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A Review on Transdermal Drug Delivery System

[1]Ms. Kokate Mayuri D., [2]Mr. Phanse Milind D., [3]Dr. Mane Sonali S., [4]Mr. Gaikwad Tushar A

[1,2,3,4]MSS's College of Pharmacy (B. Pharmacy) Medha, Mahalaxmi Homeopathic Medical College Hospital and Research Center Raigaon, Satara and Late N. B. Chahabada Institute of Pharmacy Raigaon, Satara.

ABSTRACT

Today about 74% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged. 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. It has various advantages. Like prolonged therapeutic effect, reduced side-effects, improved bioavailability, better patient compliance and easy termination of drug therapy The stratum corneum is considered as the rate limiting barrier in transdermal permeation of most molecules.

There are three main routes of drug penetration, which include the appendageal, trans cellular and intercellular routes Skin age, condition, physicochemical factors and environmental factors are some factors that are to be considered while delivering drug through this route. Basic components of TDDS include polymer matrix membrane, drug, penetration enhancers, pressure- sensitive adhesives, backing laminates, release liner, etc. Transdermal patches can be divided into various systems like reservoir system, matrix system and micro-reservoir system, which are used to incorporate the active ingredients into the circulatory system via the skin After preparation of transdermal patches, consistent methodology are adopted to test the adhesion properties, physicochemical properties, in rare drug release studies, in rimo skin permeation studies, skin station studies and stability studies. According to the duration of therapy, various drugs are commercially available in the form of transdermal.

Keywords – Transdermal delivery, enhancer, transdermal patches.

1. INTRODUCTION

Transdermal drug delivery system are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders. Transdermal drug delivery is the non-invasive delivery of medications from the surface of skin-the largest and most accessible organ of human body- through its layers, to the circulatory system TDDS offers many advantages over conventional injection and oral methods. (1)

Transdermal patch (Skin patch) uses a special approved, membrane to control the rate at which the liquid drug for drugs contained in the reservoir within the patch can pass nicotine, through the skin and into the Bloodstream. Some scopolamine drugs must be combined with substances, such as combination alcohol, that increase their ability to penetrate the skin hormone r in order to be used in a skin patch. Drugs administered patches g through skin patches include scopolamine (for motion major ad sickness), nicotine (for quitting smoking), estrogen delivery (for menopause and to prevent osteoporosis after meno bioavailable pause), nitroglycerin (for angina), and lidocaine to relieve the pain of shingles (herpes zoster). Molecules frequency, of insulin and many other substances, however, are too due to ma large to pass through the skin. Patches applied to the dosing skin eliminate the need for vascular access by syringe levels or the use of pumps. Transdermal patches were Transderm developed in the 1970s and the first was approved by new approved by the FDA in 1979 for the treatment of motion reducing sickness. (2)

1.1 ADVANTAGES-

- Transdermal drug delivery enables the avoidance of gastrointestinal absorption, with its associated pitfalls of enzymatic and pH associated deactivation.
- This method also allows for reduced pharmacological dosaging due to the shortened metabolization pathway of the transdermal route versus the gastrointestinal pathway.
- Self-administration is possible. (3)
- Plasma drug concentration becomes maintained.
- Side effect gets reduced. (4)

1.2. DISADVANTAGES-

- Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
- Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's impermeability. (5)
- Ionic drugs cannot be delivered by the body's immune system.
- Loss of dose may be due to the binding of medicine on the skin. (6)

2. ANATOMY & PHISIOLOGY OF THE SKIN-

Skin of an average adult body covers a surface of approximately 2 m. sq. and receives about one-third of the blood circulating through the body. Skin contains (Figure 1) an uppermost layer, epidermis which has morphologically distinct regions; basal layer, spiny layer, stratum granulosum and upper most stratum corneum, it consists of highly cornified (dead) cells embedded in a continuous matrix of lipid membranous sheets.

