ABSTRACT

Human skin is a readily accessible surface for drugs delivery. The skin of the average adult body is about a third of about 2m2. Blood that circulates throughout the body. Over the past few decades, Development of controlled drug delivery increasingly important in the pharmaceutical industry. Of the average human skin surface is 10-70 hair follicles and 200-250 sweat glands in each square Centimeters of skin surface. it is one of the easiest accessible organs of the human body. there are quite a few Interest in the skin as a drug application site for both Local and systemic effects. But especially the skin The stratum corneum represents a formidable barrier to drugs Penetration, thereby limiting topical and transdermal bioavailability. A transdermal patch is a medicated patch placed on the skin to deliver a specific dose of medicine through the skin and into the bloodstream. Often this promotes healing of injured areas body. Advantages of the transdermal route of drug delivery over other types Administration of drugs, such as oral, topical, intravenous, intramuscular. is to ensure the controlled release of the drug to the skin by the patch to Patients usually. A thin layer of embedded drug or drug that melts at body temperature with glue. The primary goal of transdermal drug delivery systems is to deliver drugs through the skin into the systemic circulation at a predetermined rate with minimal inter- and intra-patient variability.

KEYWORDS:- Transdermal, Patch, Skin, bioavailability, Penetration.
1. INTRODUCTION
Although many drugs are administered orally these days, it no longer effectively monitors when needed, upgrade a character TDDS was created. Administered drug delivery called to achieve the systemic effect of a drug through the skin as a transdermal drug delivery system.[1] These are art Dosage forms containing drug delivery at reasonable prices epidermis of the skin, sometimes dermal tissue therapeutic effect.[2] Although very important.

Drug divisions are carried in the blood throughout the body traffic jam. The transdermal skin patch is marked as Medicated adhesive plaster to be applied to the skin release a certain amount of drug through the skin. Determined release rate before entering circulation system.[3]

1.1. Advantages of transdermal drug delivery systems[4,5]
1. Self-medicating possible.
2. Less side effects.
3. Plasma drug concentration is maintained.
4. GIT incompatibilities are avoided.
5. Reduced frequency of administration.
6. Easy to remember and used wider range of application than nasal and oral cavity.

1.2. Disadvantages of transdermal drug delivery system[6,7]
1. Possibility of allergic reactions.
2. High-molecular-level drugs have no therapeutic effect.
3. Delivered to Ion Pharmaceuticals.
4. Significant time lag required.

1.3. Anatomy and Physiology of the skin
Human skin consists of three distinct parts but interdependent tissues.[8-11]  
a) Stratified, Vascular, Cells called “Epidermis”
b) Lower dermis connective tissue,
c) Subcutaneous layer

- Cuticle
Different layers of epidermis in thickness, depending on the size and number of cells cuticles, from 0.8 mm on the palm and base up to 0.06 mm above the eyelid. It has outer stratum corneum & Viable epidermis.
i) **Stratum corneum**

It is also the outermost layer of the skin called the stratum corneum. It is about 10 mm. thick when dry but swells many times this thickness when fully hydrated. It contains 10 to 25 layers keratinized dead cells are called keratinocytes. It's flexible but relatively waterproof. The stratum corneum is major barrier to drug penetration. The architecture of the stratum corneum can be modeled as a wall like structure. In this model, keratinized cells function as "bricks" of proteins combined with lipids "mortar." Lipids are arranged in many bilayers. There is enough amphoteric matter in lipid fractions, such as polar free fatty acids and cholesterol, to maintain the bilayer shape.

ii) **Viable epidermis**

The epidermis lies below the stratum corneum and varies in thickness from 0.06 mm on eyelids to 0.8 mm on the palm. Inside, it includes different layers such as light layer, layer seeds, spines, and bottoms. In the basal layer, cells mitosis continuously renew the epidermis and this proliferation compensate for the loss of dead horny cells from surface of the skin. When cells are generated by the base layer move out, they change form and chemically, undergoes keratinization to form the outermost layer of the stratum corneum.

