INTRODUCTION

High blood pressure is a known indicator of cardiovascular disease. Cardiovascular disorders, such as coronary artery disease and stroke, have been linked to elevated blood pressure. The risk of dying from a heart attack or stroke increases in the populace who have hypertension. Tight BP management is acknowledged to be important, and it is estimated that approximately half of all hypertension patients have insufficiently managed BP. Antihypertensive drugs are good for transdermal drug delivery systems (TDDS) because their first-pass metabolism is high and their bioavailability varies. The study reviewed amlodipine besylate, nicardipine hydrochloride, timolol maleate, captopril, atenolol, clonidine, indapamide, labetalol, pinacidil, metoprolol tartrate, verapamil hydrochloride, nitrendipine, nicorandil, propranolol, diltiazem, nifedipine, carvedilol, and lisinopril. TDDS is a controlled way to get drugs through the skin. Improved TDDS are an example of CDDS category. The procedure is usually well-liked by patients and causes no discomfort. It can be utilized to provide same-day local delivery. Continuous transdermal drug administration through the skin is gaining popularity as a safer alternative to intravenous drug infusion. Transdermal patches are adhesive patches containing medicine that are applied to skin to administer a controlled quantity of medicine transdermally for the treatment of systemic disorders. This iteration of the transdermal therapeutic system (TTS) has been available commercially since the 1980s.

Skin and Its Composition

The skin covers almost every other part of the body. The skin protects the interior of the body from environmental hazards; it has a surface area of around 1.5 to 2 m². It regulates body temperature, defends against viruses, maintains electrolyte balance, and shields the body from chemical agents, physical damage, and ultraviolet radiation, to name a few of its many functions. Drugs can enter the body and have an effect via the skin, making it a significant drug delivery system. There are three distinct layers to the skin: the epidermis, the dermis, and the hypodermis (subcutaneous tissue). It is totally unique compared to the rest of the layers. Structured like bricks and mortar, it is formed of dormant keratinocytes and intercellular lipids. Intercellular lipids constitute the mortar, whereas protein-rich keratinocytes are the bricks. It is the chief component of the skin barrier and the primary factor in reducing the rate of percutaneous absorption, despite its very modest thickness (only 10–20 m). Drugs can enter the body through one of two routes. The first is via the skin's innate pathways. These tiny, water-safe passageways are ideal for transporting liquids. The alternative route involves crossing the epidermis, penetrating it and deeper epidermis, and finally entering the dermis and the capillaries from there. Stratum corneum can be penetrated by medicines in two different ways. Keratinocytes and intercellular lipids allow chemicals to enter the skin and be transferred along the transcellular pathway.
The drug may not be able to reach its target since it must first pass through water-loving and water-hating tissues. Drugs can also enter it through intercellular spaces, but this is a less likely route. Cutting through the lipid membranes that protect the keratinocytes is a time-consuming process.

*First generation transdermal patches*

As the 1st kind of patch, they have been utilized in a lot of clinical settings. On the transdermal patch, drugs are kept in a reservoir. The patch is then stuck to the skin with an adhesive and a backing that doesn’t let the skin breathe. Most of the time, the first generation of transdermal patches can only reach the stratum corneum.

*Second-generation transdermal patches*

Improved drug delivery and skin permeation are made possible by the innovative method used in the latest generation of transdermal patches. Chemical enhancers, non-cavitation ultrasound, & iontophoresis are all examples of modern enhancement techniques that have struggled to strike a satisfactory balance between deeper penetration into the stratum corneum and protection of deeper tissues.

*Third-generation transdermal patches*

To disrupt stratum corneum devoid of damaging deeper tissues, third-generation of transdermal delivery methods employ a specialized approach.