These extracellular membranes are unique in their compositions and are composed of ceramides, cholesterol and free fatty acids. The human skin surface is known to contain, on an average, 10-70 hair follicles and 200-250 sweat ducts on every square centimeters of the skin area. It is one of the most readily accessible organs of the human body. (7)

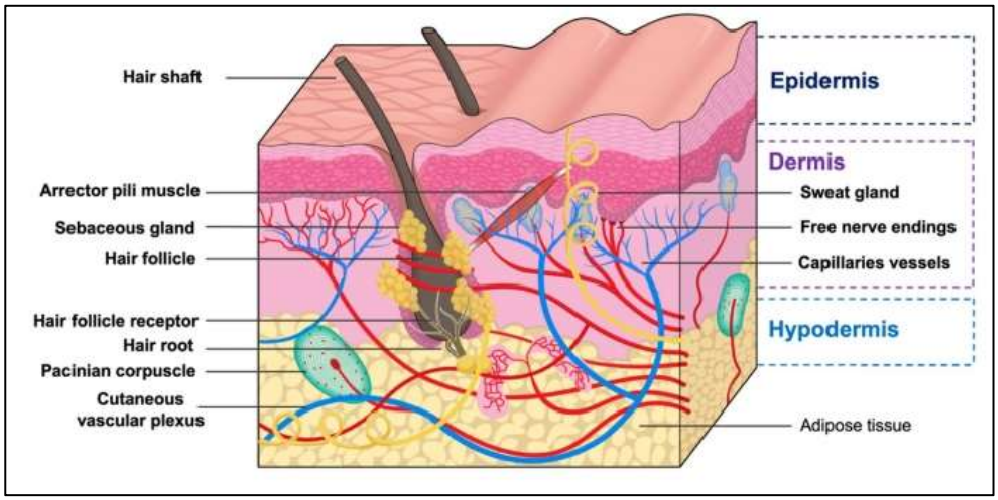

Fig.1. ANATOMY OF THE SKIN

2.1 Epidermis-

The epidermis the most superficial layer of the skin and is composed of stratified keratinisquamous epithelium which varied in thickness in different part of the body. It is thickest on the palms of the hands and soles of the feet. There are blood vessel or nerve ending in the epidermis, but its differ layers are bathed in interstitial fluid from the dermis which, provides oxygen and nutrient, and drains away as lymph. The maintenance of healthy epidermis depends upon three processes:

- Desquamation of the keratinized cell from the surface
- Effective keratinization of the cell approaching surface
- Continual cell division in the dipper layers with newly formed cells being pushed to the surface. (8)

2.2. Dermis –

Dermis is 3 to 5 mm thick layer and is made out of a lattice of connective tissue, which contains veins, lymph vessels and nerves. The cutaneous blood supply has basic capacity in direction of body temperature. It additionally gives supplements and oxygen to the skin while removing toxins and squander items. Vessels reach to inside 0.2 mm of skin surface and give sink conditions to most atoms entering the skin hindrance. The blood supply in this manner keeps the dermal centralization of a saturate low and the subsequent fixation contrast over the epidermis gives fundamental focus inclination to transdermal penetration.(4)

2.3. 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 three layers and reach in systemic circulation. (9)

3. Component of transdermal patch-

Fig.2. Component of transdermal patch

There are various components of transdermal patches of -

3.1. Polymer matrix –

The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in transdermal patches.

- Molecular weight, chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
- The polymer should be stable.
- The polymer should be nontoxic
- The polymer should be easily of manufactured.
- The polymer should be inexpensive
- The polymer and its deagration product must be non-toxic or non- antagonistic to the host.
- Large amounts of the active agent are incorporated into it.(10)

3.1.1. Polymer matrix is classified as,

(1) Natural polymers: Cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber, chitosan, etc.

(2) Synthetic elastomers: Polybutadiene, hydrin rubber, polyisobutylene, silicon rubber. Nitrile, acrylonitrile, neoprene, butyl rubber, etc.

(3) Synthetic polymers: Polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyuria, polymethylmethacrylate etc.(11)

3.2. DRUG -

The selection of drug for transdermal drug delivery depends upon various factors.

3.2.1. Physicochemical properties-

1) The drug should have some degree of solubility in both oil and water (ideally greater than 1 mg/ml)

2) The substance should have melting point less than 200 °F. Concentration gradient across the membrane is directly proportional to the log solubility of drug in the lipid phase of membrane, which in turn is directly proportional to the reciprocal of melting point (in degree absolute of the drug). In order to obtain the best candidates for TDD, an attempt should be made to keep the melting point as low as possible.

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

4) A saturated aqueous solution of the drug should have a pH value between 5 and 9. Drugs highly acidic or alkaline in solution are not suitable for TDD; because they get ionized rapidly at physiological pH and ionized materials generally penetrate the skin poorly.

