IJPPR (2021), Vol. 13, Issue 1 *Research Article*

INTERNATIONAL JOURNAL OF BIOPHARMACEUTICAL & TOXICOLOGICAL RESEARCH

TRANDERMAL DRUG DELIVERY SYSTEM: FORMULATION ASPECTS & EVALUATION

Shekhar singh1, Shaweta sharma

Teerthanker Mahaveer college of Pharmacy, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh

Keywords:
Transdermal Drug Delivery, Skin, etc.

Corresponding Author-
Shekhar singh Assistant Professor
Teerthanker Mahaveer college of Pharmacy Teerthanker Mahaveer University
E-mail-
shekharsingh@gmail.com
Mobile- +91-8273680419

ABSTRACT:
A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. 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. The main disadvantage to transdermal delivery systems stems from the fact that the skin is a very effective barrier; as a result, only medications whose molecules are small enough to penetrate the skin can be delivered in this method. A wide variety of pharmaceuticals are now available in transdermal patch form.

Introduction:
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.1

Transdermal drug delivery system (TDDS) is topically administered medicaments in the form of patches or semisolids (gels) that deliver drugs for the systemic effects at a predetermined & controlled rate.

Transdermal drug delivery system has many advantages over conventional modes of drug administration, it provides a controlled rate release of medicaments, it avoids hepatic metabolism, ease of termination and long duration of action. Study has been carried out to provide an anti-hypertensive drug in Transdermal patches. The main objective is to evaluate the feasibility of controlled delivery of therapeutically effective amount of drug in matrix type drug delivery. The Transdermal drug delivery system

has gained popularity over the fast decades the major penetration pathway of drug molecules through the stratum corneum of impact human skin is by diffusing through lipid envelopes of the skin cell.2

Transdermal patch (Skin patch) uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. Some drugs must be combined with substances, such as alcohol, that increase their ability to penetrate the skin in order to be used in a skin patch. Drugs administered through skin patches include scopolamine (for motion sickness), nicotine (for quitting smoking), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), and lidocaine to relieve the pain of shingles (herpes zoster). Molecules of insulin and many other substances, however, are too large to pass through the skin. Patches applied to the skin eliminate the need for vascular access by syringe or the use of pumps.

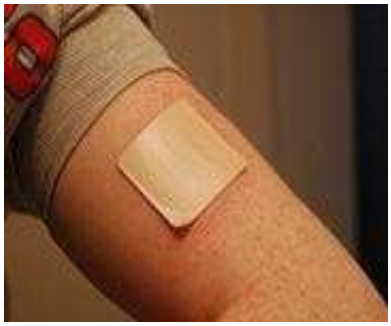
Transdermal patches were developed in the 1970s and the first was approved by the FDA in 1979 for the treatment of motion sickness. It was a three-day patch that delivered scopolamine. In 1981, patches for nitroglycerin were approved, and today there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, estradiol, 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. The major advantages provided by transdermal drug delivery include the following: improved bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency, reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms.

Transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first-pass drug-degradation effects. Patches can also reduce side effects; for example, oestradiol patches are used by more than a million patients annually and, in contrast to oral formulations, do not cause liver damage. of two major sub-categories therapeutic and cosmetic), aroma patches, weight loss patches, and Nonmedicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists patches that measure sunlight exposure).3

Transdermal patches are dosage forms designed to deliver a therapeutically effective amount of drug across a patient‟s skin. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively4.

Definition:

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the blood stream.



Advantages of transdermal patches:

1. Topical patches are a painless, noninvasive way to deliver substances directly into the body.

2. 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.

3. Topical patches over a controlled, steady delivery of medication over long periods of time.

4. Topical patches have fewer side effects than oral medications or supplements.

5. Topical patches are easier to use and remember.

6. Topical patches over an alternative to people who cannot, or prefer not to take medications or supplements orally.

7. Topical patches are cost-effective.

8. They can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administration drug.

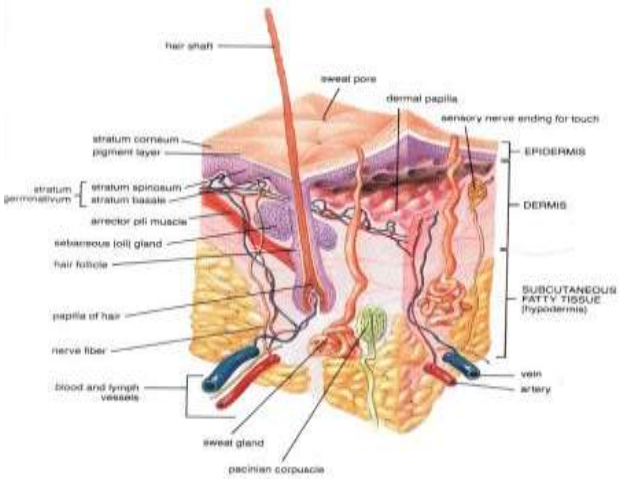
Limitation:

1. TDDS cannot deliver ionic drugs.
2. TDDS cannot achieve high drug levels in blood/plasma.
3. It cannot develop for drugs of large molecular size.
4. TDDS cannot deliver drugs in a pulsatile fashion.
5. TDDS cannot develop if drug or formulation causes irritation to skin.
6. Limitation of TDDS can be overcome to some extent by novel approaches such as Iontophoresis, electroporation and ultrasound.3

Anatomy and physiology of skin

Human skin comprises of three distinct but mutually dependent tissues:

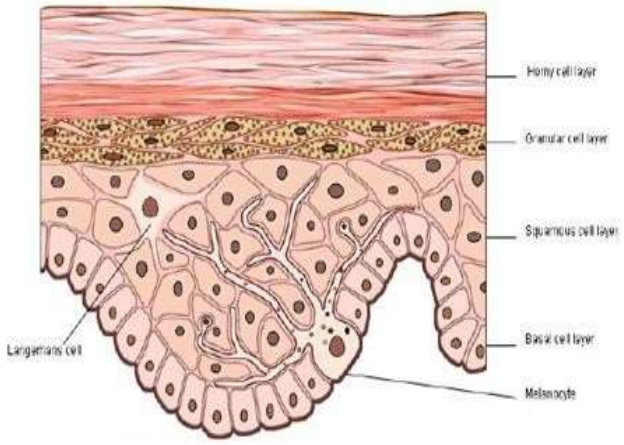
A) The stratified, vascular, cellular epidermis,
B) Underlying dermis of connective tissues and
C) Hypodermis



Structure of skin

Epidermis

The multilayered epidermis varies in thickness, depending on cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Table 1 gives thickness, water permeability and diffusivity of water through epidermis. It consists outer stratum corneum and viable epidermis.



a) Stratum corneum: This is the outermost layer of skin also called as horney layer. It is approximately 10mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of dead, keratinized cells called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration of drug. The lipids are arranged in multiple bilayers. There is sufficient amphiphilic material in the lipid fraction, such as polar free fatty acids and cholesterol, to maintain a bilayer form.

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

Dermis

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

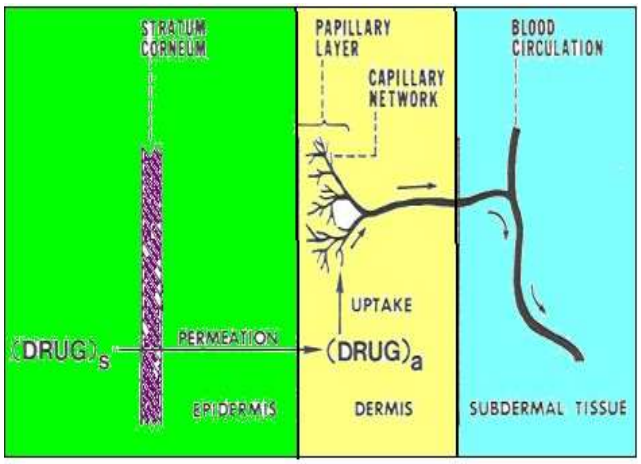
Hypodermis

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

For transdermal drug delivery, drug has to penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery only penetration through stratum corneum is essential and then retention of drug in skin layers is desired.5

ROUTES OF PENETRATION

The diffusant has two potential entry routes to the blood vasculature; through the epidermis itself or diffusion through shunt pathway, mainly hair follicles with their associated sebaceous glands and the sweat ducts. Therefore, there are two major routes of penetration.



Multilayer skin model showing sequence of Transdermal permeation of drug for systemic Delivery

A. **Stratum corneum as skin permeation Barrier:** The average human skin contains 40-70 hair follicles and 200-250 sweat ducts per square centimeter. Especially water-soluble substances pass faster through these ducts, still these ducts don‟t contribute much for skin permeation. Therefore, most neutral molecules pass through stratum corneum by passive diffusion.

B. **Tracellular verses transcellular diffusion:** Intracellular regions in stratum corneum are filled with lipid rich amorphous material. In dry stratum corneum intracellular volume may be 5% to 1% in fully hydrated stratum corneum.