**Mechanisms of Transdermal Permeation**

In order for a medicine having systemic effects to reach its intended target, that drug must first be absorbed via the skin and then taken up by the dermal papillary capillary network. Permeation rates (given as $\frac{dQ}{dt}$) through different dermal layers are common.

$$\frac{dQ}{dt} = Ps(Cd - Cr) \quad \text{(1)}$$

In this equation, $Ps$ represents the total permeability coefficient of the skin, while $Cd$ and $Cr$ represent the conc. of skin penetration inside this donor phase (stratum corneum) and also the receptor phase (systemic circulation), correspondingly.

$$Ps = Ks \frac{Dss}{hs} \quad \text{(2)}$$

Where,
- $Ks$ = Partition coefficient
- $Dss$ = Apparent diffusivity
- $hs$ = Thickness of skin

As the terms $Ks$, $Dss$, and $hs$ in equation (2) are constants under the given conditions, the permeability coefficient ($Ps$) might likewise be constant. If $Cd > Cr$, then we can simplify the drug permeation rate equation (1) to

$$\frac{dQ}{dt} = Ps.Cd \quad \text{(3)}$$

If $Cd$ value is relatively stable over the period of skin permeation, then the skin permeation rate ($dQ/dt$) will also be stable. In order to keep the $Cd$ steady, the drug’s release rate ($Rr$) must be higher than the skin’s absorption rate ($Ra$), or $Rr >> Ra$.

This wants to make sure that drug’s $Cd$ at the skin’s surface is always higher than drug’s sc solubility at saturation ($Cs$).

Given the comparison in equation (4), this means that $Cd$ is more permeable through the skin than cesium:

$$\frac{dQ}{dt} = Ps.Cs$$

The amplitude of ($dQ/dt$) m appears to be determined by the drug’s skin permeability coefficient ($Ps$) and its optimum dissolution in the stratum corneum ($Cs$).  

**Components of Transdermal Patch**

*Polymer matrix*

While designing a system to administer medications transdermally, polymers play a vital role. The drug reservoir or polymer matrix in transdermal delivery systems is sandwiched between two polymers: an outer impermeable polymeric layer that acts as an adhesive and rate-controlling membrane. While designing effective transdermal delivery systems, it is essential to think about the polymers used and how they are built. The primary confrontation is in the design of the polymer matrix, namely in optimizing the drug-loaded matrix for release qualities, adhesion, physicochemical properties, stability, and overall compatibility with the rest of the system and skin. Natural polymers, synthetic elastomers and synthetic polymers are employed.

*Drug*

The medicine must have the ideal physical, chemical, and pharmacokinetic qualities for TDDS to be effective. Drugs are released slowly through the skin using transdermal patches. This is particularly important for drugs that have a small therapeutic window, require substantial first-pass metabolism, or have a short half-life and thus raise the risk that individuals will forget to take their prescription as prescribed. Methylphenidate treatment of attention deficit hyperactivity disorder (ADHD), imipramine hydrochloride for depression, and benzotropine for Parkinson’s disease are just a few examples of recently authorized medications.

*Permeation enhancers*

Enhancers use proteins or lipids, which are structural parts of the stratum corneum, to continue increasing permeability and get higher therapeutic drug levels. Enhancers converse to proteins or lipids in the stratum corneum to increase permeability and, in turn, therapeutic drug levels. This is likely how enhancers help oil-soluble medicines get into the skin. Chemical enhancers strip the skin of some of its lipids, making it more permeable to oil-soluble medicines. This increases the skin’s permeability, both transcutaneously and transfollicularly, so that it can be more easily soaked up by liquids. The efficiency with which water-soluble medicines are absorbed via the skin may be attributable to the miscibility as well as solubility of such permeation enhancers employed.

Drugs can penetrate the skin more easily with the use of physical procedures as iontophoresis, electroporation, sonophoresis, and microscopic projection. In addition to thermal magnetophoresis, permeation, and photomechanical waves, other ways is employed to apply the transdermal patches.
Pressure sensitive adhesive

A pressure-sensing adhesive (PSA) keeps patch securely adhered to the skin. It ought to stick quickly when you press your finger on it, stay put securely, and feel aggressive when you press down. Polycrylates, polyisobutylene, and silicon-based adhesives all fall within this category. The patch’s design and the drug’s composition are two of the many considerations when deciding on an adhesive. Physical stability adjuncts (PSA) should be biocompatible and not affect drug release. PSA can be found anywhere on the device, but most commonly on the front (as in a reservoir system) or the back (with a peripheral extension).

Backing laminate

Backing laminate primarily serves as a support system. The adhesive must be chemically stable and compatible with the excipients. The excipients, medication, or permeation enhancer may pass through the backing layer if they are in contact with it over an extended period of time, and the additives may seep out. They should let less moisture vapor through. They must be highly resilient, versatile, and sturdy.