5) Hydrogen bonding groups should be less than 2. (12)

3.3. Backing membranes:

These are flexible and they provide a good bond to drug reservoir, and also accept printing it is impermeable substance that protects the product during use on the skin. Examples of baking membranes: Metallic plastic laminate, flexible adhesive foam pad with occlusive base plate, plastic backing with absorbent pad and occlusive base plate (aluminum foil) disc (8).

3.4. Permeation Enhancers:

The chemical compounds that enhance the permeability of stratum corneum so as to attain therapeutic levels of the drug candidate. They improve the permeability by interacting with Stratum corneum.

3.4.1. Ideal Properties of Permeation Enhancer:

- They should be non-irritating, non-toxic & non- allergic.
- They should not bind to receptor site i.e. not showing any

Pharmacological activity.

- They should be cosmetically acceptable with and appropriate skin feel. (14)

3.5. Release Liner:

This is the primary packaging material that can protect the patch during application. It is made up of base layer which may be

a) Non-occlusive (e.g. paper fabric)

b) Occlusive (e.g. polyethylene, polyvinylchloride)

It is made up of silicon or Teflon. Release liner should be chemically inert & it should be permeable to drug, penetration enhancers & water.(14)

3.6. Other excipients such as plasticizers and solvents

Various solvents: Chloroform, methanol, acetone, isopropanol, and dichloromethane are used to prepare drug reservoir. Plasticizers: Dibutyl phthalate, triethyl citrate, PEG, and Propylene glycol added to provide plasticity to TD patches. (15)

4. Types of transdermal patch:

There are various types of transdermal patches -

4.1. Single-layer Drug-in-Adhesive:

The adhesive layer of this system also 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 surround by a temporary liner and a backing.(16)

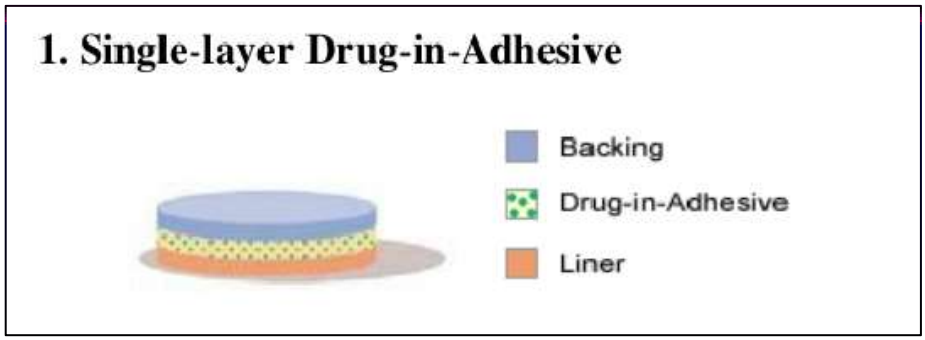

Fig.3. Single-layer Drug-in-Adhesive

4.2. Multi-layer drug in adhesive

Similar to the single layer drug in adhesive, the multi-layer drug in adhesive incorporates the medication right into the glue. However, the term "multi-layer" includes the insertion of a membrane between two different drug in adhesive layers as well as the placement of additional drug in adhesive layers beneath a single backing film. (17)

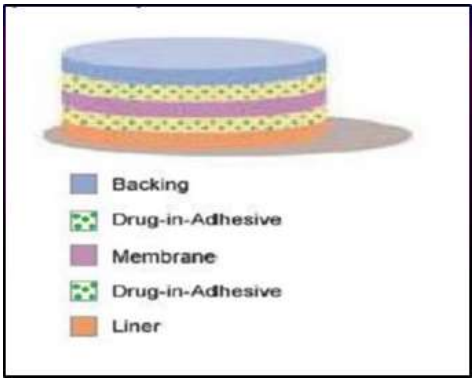

Fig.3. Multi-layer drug in adhesive

4.3. 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.(18)

