Transdermal Drug Delivery System: A Review

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Abstract: Despite making significant contributions to medical practice, transdermal medication administration has not yet reached its full potential as a substitute for oral delivery and hypodermic injections. The transdermal drug delivery system (TDDS) is the most appealing approach due to its low rejection rate, exceptional administration ease, and exceptional patient comfort and persistence. TDDS may find use not just in the pharmaceutical sector but also in the skin care sector, which includes cosmetics. because the primary component of this approach is local government Yep. A significant portion of drugs are carried into the systemic blood circulation using transdermal drug delivery systems (TDDS), which are dosage forms that entail delivering drugs to the skin's viable epidermal and/or dermal tissues for a local therapeutic impact. The quality, safety, and efficacy of the transdermal drug delivery system depend on the adhesive. Topical administration of medicinal substances offers a number of benefits over conventional oral and invasive medicine delivery methods. Transdermal drug delivery has several important advantages, including reducing hepatic first-pass metabolism, enhancing therapeutic efficacy, and preserving a steady medicine plasma level. This page provides a summary of transdermal patch types, preparation methods, and physicochemical evaluation approaches.

1. INTRODUCTION

Transdermal Devices for transdermal drug delivery, sometimes called "patches," are dosage forms designed to apply a therapeutically effective amount of medication to a patient's skin. To transfer therapeutic substances through the human skin for systemic effects, it is necessary to take into account the skin's entire morphological, biophysical, and physicochemical characteristics. Because hepatic first pass delivery is limited, transdermal drug delivery provides a significant benefit over injectables and oral routes by decreasing first pass metabolism and improving patient compliance, respectively. [1] Transdermal delivery removes pulsed entry into the systemic circulation, which frequently results in unwanted side effects, and permits continuous input of medications with short biological half-lives. It also offers controlled, continuous drug administration. As a result, a variety of innovative medication delivery methods, including transdermal, controlled release, and transmucosal, were developed. Numerous crucial metabolic processes, improved therapeutic efficacy, and sustained medication plasma levels. In 1979, the FDA approved Transdermal-SCOP, the first transdermal device, to reduce travel-related nausea and vomiting, especially when traveling by sea. Indicators of percutaneous drug absorption include the patient's clinical response to the recommended pharmacological therapy, detectable drug and metabolite excretion in the urine, and measurable drug levels in the blood. [2]

The following are typical ingredients used in the production of TDDS.

- Drug: There is direct interaction between the medication and the release liner. For example, nicotine, methotrexate, and estrogen.
- Liners: Preserve the patch while it's being stored. For example, polyester film.
- Adhesive: Helps the patch stick to the skin so the medication is delivered throughout the body. For example, silicones, polyisobutylene, and acrylates.
- Enhancers of Permeation: Regulate Drug Release. For example, pyrrolidones, terpenes, and terpenoids. solvents such as methanol, ethanol, and alcohol. Surfactants such as Pluronic F127, Pluronic F68, and Sodium Lauryl Sulfate.
- Backing layer: The backing layer shields the patch from the outside world. Examples include polypropylene silicone rubber, polyvinyl alcohol, and cellulose derivatives.

TDDS BENEFITS [4][5]

- Prevents first-pass metabolism in the liver.
- Keeps blood levels steady for an extended amount of time.
- Make bioavailability better.
- Lower the dosage that has to be given.

- Reduce adverse or undesirable effects.
- Reduce adverse effects on the gastrointestinal tract.
- Simple to stop if hazardous symptoms occur.
- Boost patient adherence.

TDDS DISADVANTAGES [4][5]

- The price is expensive.
- Ionic medications cannot be delivered via TDDS.
- High drug levels in the blood or plasma cannot be achieved via TDDS.
- Is unable to create TDDS for medications with big molecules.
- TDDS is unable to provide pulsatile medication delivery.
- If a medication or formulation irritates the skin, TDDS cannot develop.