Release liner

Because the medicine has now gone inside the sticky layer, the release liner prevents it from being misplaced or contaminated during storage. Hence, it is not considered to be a component of the drug’s dosage form but a rather primary packaging. The released liner consists of a non-obstructive base layer (often paper cloth) and a release coating layer (typically silicon or Teflon), both of which aid in releasing the product. You can also build TDDS-release liners out of polyester foil or metalized laminate.

Other excipients

Methanol, chloroform, acetone, isopropanol, and dichloromethane are some examples of solvents that can be employed to create a drug reservoir. Plasticizers such as dibutyl phthalate, triethyl citrate, polyethylene glycol, & propanediol are added to the transdermal patch so that it may be applied more easily and has a greater range of motion.8

Method of Preparing Transdermal Patches

The process of creating TDDS can be summed up by modifying the original report. The patches are manufactured using a process called solvent casting, as seen in (Figures 1 and 2). Polymers such as PVP/HPMC are placed in a beaker containing the smallest possible amount of solvent. Then, the other polymers (such as PVA) are added to the solvent mixture, first slowly and subsequently more quickly. The plasticizer is poured in and thoroughly combined. To increase the volume, the medicine is added and swirled for several minutes. The films are poured into a custom-made glass mold before being cured in an oven set to 40°C. The films are removed by sliding a sharp blade along the film’s edges and then pulling the blade out.9,10

Modern Techniques for Transdermal Drug Delivery System

Different methodologies have been developed to enhance transdermal drug absorption, including permeation enhancement through iontophoresis, electroporation, ultrasound etc.

Iontophoresis

By keeping an electrode in constant contact with the drug being administered, and applying a very low current (just a few milliamperes), this technique improves the effectiveness of antihypertensive medication. Increased drug penetration can be attributed to electrorepulsion, electro-osmosis, and electroperturbation, as demonstrated in (Figure 3). Transdermal indomethacin patch, to give one example.
Electroporation
To temporarily disrupt the structure of lipid bilayer membranes, electroporation can be utilized (Figure 4). Evidence suggests that transdermal medication delivery is significantly enhanced when applied topically. It is hypothesized that electroporation makes the skin more permeable by temporarily creating pores. Electroporation is a physical transfection method that uses an electric pulse to create pores in cells. This method increases diffusion across biological membranes. E.g., Ibuprofen transdermal patch, zudovidine transdermal patch.

Magnetophoresis
The purpose of a magnetic field to improve the transdermal delivery of a nonmagnetic solute is known as magnetophoresis. The magnetic field provides an extra push. Exposure to a magnetic flux may also induce structural changes in the skin that increase its permeability. Researchers found that the strength of a magnetic field had an effect on the rate at which carboxylic acids flowed in vitro. The influence of magnetic flux just on the diffusion flux of a pharmacological ingredient was observed to increase by growing magnetic flux strength. This system can only use with diamagnetic material. E.g., lidocaine hydrochloride transdermal patch.

Ultrasound (phonophoresis, Sonophoresis)
This technique has found widespread application in the fields of sports medicine and physical rehabilitation. A medicine is placed on the skin, and also the area is massaged with ultrasound waves. It utilizes ultrasonic energy to boost the quantity of solute absorbed through the skin. It can also be called phonophoresis or sonophoresis (Figure 5). Ultrasonic energy breaks up how the lipids in SC are packed together through a process called cavitation. By making the free volume space in bimolecular leaflets bigger, shock waves from collapsed vacuum cavities make it easier for drugs to get into tissues. E.g., amlodipine transdermal patch.

Microscissuining
This technique uses sharp microscopic metal grains to erode the skin’s impervious outer layers, thereby creating microscopic passageways. Transdermal patches like clonidine, for instance.

Microporation
Microporation is the process of making the skin more permeable by puncturing it with extremely fine needles. Microneedles are needles that range in size from 10 to 200 microns in height and 10 to 50 microns in width. Patients feel no pain or discomfort since microneedles do not activate nerves. Common examples are solid silicon spikes with a drug coating or hollow metal needles containing medicines. One such patch is lopinavir transdermal.

Skin abrasion
Outer layer of skin are scraped off otherwise disrupted to facilitate the absorption of topical drugs. Devices developed from the same principles as those used among dermatologists during superficial skin resurfacing can be effective in treating acne, scars, pigmentation, or other skin defects (such as microdermabrasion). Like as the transdermal patch rivastigmine.