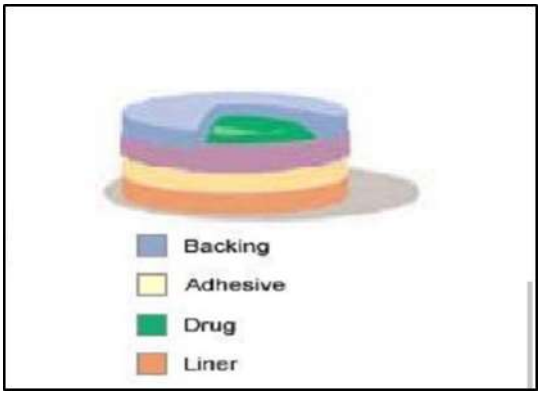

Fig.4. Reservoir

4.4. Drug matrix-in-adhesive:

This system is designed by inclusion of semisolid matrix having drug in solution or suspension form which is in direct contact with the release liner. (19)

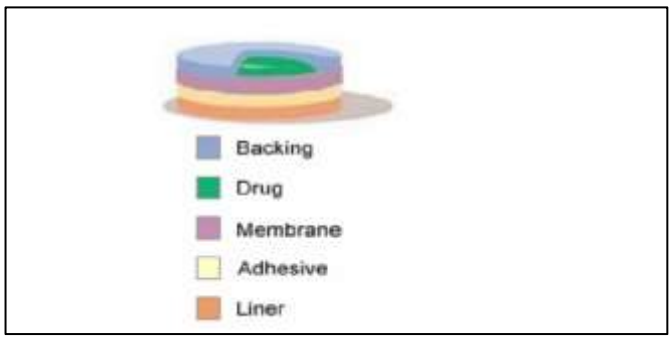

Fig.5. Drug matrix-in-adhesive

4.5. Vapour Patch:

Single layer of sticky polymer that has a vapour release feature On the market, there are a variety of various purposes For instance, nicodem is a type of nicoderm. CO patches are nicotine vapour transdermal patches with essential oils that, when activated, release nicotine vapour Can assist you in quitting smoking in 2007 this product was first launched to the European market. Another form of vapour patch that can be utilized in cases of decongestion altacura vapour patches, which included essential oils. There are also vapour patches that include antidepressant medications or sedatives on the market.(20)

5. APPLICATION 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

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 sometimes prescribed for the treatment of angina pectoris.

5. The anti-hypertensive drug Clonidine is available in transdermal patch form.

6. Transdermal form of the MAOI selegiline, became the first transdermal delivery agent for an antidepressant.(21)

6. FACTORS AFFECTING TDDS:

There are various factors which affects TDDS-

6.1. PH:

The pH of the skin is acidic (4-6). Generally said that the acidic pH of skin provides a defensive mechanism against microbes. The pH of the skin affected the penetration of unionized drugs for absorption. The skin is destroyed if the formulation has a very low or very high PH. (22)

6.2. Skin age:

The young skin is more permeable than older. Children are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug in TDDS. (23)

6.3. Skin temperature

The human body maintains a temperature gradient across the skin from around 37°C to around 32°C at the outer surface. Since diffusion through the stratum corneum is a passive process, elevation of the skin temperature can induce structural alterations within the stratum corneum, and these modifications can also increase diffusion through the tissue. (24)

6.4. Body site:

It is readily apparent that skin structure varies to some degree over the human body. However, the relative permeability of different skin sites is not simply a function of stratum corneum thickness as different permeates exhibit varied rank orders through different skin sites. It is apparent that genital tissue usually provides the most permeable site for transdermal drug delivery. The skin of the head and neck is also relatively permeable compared to other sites of the body such as the arms and legs. (24)

6.5. Hydration of skin:

The skin permeability increased when our skin saturated by water. In saturated condition skin, cells become soft and swell. At that condition, drug molecule can easily pass through the skin membrane. Some moisturizing agents are uses to the formulation of TDDS, like humectant. (25)

6.6. Blood flow:

Changes in peripheral circulation can affect transdermal absorption. Regional skin sites Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration. Skin metabolism Skin metabolizes steroids, hormones, chemical carcinogens and some drugs.so skin metabolism determines efficacy of drug permeated through the skin. (26)

6.7. 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.(27)

6.8. Drug concentration:

The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of will be more across the barrier.(27)

6.9. Species differences:

Mammalian skin from different species display wide differences in anatomy in much characteristics as the thickness of stratum corneum number of sweat glands and hair follicles per unit surface area. (28)

6.10. Molecular size and shape:

Drug absorption is reciprocally associated with molecular weight, small molecules.(29)

6.11. Partition coefficient:

The optimal partition coefficient (K) is needed for good action. Drugs with high K don't seem to be able to leave the spoid portion of skin. Also, medication with low K won't be permeated.(29)

