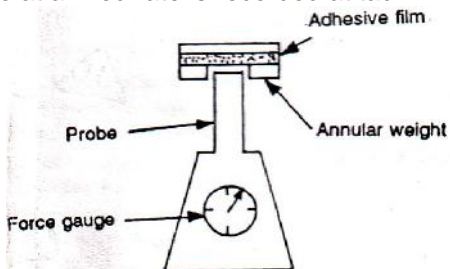


Fig. 8: Quick stick test for adhesive evaluation

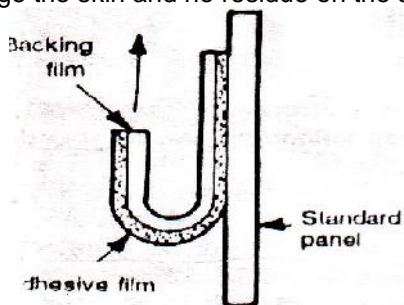
**d)Probe tack test1**

The force required to pull a probe away from on adhesive at a fixed rate is recorded at tack.



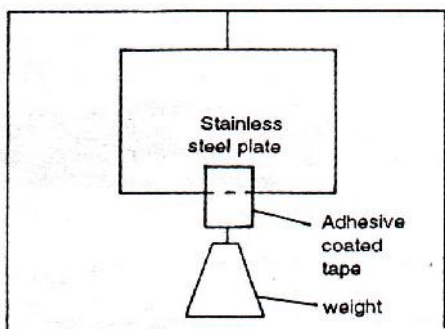
**Fig. 9:** Probe tack test for adhesive evaluation  
(x)Peel adhesion properties

Peel adhesion is the force required to remove an adhesive coating from a test substance. It is tested by measuring the force required to pull a single coated tape, applied to a substance at 180o angle. It should not damage the skin and no residue on the skin.



**Fig. 10:** Peel adhesion test for adhesive evaluation  
(xi)Shear strength properties

Shear strength is the measurement of the cohesive strength of an adhesive polymer. Adequate cohesive strength of a device will mean that the device will not slip on application and will leave no residue on removal. It is determined by measuring the time it takes to pull on adhesive coated tape off a stainless steel plate when a specified weight is hung from the tape which pulls the tape in a direction parallel to the plate.



**Fig. 11:** Shear strength test for adhesive evaluation

**(xii)Tensile strength**

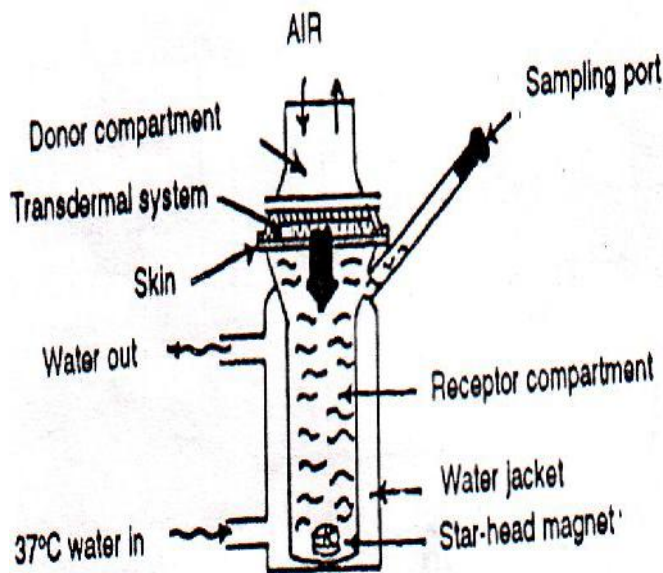
The mechanical properties are determined using plastic tensile test performed using an instron instrument.

**(B)Invitro method**

These are valuable techniques for screening and for measuring fluxes. Partition coefficients and diffusion coefficients because the investigator can closely control laboratory conditions.