2. ANATOMY AND PHYSIOLOGY OF SKIN

The skin has developed into a very effective barrier that keeps xenobiotics from entering the body and stops excessive water loss. It makes it possible for us to endure a wide variety of environmental difficulties. For the sake of this chapter, the numerous reasons for this can be summed up simply. Almost all substances diffuse through the stratum corneum, the outermost layer of the skin, which acts as a rate-controlling barrier. It is made up of corneocytes, which are keratin-rich, dead, and flattened cells. A unique blend of intercellular lipids envelops these thick cells. They include ceramides, free fatty acids, cholesterol, and cholesterol sulfate. The fact that they are organized into orderly bilayer arrays is their most significant characteristic. Intercellular diffusion seems to be the most common way for molecules to get across the stratum corneum. [6] Because of the barrier qualities, penetration across epithelial boundaries occurs slowly. The stratum corneum in particular has a barrier against drug penetration because of its low moisture of 15 to 20% and high density (1.4 g/cm2 in a dry condition). The stratum corneum's constant replenishment further aids the barrier function, reducing topical and transdermal bioavailability. As a result, a lot of research has been done in the field of penetration improvement in recent years [7]. Slow penetration rates, a lack of dosage flexibility, and the restriction to relatively low dosage medications are some of the limitations. [8]

The human skin is composed of three distinct yet interconnected tissues:

- The stratified epidermis is cellular and vascular.
- Connective tissue's underlying layer.
- The Hypodermis.

A. Epidermis-

With thicknesses ranging from 0.8 mm on palms and soles to 0.06 mm on eyelids, the multilayered epidermis is dependent on the size of its cells and the number of cell layers. There is a viable epidermis and an exterior stratum corneum.

B. Horney layer (Stratum corneum)-

The Horney layer is another name for this topmost layer of skin. It is roughly 10 µm thick while dry, but when completely hydrated, it swells to many times its thickness. Corneocytes are dead, keratinized cells that make up 10 to 30 layers of it. There are three ways that medication molecules can enter the stratum corneum. There are several ways that a drug can be absorbed through the skin, depending on its physicochemical properties. Drugs that are hydrophilic or lipophilic are absorbed through different pathways.

- Transcellular route
- Intercellular route
- Trans follicular route

C. Viable epidermis-

This is located underneath the outermost layer and ranges in thickness from 0.8 mm on the palms to 0.06 mm on the sole of the eyelids. It is composed of several layers that run inward, including the stratum lucidum, stratum spinosum, stratum granulosum, and the stratum basal. The epidermis is continuously reproduced by cell divisions in the basal layer, and this multiplication makes up for the loss of dead Horney cells from the skin's surface.

D. Dermis-

The dermis is a 3–5 mm thick layer made up of a connective tissue matrix that includes nerves, lymphatic and blood arteries. One important factor in controlling body temperature is the cutaneous blood supply. It provides the skin with oxygen and nourishment while eliminating waste and impurities. Capillaries, which are 0.2 mm from the skin's surface, are where the majority of molecules that

break through the skin barrier sink. Transdermal penetration depends on the concentration gradient that results across the epidermis, which is maintained by the blood supply at a very low dermal concentration of a permeant.

E. Hypodermis-

The hypodermis, also referred to as subcutaneous fat tissue, supports the dermis and epidermis. It serves as a fat storage space. This layer helps regulate temperature, provides mechanical protection, and supports nutrients. It may have organs that sense pressure and links the skin to the body's main blood arteries and nerves.

3. ROUTE OF DRUG PENETRATION THROUGH HUMAN SKIN

A molecule comes into contact with sebum, bacteria, cellular debris, and other substances when it reaches intact skin. The diffusant can then enter the living tissue in three different ways: through the sweat ducts, the continuous stratum corneum between these appendages, or the hair follicles and the sebaceous glands that are connected to them. The stratum corneum's intracellular zone is filled with lipid-reach amorphous material, according to electron photomicroscopic analysis. The lipid composition changes from polar to neutral components during cornification. Intracellular diffusion volume in the dry stratum corneum can be at least 1% and up to 5% of the fully hydrated stratum corneum. Intracellular diffusion may be important because this intracellular volume is at least an order of magnitude larger than the intra-appendageal pathway's estimated volume (about 0-2%). Cell membranes most likely have only minimal effects on skin permeability; the hydrated protein inside corneocytes and the organized lipid environment between cells both play substantial roles. Two possible drug penetration pathways are depicted in these pictures.