- **Dermis**

The dermis is a layer 3 to 5 mm thick and consists of a matrix of connective tissue, where contains blood vessels, lymphatic vessels, and nerves. THE Blood circulation in the skin has an essential function in regulate body temperature. It also provides nutrients and oxygen to the skin while removing toxins and waste. The capillaries get inside 0.2 mm of skin surface and good conditions for Most molecules cross the skin barrier. Blood provides thus maintaining skin concentration of a Very low permeability and resulting concentration Differentiation through the epidermis provides the essentials concentration gradient for transdermal penetration.

- **Hypodermis**

Subcutaneous layer or subcutaneous adipose tissue Supports the dermis and epidermis. It serves as fat storage area. This layer helps regulate the temperature, Provides nutritional and mechanical support protection. It carries large blood vessels and nerves to the skin and may contain pressure-sensing organs. Because drug transport through the skin, the drug should penetrate through these three layers and achieve the system circulation while taking only the
topical medication penetration through the stratum corneum is essential and it is desirable to keep the drug within the layers of the skin.

![Structure of human skin](image)

**Figure 1:** Structure of human skin.

1.4. **Factors affecting transdermal bioavailability**[12-13]?

Two main factors influence the bioavailability of Drugs that penetrate the skin:

- **Physicochemical factors**

**Skin moisturizing**

Contact with water permeability of the skin increased significantly. Hydration is the best Important factors increase the permeability of skin. Therefore, the use of moisturizers is transdermal transport.

**Temperature and pH**

The osmolarity of the drug increases 10 times with temperature variation. diffusion coefficient decrease as the temperature decreases. weak acid and weak bases dissociate depending on pH and pKa or pKb value. The ratio of the decisive combination drug drug concentration in the skin. Therefore, temperature and pH are important factors affect drug absorption.

**Diffusion coefficient**

Drug penetration depends on diffusion drug coefficient. At constant temperature, The diffusion coefficient of the drug depends on drug properties, means of delivery, and interaction between them.
Drug concentration
Flux is proportional to concentration the slope through the fence and the concentration the gradient will be higher if the concentration of more drugs will cross the barrier.

Partition coefficient
Optimal partitioning factor (K) is required for a good deed. High K drug is not ready leave the lipid part of the skin. In addition, the drug has Low K will not be impregnated.

Molecular Size and Shape
Drug absorption is inversely proportional to molecular weight, small molecules penetrate faster than adults.

- Biological factors

Skin state
Acids and alkalis, many solvents such as chloroform, methanol damages skin cells and promotes infiltrate. The patient's health status changes skin disease. Intact skin is a better barrier but the above conditions affect infiltrate.

Skin age
Young skin is more permeable than old skin. Children are more easily absorbed by the skin of poison. Thus, the age of the skin is one of the factors affect the penetration of drugs into TDDS.

Blood flow
Changes in the peripheral circulation can affect absorbed through the skin.

Skin metabolism
Skin metabolizing steroids, hormones, chemicals carcinogens and some drugs. Therefore, the metabolism of the skin determine the effectiveness of the impregnated drug through skin.

1.5. Components of TDDS[14]
The main ingredients of the transdermal patch are:

I. Release liner
Protect patches during archiving. The lining is remove before use.
II. Drug reservoir
The most important part of the TDDS is the medicine container. It consists of drug particles dissolved or dispersed in matrix. To make the drug soluble, the solvent and co-solvent is used. Effect of solvent and cosolvent should be considered when implementing selective.

III. Adhesive
Used to adhere to patch components as well as the stickiness of the patch on the skin. The adhesive must have sufficient adhesion ownership to keep TDDS in place in a long time. Pressure sensitive adhesive is commonly used for transdermal patch to maintain skin. The commonly used adhesive is silicone adhesives and poly isobutylene adhesives.