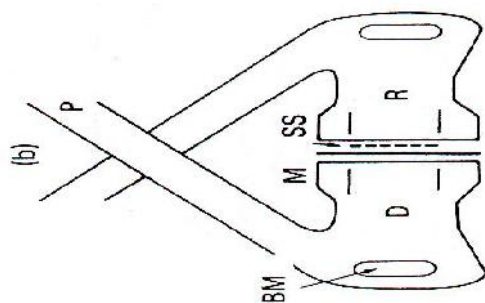
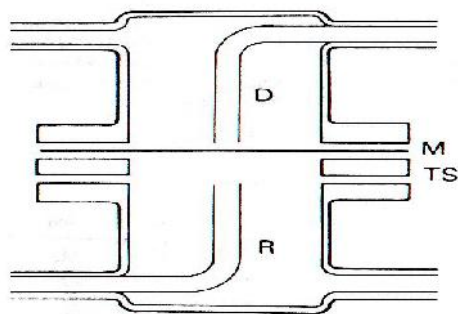
**(i)In-vitro permeation studies**

K-C cell (Keshary –chein) diffusion cell is used if skin of rats are used. Hairless skin is used and skin is thoroughly cleaned of any adhering tissues or blood vessels and equilibrated for an hour in pH 7 buffer before running for experiment. The K.C. cell or skin piece was mounted between the compartment of the diffusion cell and donor compartment and epidermal part of skin upward or toward donor compartment. The patch to be tested was placed on skin. Specific butter media at 37o C + 10 C is used as receptor phase and stirred with magnetic stirrer. Specific amount of sample withdrawn at regular period through the sampling port and fresh receptor fluid was added. Absorbance of sample is measured spectrophotometrically at against blank. The cumulative amount of drug permeated is plotted against



**Fig. 12:** K.C. Method of In-vitro permeation studies



**(i)Animal models****Fig. 13:** Simple Glass Diffusion Cell**Fig. 14:** Glass Cell with Continuously Suitable for Human Skin Circulating Donor and Receptor Solution

D = Donor Compartment; R =receptor compartment; M =membrane; TS= Teflon Support

**(ii) In-vitro drug release studies**

A modified dissolution apparatus consisting of a jacketed vertical glass beaker 18cm long and 48cm in diameter was used for assessment of the release of drug from patches. The specific amount of formulation of buffer solution. The patch to be evaluated is struck on to the depression (15mm internal diameter and 1.5mm depth) on a teflon block fabricated for the purpose and is put into the glass beaker containing the dissolution medium. The apparatus was equilibrated to  $37 \pm 20$  C and operated at 50 rpm. Specific amount of sample pipette out of regular interval of time. Sample are filtered out through filter paper and finally membrane filtered the sample is analyzed by the HPLC or U.V. spectrophotometer.

**(C)In-Vivo methods**

In vivo evaluation of transdermal patch can be carried out using –

- i) Animal models
- ii) Human Volunteers

In *Vivo* animals models are preferred because considerable time and resources are required to carry out studies in humans. Some of the species are used : mouse, rat, guinea pig, rabbit, rat, cat, dog, pig, house, monkey small hairy animals (e.g. rat, rabbit) or rhesus monkey is most reliable or in vivo evaluation of transdermal patches standard radiotracer methodology used. The application site is generally the abdomen which are the least hairy site on the animals body. The compound is applied after light clipper showing of the site.

**ii)Human models**

Human subjects should give pertinent information with minimum risk to the subjects within responsible period. It is first described by Fieldman and Maibach. They includes determination of percutaneous absorption by an indirect method of measuring radioactivity in excreta following topical application of the labeled drug.  $^{14}\text{C}$  is generally used for radio labeling. Determination of absorption following topical administration requires the investigator to know the amount of radioactivity retained in the body or excreted by routes. The percentage of dose absorbed transdermally is then calculated as.

$$\% \text{ Dose absorbed} = \frac{\text{Total radioactivity excreted after topical Administration}}{\text{Total radioactivity excreted intervenes was Administration}}$$

The procedure takes 5-7 days for completion. Other following method.