- Intracellular: in the space between cells and
- Transcellular: spanning an area rich in lipids.

The transcellular route serves as the primary mechanism during percutaneous absorption, at least for polar medicines. Since there is very little fractional area available for absorption, the transappendageal pathway usually cannot make a substantial contribution to the steady state flow. For ions and big polar compounds, which have trouble passing through intact stratum corneum, this pathway might be crucial.

4. BIOPHARMACEUTICAL FACTORS IN TRANSDERMAL PATCH DRUG SELECTION [9]

The dosage should be minimal, less than 20 mg per day.

- The ideal half-life is 10 hours or less.
- The molecular weight ought to be less than 400.
- Log P (octanol-water) should be the partition coefficient, and it should range from 1.0 to 4.
- Skin permeability should be less than 0.5 x 10-3 cm/h.
- Skin irritation or hypersensitivity should not result from the drug.
- Oral bioavailability ought to be minimal.
- A low therapeutic index is ideal.

5. TYPES OF TRANSDERMAL PATCHES [1][10]

- Single-layer drug-in-adhesive.
- The Multi-layer drug-in-adhesive.
- Drug Adhesive Reservoir.
- Drug Matrix-in-Adhesive
- Vapour patch.

1. Single-layer Drug-in-Adhesive:

This type of adhesive is unique in that the medication is integrated directly into the skin contacting substance. The adhesive in this transdermal system design serves as both the foundation for the formulation and a way to adhere the system to the skin. It holds the medication and all excipients together in a single backing sheet. The rate at which the drug diffuses through the skin affects the medicine release rate of this kind of system.

2. The Multi-layer Drug-in-Adhesive:

The medicine is integrated into the adhesive itself, making this kind of drug-in-adhesive similar to single-layer drug-in-adhesive.When two separate drug-in-adhesive layers are placed on top of a single backing film, the term "multi-layer" refers to the addition of a membrane or multiple drug-in-adhesive layers.

3. Drug Adhesive Reservoir:

The addition of a liquid compartment with a medication solution or suspension that is kept apart

from the release liner by an adhesive and semi-permeable membrane is what distinguishes it. It is possible to incorporate the adhesive component of the product that is responsible for skin adhesion in a concentric design around the membrane or in a continuous layer between the membrane and the release liner.

4. Drug Matrix-in-Adhesive:

A semisolid matrix containing a medication suspension or solution that comes into direct touch with the release liner is what sets this type of adhesive apart. The skin-adhesive component is integrated into an overlay and surrounds the semisolid matrix in a concentric pattern.

5. Vapour Patch:

This kind of patch has an adhesive layer that releases vapor in addition to gluing the several layers together.The market for vapour patches, which may release essential oils for up to six hours, is just getting started. Vapour patches, which can release essential oils for up to six hours, are a relatively new product. Essential oils are released by the vapor patches, which are mostly used to treat decongestion cases. Alternatives include controller vapour patches, which improve the quality of sleep. Additionally, there are vapour patches available that can reduce a person's monthly cigarette use. Additionally, months are offered for sale [11].

1. TDDS components [12]:

The primary components of a transdermal patch are as follows:

Liner of Release

keeps the patch safe while being stored. Before using, the liner is taken out.

Drug storage facility

TDDS's drug reservoir is its most crucial component. The drug particles are dissolved or scattered throughout the matrix. To render the medication soluble, a variety of solvents and cosolvents are employed. When making a choice, one should take the effects of the solvent and cosolvent into account.

Adhesive

Adhesive aids in securing the patch to the skin and holding its constituent parts together. For the TDDS to stay in place for an extended period of time, the glue must have enough adhesion properties. Transdermal patches are frequently held in place by pressure-sensitive adhesives. Poly isobutylene adhesives, silicone adhesives, and adhesives based on polyacrylate are frequently utilized.

The Membrane

The membrane controls the drugs release from the reservoir and multi-layer patches. It might or might not have a membrane that controls its rate. It must be sufficiently flexible to avoid splitting. It needs to be flexible enough to prevent splitting. Or break when bent or stretched. Cellulose acetate, polyethylene sheets, and ethylene vinyl acetate copolymer are a few examples of rate-controlling membranes.