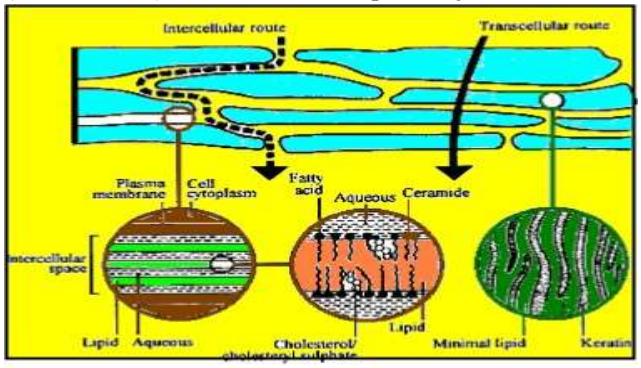
C. **Permeation pathways:** Percutaneous absorption involves passive diffusion of the substances through the skin. A molecule may use two diffusional routes to penetrate normal intact skin, the appendageal route and the epidermal route.

Appendageal route:

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

Epidermal route:

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



Drug permeation Epidermal routes

i) Transcellular: Transcellular pathway means transport of molecules across epithelial cellular membrane. These include passive transport of small molecules, active transport of ionic and polar compounds and endocytosis and transcytosis of macromolecules.

ii) Paracellular: Paracellular pathway means transport of molecules around or between the cells. Tight junctions or similar situations exist between the cells.

The principal pathway taken by a permeant is decided mainly by the partition coefficient (log k). Hydrophilic

drugs partition preferentially into the intracellular domains, whereas lipophilic permeants traverse the stratum corneum via the intercellular route. Most permeants permeate the stratum corneum by both routes. However, the tortuous intercellular pathway is widely considered to provide the principal route and major barrier to the permeation of most drugs.5

Popular uses of transdermal patches:

1. The highest selling transdermal patch in the United States is the nicotine patch, which releases nicotine in controlled doses to help with cessation of tobacco smoking. The first commercially available vapour patch to reduce smoking was approved in Europe in 2007.

2. Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form: Fentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans).

3. Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis. Other transdermal patches for hormone delivery include the contraceptive patch (marketed as Ortho Evra or Evra).

4. Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills.

5. The anti-hypertensive drug Clonidine is available in transdermal patch form under the brand name Catapres-TTS.

6. A transdermal form of the MAOIselegiline, became the first transdermal delivery agent for an antidepressant approved for use in the U.S. in March 2006.

Conditions in which Transdermal patches are used:
Transdermal patch is used when:

1) When the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternative method of drug delivery.

2) Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia.

3) It can be used in combination with other enhancement strategies to produce synergistic effects.

Conditions in which Transdermal patches are not used The use of transdermal patch is not suitable when:

1) Cure for acute pain is required.

2) Where rapid dose titration is required.

3) Where requirement of dose is equal to or less than 30 mg/24 hrs.

Care taken while applying transdermal patch

1) The part of the skin where the patch is to be applied should be properly cleaned.

2) Patch should not be cut because cutting the patch destroys the drug delivery system.

3) Before applying a new patch it should be made sure that the old patch is removed from the site.

4) Care should be taken while applying or removing the patch because anyone handling the patch can absorb the drug from the patch.

5) The patch should be applied accurately to the site of administration.

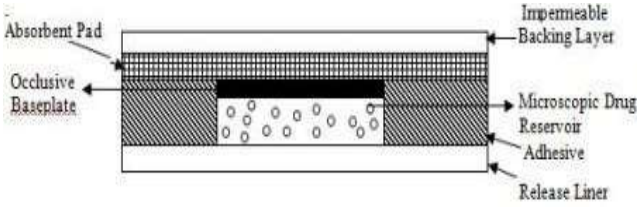
Types of Transdermal Patches

A. Single-layer Drug-in-Adhesive- The adhesive layer of this system contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

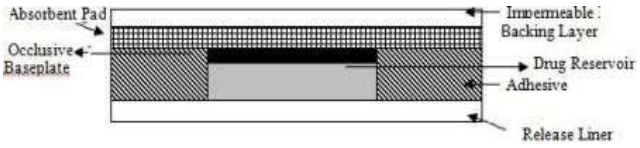
B. Multi-layer Drug-in-Adhesive- The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. One of the

layers is for immediate release of the drug and other layer is for control release of drug from the reservoir. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing.

C. Reservoir- Unlike the Single-layer and Multi-layer Drug-in-adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system, the rate of release is zero order.



D. Matrix- The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it. Also known as a monolithic device.



E. Vapour Patch- In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapour patches release essential oils and is used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market.6

The common Requirements which are used for the preparation of TDDS are as follows: -

1. Drug: Drug is in direct contact with release liner. Ex: Nicotine, Methotrexate and Estrogen.
2. Liners: Protects the patch during storage. Ex: polyester film
3. Adhesive: Serves to adhere the patch to the skin for systemic delivery of drug. Ex: Acrylates, Polyisobutylene, Silicones.
4. Permeation enhancers: Controls the Release of the drug. Ex: Terpenes, Terpenoids, Pyrrolidones. Solvents like alcohol, Ethanol, Methanol Surfactants like Sodium lauryl sulfate, Pluronic F127.