**(a)Reservoir technique**

It makes use of the relationship between stratum corneum reservoir function and in vivo percutaneous absorption to predict in vivo penetration. This method is involves a simple, short exposure of the skin to the compound under study followed by removal of the stratum corneum by tape stripping and analysis of the content of the compound in the stratum corneum. For this analysis, it is possible to predict the amount of drug that will penetrate over a longer period of time.

**(b)Mass balance technique**

The application site is covered with an occlusive chamber, the chamber being replaced by a new one after a particular time interval. The site is also subjected to washing at these time. Radio labeling techniques are used and the chamber, washing and the faces and urine of the patients are subjected to analysis. In this technique include achievement of



Mars balance between the applied close and exertion level and measurement for predicting percutaneous.

### **(c)Cutaneous toxicological evaluation**

The major cutaneous toxicological reaction and the method are following

#### **(i) Contact dermatitis**

It can be either contact irritant or contact Allergic dermatitis.

#### **(ii)Contact irritant dermatitis**

It results from direct toxic injury to cell membrane, cytoplasm or nuclei. This is generally manifested (to show, clearly especially a feeling) by inflammation and itching and can occurs from the drug, vehicle, absorption an enhancer. Contact irritant dermatitis involves use of animals like rabbits and guinea pig. A major part of the screening deals with testing in humans. Two types of protocols are used.

#### **# Ten day primary skin irritation test**

A panel of ten subjects has the test agent applied daily for two weeks at the site to be used in clinical situation. The test agent is left in place over the weekend between the first and second five days of repeated application, Adverse reaction consists of erythema and scaling which are graded daily prior to the reapplication of the agent on a 0 to 3 scale of none, mild, moderate and servers or a 0 to 6 scale to permit more discrimination.

#### **#Twenty one day skin irritation test**

Same procedure as about is repeated but there are 25 volunteers and application is on a daily basis for 5 day a week for 21 day. The following test are the newer methodologies for assessing cutaneous toxicity and are noninvasive procedure.

#### **(a)Laser Doppler**

This test is based upon the fact that as a laser light beam passes through a specimen. It is scattered when it impinges (strike or fall against) upon either static structure or moving object. Light beam scattered in static tissue will not undergo any frequency shift while those encountering moving object will. Doppler effect by illuminating the skin with a monochromatic laser light and electronically process. the frequency mix of the back scattered light collected by a photo editor system at the skin surface, a continuous measure of the red cell flux. In the microvascular bed can be

obtained. The irritation will lead to an increase in cutaneous flow and thus increased red cell flux.

### **(b)Evaporative water loss measurement**

Contact irritation also disturb the skin barrier and causes an excessive water loss from the damaged surface than can be measured by means of evaporimetry.

### **(c)Contact allergic dermatitis**

Contact allergic dermatitis involves a fast immunological reaction to an antigen. The antigen is viewed to be a complex formation an externally applied compound and skin proteins. The reaction easily distinguished clinically from contact irritation types of reaction. Two protocols are employed- (I) 25 volunteers and low grade dermatitis is included in them by application of 1- 5% Sodium lauryl sulphate to enhancer penetration and maximize any allergic potential. In first 5 day in two weeks and closed test is performed. (II) 75-200 volunteers under occlusive patch test for 5 applications. The test agent is applied in between 24 hr. rest or 48 hr. without rest. After 7-10 day rest period, challenge is done by closed patch testing, interpretation of result. Agent show an allergenic potential may still be used by millions of patients with adverse effect.

### **CONCLUSION**

Transdermal drug delivery system is useful for topical and local action of the drug. Transdermal Drug Delivery System a realistic practical application as the next generation of drug delivery system. Transdermal drug delivery systems (TDDS) are dosage forms involves drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. The adhesive of the transdermal drug delivery system is critical to the safety, efficacy and quality of the product. Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. This article provides valuable information regarding the formulation and evaluation aspects of transdermal drug delivery systems. TDDS is a realistic practical application as the next generation of drug delivery system.

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