Backing

The backing protects the patch from the surroundings. Drugs and penetration enhancers should not be able to pass through the backing layer. It keeps the entire system in place and shields the medication reservoir from the air. Polyesters, siliconized polyethylene terephthalate, and aluminized polyethylene terephthalate are the most often until.

6. DIFFERENT TECHNIQUES FOR TDDS PREPARATION

i) The method of asymmetric TPX membrane

Concave polyester film (type 1009, 3m) with a 1 cm diameter and heat-sealing capabilities will be used to create the backing membrane for the prototype patch. Once the drug sample has been distributed throughout the concave membrane, the TPX poly (4-methyl-1-pentene) asymmetric membrane is sealed with an adhesive [13].

ii) The Teflon mold technique

In an organic solvent, solutions with different ratios of polymers are employed. Half the amount of the same organic solvent is used to dissolve the calculated amount of medication. The remaining half of the organic solvent is used to dissolve enhancers at varying concentrations, which are then added. A plasticizer called di-N-butyl phthalate is added to drug polymer solutions. Stir the mixture for 12 hours, then pour it into a circular Teflon mold. To regulate solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s, the molds must

be set up on a level surface and covered with an inverted funnel. The solvent is allowed to evaporate for twenty-four hours. To remove the effects of aging, the dried films must be kept in a desiccator with silica gel for a further 24 hours at 25±0.5°C prior to analysis. Within a week of being prepared, the type films need to be assessed [14].

iii) The technique of mercury substrate

The plasticizer and medicine are dissolved in a polymer solution. Once the previously mentioned solution has been agitated for 10 to 15 minutes to create a homogeneous dispersion, it should be poured over a flat mercury surface and covered with an inverted funnel to control solvent evaporation. [15]

iv) By using IPM membranes method

This technique involves dispersing the medication in a solution of water and propylene glycol that contains the carbomer 940 polymer, and then stirring the mixture for 12 hours using a magnetic stirrer. Triethanolamine is added to the dispersion to neutralize it and make it viscous. Buffer pH 7.4 can be used to create a solution gel if the medicine has extremely low solubility in aqueous solution. The IPM membrane will integrate the gel that has been created [16].

v) By applying the EVAC membranes technique

The necessary transdermal treatment system can be constructed using rate control membranes such as polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes, and 1% Carbopol reservoir gel. If the drug is insoluble in water, propylene glycol is used to make gel. The medication is dissolved in propylene glycol, followed by the addition of carbopol resin and neutralization with a 5% w/w sodium hydroxide solution. On a backing layer sheet, the medication (in gel form) is applied to the specified location. The gel will be covered with a rate-controlling membrane, which will be heated to seal its edges and create a leak-proof device.

vi) The adhesive film approach with an aluminum backing

Unstable matrices may arise if a transdermal drug delivery device's loading dose exceeds 10 mg. It is appropriate to use the sticky film approach with an aluminum backing. Since most medications and adhesives dissolve in chloroform, it is the solvent of choice for making the same. After the medicine has been dissolved in chloroform, sticky material is added and dissolved in the drug solution. Aluminum foil is used to line a custam-made aluminum former, and precisely fitted cork blocks are used to blank off the ends [18].

vii) Using Pro liposomes to Prepare TDDS

The pro liposomes are made using the carrier strategy and the film deposition method. Lecithin and the aforementioned reference drug work best together at a ratio of 0.1:2.0. 5mg of mannitol powder is added to a 100 ml round-bottom flask that is maintained between 60 and 70°C in order to generate the pro liposomes. For 30 minutes, the mannitol is vacuum-dried while the flask rotates at 80 to 90 rpm. Following drying, the water bath's temperature is maintained between 20 and 30°C. 0.5 cc of the organic solution is added to the round-bottomed flask and heated to 37°C once the medication and lecithin have been dissolved in the proper organic solvent mixture. Another 0.5 ml aliquot of the solution is to be added once the flask has completely dried. Following the final loading, the flask holding the pro liposome is attached to a lyophilizer. After spending the full night in a desiccator, the drug-loaded mannitol powders (pro liposomes) are sieved through 100 mesh. Before being characterized, the collected powder is kept in a glass bottle at the freezing temperature. [19][20]