5. Backing layer: Protect patch from outer environment. Ex: Cellulose derivatives, poly vinyl alcohol, Polypropylene Silicon rubber.7

FORMULATION DESIGN

A transdermal therapeutic system is essentially a multilaminate structure that is composed of following constituents:

A. **Polymers:** Polymers are the backbone of a transdermal drug delivery system. Systems for transdermal delivery are fabricated as multilayered polymeric laminates in which a drug reservoir or a drug–polymer matrix is sandwiched between two polymeric layers: an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive and/or rate- controlling membrane.8

Some of the polymers used for transdermal devices are as follows:

Natural polymers

Cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.

Synthetic elastomers

Polybutadiene, polysiloxane, acrylonitrile, butyl rubber, Neoprene, polyisoprene, ethylene-propylene- dieneterpolymer etc.

Synthetic polymers

Polyvinyl alcohol, polyvinyl chloride, polyethylene, polystyrene polyester,

polyacrylate, polymethylmethacrylate, polypropylene etc.

The polymers like cross linked polyethylene glycol,eudragits, ethyl cellulose, poly vinyl pyrrolidone and hydroxyl propyl methyl cellulose are used as matrix formers for TDDS. Other polymers like ethylene vinyl acetate, silicon rubber and polyurethane are used as rate controlling membrane.

B. **Drug:** Judicious choice of drug is critical in the successful development of a transdermal product. The important drug properties that affect its diffusion from device as well as across the skin include molecular weight, solubility, physical properties and melting point. The structure of the drug also affects the skin penetration. Diffusion of the drug in adequate amount to produce a satisfactory therapeutic effect is of prime importance. Other parameters such as skin irritation and clinical need should be considered before a drug is chosen.

Selection of Drug-

Drug should be chosen with great care, various parameters to be considered for the selection of drug includes:

1) Physicochemical properties of drug

1. Should have molecular weight less than 1000 daltons.
2. Should have affinity for both lipophilic and hydrophilic phase.
3. Should have low melting point.

2) Biological properties of drug

1. Should be potent with daily dose of few mg.
2. Should have short half life.
3. Drug must not induce cutaneous irritation or allergic response.
4. Drug which degrade in GIT or are inactivated by hepatic first pass effect are suitable candidates.
5. Tolerance to drug must be developed under near zero order release profile of transdermal delivery.
6. Drugs which have to be administered for long period of time or which causes adverse effect to non target tissues can also be formulated.

C. **Permeation enhancers:** These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. Permeation enhancers are hypothesized to affect one or more of these layers to achieve skin penetration enhancement. A large number of compounds have been investigated for their ability to enhance stratum corneum permeability. These may be conveniently be classified under the following main headings:

i. Solvents

These compounds increase penetration possibly by swelling the polar pathway and/or by fluidizing lipids. Eg.,water alcohols-methanol and ethanol; alkyl methyl sulfoxides-dimethyl sulfoxide, dimethyl acetamide and dimethyl formamide,miscellaneous solvents-propylene glycol, glycerol, isopropyl palmitate.

ii. Surfactants

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. Anionic surfactants can penetrate and interact strongly with the skin. Cationic surfactants are reportedly more irritant than the anionic surfactants and they have not been widely studied as skin permeation enhancers. Of the 3 major classes of surfactants, then Non-ionics have long been recognised as those with the least potential for irritation and have been widely studied.

Anionic surfactants: Dioctyl sulphosuccinate, Sodiumlauryl sulphate, Decodecylmethyl sulphoxide etc. Nonionic surfactants: Pluronic F127, Pluronic F68, etc.

Bile salts: Sodiumtaurocholate, Sodiumdeoxycholate, Sodiumtauroglycocholate.

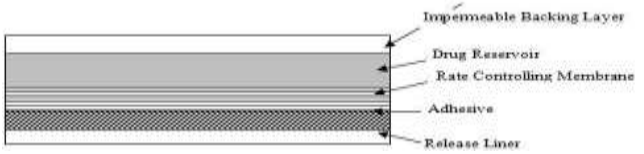
iii. Binary systems

These systems apparently open up the heterogeneous multilaminate pathway as well as the continuous pathways. E.g. Propylene

glycol-oleic acid and 1,4-butane diol-linoleic acid.