7. Approaches to Development Transdermal Therapeutic systems:

Several technologies have been successfully developed to provide a rate control over the release and the transdermal permeation of drugs. These technologies can be classified into four approaches as

Follows:

7.1. Membrane permeation-controlled systems

7.2. Adhesive dispersion - type systems.

7.3. Matrix diffusion-controlled systems.

7.4. Micro reservoir type micro or dissolution controlled systems.

7.1. Membrane Permeation - Controlled Systems

In this type of system, drug reservoir is encapsulated in a shallow compartment moulded from a drug- impermeable metallic plastic laminate and a rate controlling polymeric membrane which may be micro porous or non-porous. The drug molecules are permitted to release only through the rate - controlling polymeric membrane. In the drug reservoir compartment, the drug solids are either dispersed homogenously in a solid polymer matrix (e.g. Polyisobutylene adhesive) or suspended in an unbleachable, viscous liquid medium (e.g. Silicon fluids) to form a paste like suspension.

The rate of drug release from this type of system can be tailored by varying the polymer composition, permeability coefficient and thickness of the rate limiting membrane and adhesive. The constant release rate of the drug is the major advantage of membrane permeation controlled system. However, a rare risk also exists when an accidental breakage of the rate controlling membrane can result in dose dumping or rapid release of entire drug content. Examples of this system are

- **Transdermal -Nitro**

Nitroglycerin releasing transdermal system for once a day medication in angina pectoris.

- **Transderm-Scop**

Scopolamine releasing transdermal system for 72hrs. Prophylaxis of motion sickness.

- **Catapres**

Clonidine -releasing transdermal system for 7 day therapy of hypertension.

- **Estraderm**

Estradiol - releasing transdermal system treatment of menopausal syndrome for 3-4 days. (30)

7.2. Adhesive Dispersion - Type Systems:

This is a Simplified form of membrane Permeation-Controlled System. In this system, drug and other selected excipients are directly incorporated into the adhesive solution. They are then mixed and casted as thin films and finally the solvent is evaporated by drying the film. The drug reservoir (film) is the then sandwiched between the banking laminate and rate-controlling adhesive polymer membrane.

- **This system have certain disadvantages:**

Physiochemical characteristics of the drug and adhesive system may provide very different release rates for hydrophilic and hydrophobic drugs. Incorporation of other excipients, such as skin permeation enhancers, into drug in adhesive system may alter drug release rates and adhesive properties. (13)

7.3. Matrix Diffusion-Controlled Systems:

In this the drug reservoir is prepared by homogeneously dispersing drug particles in a hydrophilic (or) lipophilic polymer matrix. The resulting polymer matrix is then moulded into discs with defined surface area and controlled thickness. The medicated disc is then moulded onto an occlusive base plate in a compartment made up of a drug impermeable backing. Finally adhesive polymer is spread along the circumference of the film.(13)

7.4. Micro Reservoir Type Controlled System:

This kind of TDDS is a combination of reservoir and matrix dispersion system. The drug reservoir is prepared by first suspending the drug in solution of water soluble polymer and then dispersing the formed drug suspension in a hydrophobic polymer homogeneously to form thousands of unreachable microscopic spheres of drug reservoir. These formulated dispersion are thermodynamically unstable and stabilized by crosslinking of polymer. (31)

CONCLUSION

TDDS is a newer approach in the area of dosage forms for many injected and orally delivered drugs having appropriate physicochemical and pharmacological properties. The purpose of this article was to provide valuable information on transdermal drug delivery systems. Transdermal drug delivery systems have been used as a safe and effective drug delivery device since 1981. Many drugs have been developed in the form of TDDS, such as hormonal therapy, various analgesics, drugs for heart disease, to prevent GI side effects and to start over. Alternative Route Indications are many, such as patients who do not like or are unable to swallow medication, oral cancer, throat and GI tract, GI tract disorders, intestinal obstruction, and intolerable side effects during administration, local pain treatment, to avoid systemic side effects, newborns / children etc. Transdermal drug delivery is not only about the patch and its use but it is a system that contains other ingredients such as ointments, creams, gels designed for use as a means of delivery of

drugs with the help of input enhancements but dosage. the concept cannot be effectively controlled by these semisolid formulations as it can be done elsewhere.

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