viii) By employing the free film technique

Casting on the surface of mercury creates a free film of cellulose acetate. Chloroform should be used to create a 2% w/w polymer solution. A 40% w/w concentration of polymer weight is required for the incorporation of plasticizers. A glass ring set over the mercury surface in a glass petri dish was filled with five milliliters of the polymer solution. An inverted funnel is placed over the Petri dish to regulate the solvent's rate of evaporation. After the solvent has completely evaporated, the mercury surface is examined to observe the film creation.
Before being used, the dried film will be separated and kept in a desiccator between the wax paper sheets. By altering the amount of the polymer solution, free films with varying thicknesses can be created [21].

ix) Easy Transdermal Patch Preparation Method
The previously published methods were modified to create a summary of the TDDS preparation process.

The solvent casting procedure was used to prepare the patches. A small amount of the solvent was added to a beaker containing the polymer (for instance, PVP/HPMC). The other polymers, such PVA, were then combined with two-thirds of the solvent and added, initially with stirring at a lower rpm and then at a greater speed. The plasticizer was added and well mixed, the medication was added while being constantly stirred, and the volume was changed. After being cast onto a properly made and planned glass mold, the films were dried at 400 degrees Celsius in an oven. A sharp blade was inserted along the film's edges to remove the films. After drying, the films were wrapped in butter paper and kept in a cool, dark area in a covered container [22][23].

7. TDDS APPLICATIONS

The nicotine patch, which distributes nicotine in controlled dosages to aid in quitting tobacco use, is the most popular transdermal patch in the United States. In 2007, Europe authorized the first vapour patch to be sold commercially to help people quit smoking.

Fentanyl CII (marketed as Duragesic) and buprenorphine CIII (marketed as BuTrans) are two opioid drugs that are frequently administered in patch form to treat severe pain 24/7.

- Hormonal patches:
- In addition to treating post-menopausal osteoporosis and menopausal symptoms, estrogen patches are occasionally given as a kind of hormone replacement therapy for transgender women.
- Patches for contraception (marketed as Ortho Evra or Evra) and
- TestosteroneWomen's (Intrinsa) and men's (Androderm) testosterone CIII patches.

Sometimes, nitroglycerin patches are prescribed instead of sublingual pills to treat angina.

Motion sickness is frequently treated with transdermal scopolamine.

Clonidine, an antihypertensive medication, comes as transdermal patches.

The first transdermal antidepressant delivery system approved for use in the US was Emsam, a transdermal form of the MAOI selegiline, in March 2006.

In April 2006, the FDA authorized Daytrana, the first transdermal administration method for methylphenidate used to treat attention deficit hyperactivity disorder (ADHD).[24]

In October 2019, the FDA approved Secuado, a transdermal version of the atypical antipsychotic asenapine.[25]

A transdermal patch can also be used to deliver vitamin B12. Transdermal patching is compatible with cyanocobalamin, a very stable type of vitamin B12.[26]

A transdermal patch, which was introduced in the UK in early 2014, is another way to give 5-hydroxytryptophan (5-HTP).[27]

In 2007, rivastigmine, a drug used to treat Alzheimer's, was made available as patches under the Exelon brand.[28]

In order to store medical information subcutaneously, Robert S. Langer and his colleagues created and patented a method in December 2019 that would allow transdermal patches to be used to label patients with invisible ink. The idea was that this would help "developing nations" where medical records are scarce due to a lack of infrastructure. A "quantum dot dye that is delivered along with a vaccine" is used in the technology.[29]

Caffeine patches, which are intended to supply caffeine to the body via the skin. (30)

8. CONCLUSION

As a helpful resource for research scientists working on transdermal drug delivery systems (TDDS), the review articles provide valuable insights on TDDS and its evaluation process. Since TDDS can be utilized to produce prospective deliverable pharmaceuticals from both hydrophobic and hydrophilic active molecules, the information above shows that TDDS have tremendous potential. To maximize this drug delivery technique, more understanding of the different biological interactions and polymer mechanisms is required. TDDS, the upcoming generation of drug delivery systems, has a useful, actual use.

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