D. **Plasticizers:** These are used to prevent the films from becoming brittle. An ideal plasticizer should possess the following properties:
   1. Should not show any pharmacological action of it‟s own.
   2. Should be chemically and physically stable.
   3. Should be compatible with the drug and the formulated components.
   4. Should be colourless, odorless and tasteless.
   5. Should be non-toxic, non-allergenic & nonirritant.
   6. Plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

E. Other Excipients: A variety of solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir.9



Transdermal therapeutic system showing rate controlling Membrane

Methods for Enhancing Transdermal Drug Delivery: -

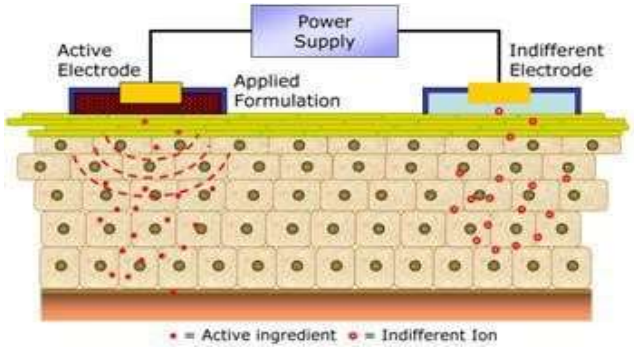
1) **Drug/prodrug-** The prodrug approach has been used to enhance the dermal and transdermal delivery of drugs with unfavorable partition coefficients the prodrug design involves addition of a promoiety to increase partition coefficient and also solubility and transport of the parent drug in the stratum corneum. Upon reaching the viable epidermis, esterases release the parent drug by hydrolysis thereby optimising solubility in the aqueous epidermis. For example: The intrinsic poor permeability of the very polar 6-mercaptopurine was increased up to 240 times using S6- acyloxymethyl and 9-dialkylaminomethyl promoieties.

2) **Eutectic system-** An eutectic system is a mixture of chemical compounds or elements that has a single chemical composition that solidifies at a lower temperature than any other composition. According to regular solution theory, the lower the melting point, the greater the solubility of a material in a given solvent, including skin lipids. The melting point of a drug delivery system can be lowered EMLA cream, a formulation consisting of a eutectic mixture of lignocaine and prilocaine applied under an occlusive film, provides effective local anesthesia for pain-free venepuncture and other procedures.

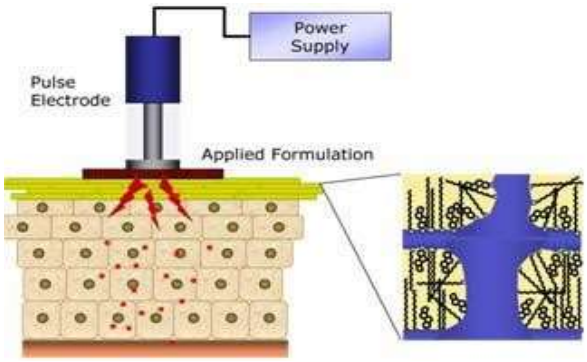
3) **Liposomes and vehicles-** Liposome are colloidal particles formed as concentric bimolecular layers that are capable of encapsulating drugs. There are many examples of cosmetic products in which the active ingredients are encapsulated in vesicles. These include humectants such as glycerol and urea, unscreening and tanning agents, enzymes, etc.

4) **Solid lipid Nanoparticles-** Solid lipid nanoparticles (SLN) have recently been investigated as carriers for enhanced skin delivery of sunscreens, vitamins A and E, triptolide and glucocorticoids. It is thought their enhanced skin penetration is primarily due to an increase in skin hydration caused by the occlusive film formed on the skin surface.

5) **Iontophoresis**-This method involves permeation of a topically applied therapeutic agent by application of low level electric current either directly to skin or indirectly via dosage form. Parameters that effect design of a ionophoretic skin delivery system include electrode type, current intensity, pH of system. Increased drug permeation as a result of this methodology can be attributed to either one or a combination of the following mechanisms: Electro-repulsion (for charged solutes), electro-osmosis (for uncharged solutes) and electro-perturbation (for both charged and uncharged).



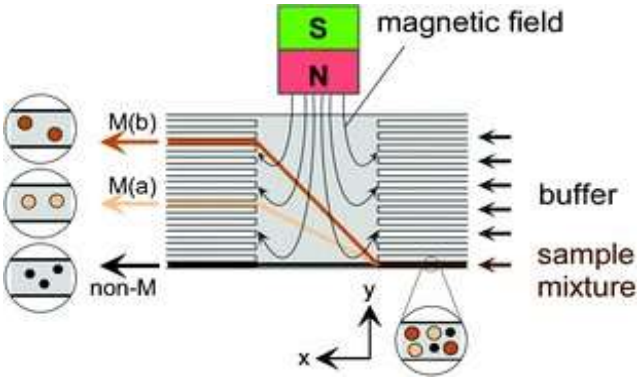
6) **Electroporation-**It involves the application of high voltage pulses to the skin that has been suggested to induce the formation of transient pores. High voltages (100V) and short treatment durations (milliseconds) are most frequently employed. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e. small molecules, proteins, peptides and oligonucleotides) including biopharmaceuticals with molecular weights greater that 7Kda.