IV. Membrane
Membranes control drug release from tanks and laminated patches. Bad luck Contains a flow control membrane. it should be flexible enough not to split or crack when bent or lengthen. Some flow control membranes are polyethylene sheet, co-ethylene-vinyl acetate polymer and cellulose acetate.

V. Backing
Protect the sticker from the outside environment. THE the substrate must be impermeable and penetration enhancer. It performs a function of keep the whole system and protect the drug atmospheric reservoir. The commonly used base material is polyester, aluminized polyethylene terephthalate and silicone polyethylene terephthalate.

1.6. Transdermal patches[15]
Topical and transdermal products are intended for external applications. However, the news dermatological products are intended for while the percutaneous drug delivery system is used for systemic drug delivery. Transdermal system delivers medication through skin directly into the bloodstream. THE the route of drug delivery through the skin becomes popular because of the large number of drugs that can be transported by this route to treat various diseases. Currently, transdermal patches are used in a number of therapeutic areas such as pain management, smoking stop, treat heart disease, hormones replacement and management of motion sickness.
1.6.1. Types of transdermal patches \[16-20\]

a) Monolayer drugs in adhesives
In this type, the adhesive layer contains the drug. The glue layer is not only used to stick the different classes from each other and are also responsible for drug release on the skin. The adhesive layer is surrounded by a temporary lining and a base layer.

b) Multi-layer adhesive
This type is similar to the single class, but it contains an immediate and different drug release layer class will be a controlled release with adhesive layer. The sticky layer has a mission drug release. This patch also has a temporary lining and a continuous support.

c) Steam patch
In this type of patch, the role of the non-stick layer only serve to make different layers stick together but also serve the market, often used for issuance essential oils in decongestants. More varieties of Steam patch is also available in the market. Used to improve sleep quality and reduce smoking conditions.

d) Reservoir system
In this system, the medicine tank is integrated between a layer of waterproof support and scale control membrane. Medicines only release through the flow control membrane, can be microporous or non-porous. In the medicine box compartment, the drug can be in the form of solution, suspension, gel or solid dispersion Polymer matrix. Hypoallergenic adhesive polymer can be applied as an outer surface polymer film drug compatibility.

e) Matrix system
i. Drug in adhesive system
In this type, the drug reservoir is formed by disperse the drug in a binder polymer and then spread the drug-binding polymer in casting or solvent molten (in case of molten adhesive) on a waterproof substrate. At top of the tank, polymer binder without intermediate layer is applied for protection.

ii. Matrix dispersion system
In this type, the drug is uniformly dispersed in a hydrophilic or lipophilic polymer matrix. This medicine contains a polymer disc that is attached to a switch base plate in the compartment made from medicine waterproof base layer. Instead of applying the sticky
substance on the surface of the medicine container, that is spread along the perimeter to form a band sticky 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.

1.7. Preparation of transdermal patches
Transdermal drug delivery patches can be prepared by Various methods:

1. Mercury substrate method
In this method, the required amount of drug is dissolved in predetermined amount of polymer solution with plasticizing. The above solution was stirred for several time to create a uniform dispersion and it is maintained aside until the air bubbles are completely removed, then poured into a glass ring placed over mercury surface in a glass Petri dish. Evaporation speed of Solvent is controlled by placing an inverted funnel on blessing bread. Dry film should be stored in a desiccator.\textsuperscript{[34-38]}

2. Round teflon mold method
Solutions containing polymers in different proportions are used in an organic solvent. Calculated amount of drug dissolved in half the amount of the same organic solvent. plasticizer added to the drug polymer solution. Total content is are stirred and then poured into a Teflon round mold. And the solvent vaporization rate is controlled with the position inverted glass funnel on teflon mold. solvent is to evaporate 24 hours. Dry film should be Store in desiccator.\textsuperscript{[39-40]}

1.8. Evaluation of transdermal patches
The transdermal patches can be characterized in terms of following parameters

- Physicochemical evaluation
- In vitro evaluation
- In vivo evaluation
1.8.1. Physicochemical evaluation