Needle-less injection
This transdermal delivery technique employs a dependable energy source to propel liquid or solid medication particles through the epidermis and dermis at supersonic speeds. The process works by pressurizing helium through a nozzle, where the drug particles are dispersed in a fast-moving jet flow that can penetrate the skin. Such is, a transdermal patch containing lidocaine hydrochloride.

Microneedles
Microneedles, as depicted in, were developed for subcutaneous drug administration (Figure 6). Microneedles made of solid material can puncture the skin painlessly. As a result, an extended-release patch is more effective at penetrating the skin and delivering its payload of tiny chemicals, nanoparticles, and proteins. Microneedles can be coated with a variety of things, including tiny chemicals, DNA, proteins, and virus particles. Microneedling was performed on the skin of healthy volunteers before they were given naltrexone in a recent study. Instance: meloxicam.

Electro-osmosis
By applying a voltage differential to the charged porous membrane, fluid can flow in large volumes without encountering any concentration gradients. The term “electro-osmosis” describes this phenomenon. E.g., polyglycidile methacrylate transdermal patch.
**Laser radiation**

In this method, a laser is used to expose the skin directly and in a controlled way. This removes the stratum corneum without hurting the epidermis too much. It has been shown that lipophilic and hydrophilic drugs work better when the stratum corneum is destroyed in this way. The emergence of temporary channels may serve as a permeabilization process; photomechanical waves make the stratum corneum much more open to drug substances. For example, the transdermal ketoprofen-cyclodextrin patch.

**Thermophoresis**

The average human body maintains a surface temperature of 32°C. It was demonstrated that increasing the temperature at the point of administration raised the dose of tetracaine plus fentanyl from transdermal patches equipped with heating devices. However, the impact of temperature on the penetrability of drugs with a molecular weight more than 500 Daltons has not been discussed. E.g., hydroxypropyl beta cyclodextrintransdermal patch.  

**Characterization of Transdermal Patch**

**Thickness**

The average thickness was determined after taking measurements with a screw gauge at various points across the patch.

**Weight variation**

The average weight was obtained after the weight of each individual 2 x 2 cm² patch was measured.

**Folding endurance**

To find out how long a patch could be folded, it was folded and opened at the same spot until it broke at the folding site. The significance was written as a number, which showed how many times the patch had to be folded to make a break.

**Loss of moisture**

The weight of 1 x 1 cm², after being dried in a calcium chloride-filled desiccator overnight at room temperature, the moisture content of the patches was measured. When there was no longer any difference in weight between patches, that’s when we knew we’d hit the target weight. The percentage of water loss was considered by dividing the change in weight from beginning to end through the final weight.

**Drug content**

For measuring the amount of drugs, 1-cm² patches are taken. Transdermal patches that were 1-cm² were cut into small pieces and mixed for 30 minutes so that the drug could be extracted better. Both the contents and the mortar were transferred to a 10 mL volumetric flask after being cleaned with a tiny amount of 0.1% sodium hydroxide. The drug concentration in the filtered solution was measured at 254 nm after the solution was filtered through Whatmann-1 filter paper and shaken for 30 minutes.

**Weight uniformity**

Before the tests, the patches were also dehydrated for 4 hours at 60°C. A computerized scale is used to weigh each piece of the patch that has been cut off. The individual weights are used to figure out the average weight and the standard deviation of weight.

**Percent moisture content**

Completed patches are reserved in a desiccator with compound calcium chloride on room temperature and weighed regularly. To figure out how much water is in the film, you re-weigh it after 24 hours and use the following formula.

\[ \% \text{ moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \]

**% moisture uptake**

Each of finished patches is measured and then stored in a desiccator through a saturated solution of potassium chloride to maintain a RH of 84% within a day. After reweighing the films, we may use the following calculation to determine how much moisture they have taken in.

\[ \% \text{ moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \]

**CONCLUSION**

One of the novel medicine delivery methods with the most promising future is transdermal drug delivery. The transdermal route is rapidly gaining popularity as a safe and effective method of administering drugs systemically without breaking the skin’s protective layer. Therapeutic drug delivery systems (TDDS) are considered to offer steady medication release via the skin at the systemic location. It improves the drug’s bioavailability while still delivering it at a low enough dose to avoid harmful side effects. One way to accomplish this is to avoid the liver’s initial metabolism.

**REFERENCES**