7) **Laser radiation and photomechanical waves-** Lasers are frequently used for treatment of dermatological conditions like acne and to confer facial rejuvenation.

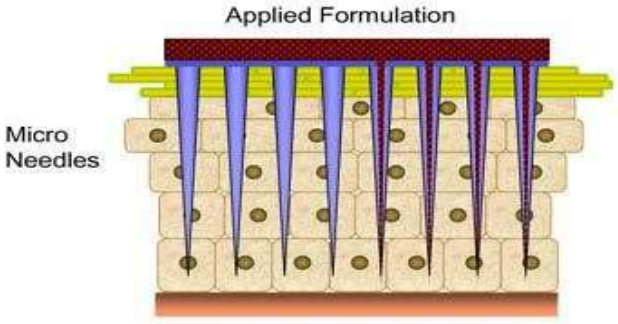
8) **Radio frequency-** It involves the exposure of skin to high frequency alternating current resulting in formation of heat induced micro channels in the membrane. The rate of drug delivery is controlled by number and depth of micro channels formed by device. Treatment duration takes less than a second.

9) **Magnetophoresis-** It involves application of magnetic field that acts as an external driving force to enhance the diffusion of a diamagnetic solute across the skin. Skin exposure to a magnetic field might also induce structural alterations that could contribute to an increase in permeability.



Technique of magnetophoresis

10) Microneedle based devices-The first ever patents for drug delivery for percutaneous administration of drug was based on this method. These microneedles ol length 50-110 micrometre will penetrate SC and epidermis to deliver drug.



Basic design of micro needle delivery devices

11. Skin Abrasion- The abrasion technique involves the direct removal or disruption of the upper layers of the skin. These devices are based on techniques employed by dermatologists for superficial skin resurfacing which are used in the treatment of acne, scars, hyperpigmentaion and other skin blemishes.

12. Needle-less Injection- Transdermal delivery is achieved by firing the liquid or solid particles at supersonic speeds through the outer layers of the skin using a suitable energy source. The mechanism involves forcing compressed gas (helium) through the nozzle, with the resultant drug particles entrained within the jet flow reportedly traveling at sufficient velocity for skin penetration.6

13. Transfersomes- This device penetrates the skin barrier along the skin moisture gradient.

Transfersome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug. Transfersomes contain a component that destabilizes the lipid bilayers and thus leading to the deformable vesicles.

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

15. Controlled Heat Aided Drug Delivery (CHADD) System- It facilitates the transfer of drug substance to the blood circulation by applying heat to the skin that increases the temperature and ultimately led to increase in microcirculation and permeability in blood vessel. CHADD system consists of small unit that is used for heating purpose, placed on top of a conventional patch device. An oxidation reaction occurs within the unit which tends to form heat of limited intensity and duration.

16. 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

17. Macroflux- These are devices having an area of around 8cm as well as 300 micro projections per cm2 with the length of individual micro projection less than 200Î¼m. Three types of Macroflux have been designed. They include, Dry-Coated Macroflux system-this is used for short period delivery that consists microprojection array coated with medicament that adhered to a elastic polymer adhesive backing.

18. Electro-Osmosis- To the porous membrane which is having some charge, a voltage difference is applied to it, thus a bulk fluid or volume flow takes place with no concentration gradients. This process is known as electro-osmosis.

19. Powderject Device- The solid drug particles are propelled across the skin with the aid of high-speed gas flow. This consists of a gas canister that allows helium gas at high pressure to enter a chamber at the end of which drug cassette containing powdered drug between two polycarbonate membranes. After release, the instantaneous rupturation of both membranes usually seen that results in the gas to expand quickly which forms a strong motion like a wave that travels down the nozzle. This takes place at the speed of 600-900 m/s.10

Properties that influence transdermal drug Delivery: - The effective transdermal drug delivery can be formulated by considering three factors as drug, skin and the vehicles. So, the factors affecting can be divided in two classes as biological factors and physicochemical factors.

A. Biological factors

i) 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.

ii) Skin age: The young skin is more permeable than older. Childrens are more sensitive for skin absorption of toxins. Thus, skin age is one of the factor affecting penetration of drug in TDDS.

iii) Blood supply: Changes in peripheral circulation can affect transdermal absorption.

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

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

vi) Species differences: The skin thickness, density of appendages and keratinization of skin vary species to species, so affects the penetration.