Transdermal patches can be physicochemically evaluated in terms of these parameters:

- **Thickness**
  The thickness of transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometer at different points of the film.\(^{[21]}\)

- **Uniformity of weight**
  Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.\(^{[22,23]}\)

- **Drug content determination**
  An accurately weighed portion of film (about 100mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. Afterward sonication and subsequent filtration, drug in solution is estimated photometrically by proper dilution.\(^{[24-25]}\)

**Content uniformity test**

10 patches selected and content determined for individual patches. If 9 out of 10 patches have content from 85% to 115% of the specified value value and we have content at least 75% at 125% of the specified value, then absorbed through the skin patches pass the content uniformity test. But if 3 patches with content between 75% and 125%, then 20 more patches are tested for drugs Content. If those 20 patches have 85% range at 115%, then the transdermal patches pass test.\(^{[26]}\)

- **Moisture content test**
  Prepared membranes are weighed separately and Store in a desiccator containing calcium chloride at room temperature for 24 hours. Movies are weighed after a specified amount of time until they show a unchanged weight. The percentage of humidity is calculated using the following formula.\(^{[27]}\)

\[
\% \text{ Moisture Content} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100
\]

- **Thumb tack test**
  Force required to remove thumb from adhesive is a measure of tack.\(^{[28]}\)
• **Ball rolling contest**
  This test involves measuring the distance that the stainless steel ball moves along an upward face sticky. The less sticky the adhesive, the more the ball will move.[29]

• **Quick stick test**
  Peeling power needed to break the link between a binder and a substrate measured by pulling ice out of the substrate at 90 at speed of 12 inches/min.[30]

• **Probe tack test**
  Force required to move a transducer away from a adhesive at a fixed rate is recorded as tack.[31]

1.8.2. **In vitro release studies**
The transdermal patch can be evaluated in vitro at Diffusion cell Franz term composed cell two compartments: donor and receiver. The receiving compartment has a volume of 5-12 ml and useful surface from 1 to 5 cm². Diffusive the buffer was stirred continuously at 600 rpm by a magnet bar. The temperature in the mass of The solution is maintained by heat-controlled circulation water through the surrounding water jacket collection compartment. The drug content is analyzed by an appropriate method, maintaining well condition is essential.[32]

![Figure 2: Franz diffusion cell][11]
1.8.3. In vivo studies
Transdermal patch can be evaluated in vivo in in vivo review terms are true representation effectiveness of the drug. Variables that could not be considered in in vitro studies can be fully explored in in vivo studies. invivo TDDS assessment can be done using human volunteer animal model.[33]

1.9. Application of transdermal patch
1) Transdermal nicotine patch, release nicotine in controlled doses to help quit smoking smoke.
2) Sometimes Nitroglycerin patches are also available prescribed for the treatment of angina.
3) Clonidine, antihypertensives and ketoprofen, Non-steroidal anti-inflammatory drugs also Available as a transdermal patch
4) The transdermal form of MAOI selegiline has become First transdermal delivery agent for a Antidepressants.
5) Dermal delivery agent for inattention Hyperactivity disorder (ADHD).

2. CONCLUSION
This article provides valuable information related to transdermal drug delivery systems and details of its evaluation process as an immediate reference for research scientists involved in TDDS. Transdermal drug delivery is a painless, convenient and Potentially effective way to deliver regular doses of multiple medicine. A wide range of drugs can be provided improve drug absorption Less complications and Low cost effect and easy to use. Skin patches are the most common form of transdermal drug delivery. Transdermal drug delivery has made important contributions to medical practice. It's a patch that delivers a specific amount of medication through the skin into the bloodstream. The main advantage of the transdermal patch is that drug delivery takes place directly into the circulatory system, bypassing the gastrointestinal system and thus avoiding the first effect of the liver.

REFERENCES