B. Physicochemical factors

i) 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 humectant is done in transdermal delivery

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

iii) 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.

iv) 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.

v) Partition coefficient: The optimal partition coefficient (K) 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.

vi) Molecular size and shape: Drug absorption is inversely related to molecular weight, small molecules penetrate faster than large ones.5

IDEAL MOLECULAR PROPERTIES OF TRANSDERMAL DRUG DELIVERY SYSTEM5

From the above considerations we can conclude with some observations that can termed as ideal molecular properties for drug penetration. They are as follows.

1. An adequate solubility in lipid and water is necessary for better penetration of drug (1mg/ml).

2. Optimum partition coefficient is required for good therapeutic action.

3. Low melting point of drug is desired (<200°C).

4. The pH of the saturated solution should be in between 5 to 9.

IDEAL PROPERTIES OF TRANSDERMAL DRUG DELIVERY SYSTEM6

S. No.	Properties	Range
1.	Shelf life	Should be up to 2.5 years
2.	Patch size	Should be less than 40 cm^2
3.	Dose frequency	Once a daily - once a week
4.	Appearance	Should be clear or white color
5.	Packaging properties	Should be easily removable of release liner
6.	Skin reaction	Should be non-irritating
7.	Release Properties	Should have consistent pharmacokinetic and pharmacodynamic profiles over time
8.	Packaging properties	Should be easily removable of release liner

VARIOUS METHODS FOR PREPARATION TDDS

A. **Asymmetric TPX membrane method:** A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly(4-methyl-1-pentene)}asymmetric membrane, and sealed by an adhesive.[(Asymmetric TPX membrane preparation): These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°c to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a gardner knife. After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath [maintained the temperature at 25°C]. After 10 minutes of immersion, the membrane can be removed, air dry in a circulation oven at 50°C for 12 hrs].

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

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

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

E. **By using "EVAC membranes" method:** In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethelene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes.

If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol, carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

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

G. **Preparation of TDDS by using Proliposomes:** The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0

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

H. **By using free film method:** Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the Petridish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.7

EVALUATION PARAMETERS:-

1. **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 such as assay, melting endotherms, characteristic wavenumbers, absorption maxima etc.7

2. **Thickness of the patch:** The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch. The thickness of transdermal film is determined by traveling microscope dial gauge, screw gauge or micrometer at different points of the film17,18.

3. **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.

4. **Folding endurance:** A strip of specific are 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.

5. **Percentage Moisture content:** The prepared films are to be weighed individually and to be kept in a desiccator 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 = [Initial weight- Final weight/ Final weight] ×100

6. **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 = [Final weight- Initial weight/ initial weight] ×100

7. **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/m2 per 24hrs.

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

8. **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 contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples.

9. **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 filtered using 0.2m membrane filter and analysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated.

10. **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.

11. **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 crosslinking 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.

12. **Peel Adhesion test:** In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. 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 180º angle, and the force required for tape removed is measured.

13. **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.

14. **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.

15. **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.

Elongation percentage = L1-L2 ×100

L2

Where, L1is the final length of each strip and L2 is the initial length of each strip.

16. **Rolling ball tack test:** This test measures the softness of a polymer that relates to talk. 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.

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

18. **Probe Tack test:** In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. 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.

19. **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± 0.5°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.

20. **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 ± 0.5°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 HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm-2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm-2).7

21. **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.14

22. **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.15

23. **Scanning Electron Microscopy:** Scanning electron microscopy has been extensively employed to study the morphology and surface topography of the film. The morphology and

surface topography of the film were examined by scanning electron microscopy (SEM-JEOL, JSM-840A, Japan). The samples to be examined were mounted on the SEM sample stab using a doublesided sticking tape. The samples mounted were coated with gold (200 A°) under reduced pressure (0.001 torr) for 5 min to improve the conductivity using an Ion sputtering device (JEOL, JFC-1100 E, Japan). The gold-coated samples were observed under the SEM and photomicrographs of suitable magnifications obtained (1000X and 2000X).

24. **Differential Scanning Calorimetry** DSC has been one of the most widely used calorimetric techniques employed to characterize the solubility and physical state of drug in the complex. Thermo grams of drug, and mixture of drug and Carbopol 934 were recorded using a differential scanning calorimeter and were compared. The samples (5 mg) were hermetically sealed in flat bottomed aluminum pans and heated over a temperature range of 40-240° C at a rate of 10° k/min using alumina as a reference standard.13

CONCLUSION

Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. 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.

The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS a realistic practical application as the next generation of drug delivery system.

REFERENCES:-

1. Sandhu Premjeet, Bilandi Ajay, Kataria Sahil and Middha Akansha, „Transdermal drug delivery system (patches) application in present scenario" published by Interanational journal of research in pharmacy and chemistry. ISSN: 2231-2781, IJRPC 2011, 1(4) Available online at www.ijrpc.com

2. Mohd. Amjad, Mohd. Ehtheshamuddin, S. Chand, Hanifa, M. Sabreesh, R. Asia, and G. S Kumar, „Formulation and evaluation of transdermal patches of atenolol" published by Advance research in pharmaceuticals & biologicals. (A peer reviewed international journal for pharmaceutical and allied research) Publication Ref No.: IJPRD/2009/PUB/ARTI/VOL-7/SEP/001

3. Patel Dipen, Chaudhary A. Sunita, Parmar Bhavesh, Bhura Nikunj, „Transdermal Drug Delivery System: A Review", published by the pharma innovation vol.1 no. 42012. Available online at www.thepharmajournal.com

4. Jain NK. "Advances in controlled and novel drug delivery", 1st Ed., CBS Publishers and distributors, New Delhi, 2001 pp.108-110.

5. Sharma Nikhil, Agarwal Geeta, Rana A.C, Bhat Ali Zulfiqar, Kumar Dinesh, „A Review: Transdermal Drug Delivery System: A Tool For Novel Drug Delivery System", published by International Journal of Drug Development & Research | July-September 2011;Vol. 3; Issue 3; ISSN 0975-9344 | Available online http://www.ijddr.in

6. Dhiman Sonia, Singh Gurjeet Thakur, Rehni kumar Ashish, „Transdermal Patches: A Recent Approch To New Drug Delivery System", published by International Journal of Pharmacy and Pharmaceutical Sciences, vol 3, 2011, Email: gurjeetthakur@gmail.com

7. Kumar J. Ashok, Pullakandam Nikhila, Prabu S.Lakshmana, Gopal V, „Transdermal Drug Delivery System: An Overview‟ International Journal of Pharmaceutical Sciences Review and Research Volume 3, Issue 2, July – August 2010; pg no. 49-54. Available online at www.globalresearchonline.net

8. Kandavilli Sateesh, Nair Vinood and Panchagnula Ramesh; „Polymers in transdermal drug delivery system‟ published by Pharmaceutical technology May 2002, available on www.pharmtech.com

9. Bhowmick Mithun, Sengodan Tamizharasi, Thangeval Sivakumar, „Anatomy of transdermal therapeutic systems: A detailed and updated perspective‟, published by International Journal of pharma sciences, aizeon publishers vol. 3, 2013.

10. Shingade GM, Aamer Quazi1, Sabale PM, Grampurohit ND, Gadhave MV, Jadhav SL, Gaikwad DD, „Review On: Recent Trend On Transdermal Drug Delivery System‟ published by Shingade et al, Journal of Drug Delivery & Therapeutics; 2012, 2(1),Available online at http://jddtonline.info

11. Brown MB, Traynor MJ, Martin GP, Akomeah FK.; Drug Delivery Systems: Skin Perturbation Devices. Methods in Molecular Biology. 2008; 437pg no:119-139

12. Peterson A. Timothy; „Drug Formulation and Process Development‟ published by Formulation, Fill & Finish 2003, pg no. 18-21

13. Patel J. Himangi, Patel S. Jitendara, Desai G. B, Patel D. Keyur. „Design And Evaluation Of Amlodipine Besilate Transdermal Patches Containing Film Former‟ International Journal of Pharmaceutical Sciences Review and Research, Publication Ref No.: IJPRD/2009/PUB/ARTI/VOL- 7/SEP/001, pg-no.3 Available online at www.ijprd.com

14. Aarti N, Louk A.R.M.P, Russsel.O.P and Richard H.G.; “Mechanism of oleic acid induced skin permeation enhancement in vivo in humans”. Jour. control. Release 1995; 37: pg no.299-306.

15. Singh J, Tripathi K.T and SakiaT.R.; “Effect of penetration enhancers on the invitro transport of ephedrine through rate skin and human epidermis from matrix based Transdermal formulations”. Drug Dev.Ind. Pharm. 1993; 19:pg no. 1623-1628.

16. Vyas SP, Khar RK.; “Targetted and controlled Drug Delivery Novel carrier system.” 1st ed. CBS Publishers and distributors New Delhi; 2002; pg no. 411- 447.

17. Rhaghuram RK, Muttalik S, Reddy S. “Once – daily sustained- release matrix tablets of nicorandil: formulation and invitro evaluation.” AAPS Pharm.SciTech. 2003; 4(4):480–488.

18. Keleb E, Sharma RK, Mosa EB, Aljahwi A-AZ. “Transdermal Drug Delivery System – Design and Evaluation”. International Journal of Advances in Pharmaceutical Sciences. 2010; 1pg no.:201-211.