International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1390-1397 www.ijprajournal.com ISSN: 2249-7781

Overview of Transdermal Patches

*R.Divyaparvathi,R.Manivannan,T.Praveenkumar,
K.Sankar.
(Department of pharmaceutics, Excel college of pharmacy, Komarapalayam, Namakkal, Tamilnadu,India)

Submitted: 17-01-2023 Accepted: 31-01-2023

ABSTRACT:
A transdermal patch, often known as a self-contained, hidden, medicated adhesive patch, offers a viable method of administration for a variety of skin and body issues. Multiple medication administration has a number of drawbacks, such as delayed administration, the possibility of overdosing, poor patient compliance, and changes in drug plasma levels. A novel technique for attaining systemic drug absorption at a set pace over an extended period of time is transdermal medication administration. Reduced dose frequency, avoiding first-pass metabolism by going straight to the systemic circulation, appropriateness for older patients who cannot take medications orally, and capacity to be administered by the patient themselves with less side effects are its main advantages.The broad topics covered in this research include drug absorption paths through the skin, absorption and distribution kinetics, multiple factors affecting transdermal permeability, various types of transdermal patches, their components, and assessment criteria. The therapeutic uses of transdermal drug delivery devices as well as a few commercially available transdermal patches have been examined. The essay also discusses the future of the transdermal medication delivery technology and many generations of its advances.
KEYWORDS: Transdermal patch, Permeation Enhancers. , Permeability, Polymer Matrix.

I. INTRODUCTION:

For conventional oral dosage forms to be effective, several doses must be administered at certain times in accurate amounts. The administration of several drugs has a number of problems, including the danger of overdosing if completed before the poor patient compliance, people missing dose, predetermine time and variations in drug blood levels.(1)To avoid such problems, transdermal medication delivery systems are developed. Discreet, self contained pharmaceutical patches that are applied directly to the skin are known as transdermal patches. configuration of delivery for a number of body and skin problems.Researchers will be able to develop ways for improved medication delivery through the skin by better understanding the basics by which chemicals arrive through the skin. A typical individual's skin has a surface area of with about 2 m2, and it accepts a third of the blood flow that the body takes.(2) Each square centimeter of skin has 10–70 hair follicles and 200–250 sweat glands. Only a few of the many variables that influence include the drug's thermodynamic activity in the formulation, how it interacts with other medications, and how instantly it is distributed through the skin.(3-4)

ADVANTAGES:
The benefits of Transdermal patches are quick, painless, and non-intrusive to use.(5-7)

- The drug can be taken over an extended period of time.
- The transdermal medication delivery technique is appropriate for drugs that are metabolized by the stomach pH,liver, or gut because the drug skips first-pass metabolism and enters straight into the systemic circulation.
- There is no interaction between a medicine and food, an enzyme and a drink, or the gastrointestinal tract bacteria.
- Suitable for older people who struggle to take medicines.
- Effective for drugs that decrease undesirable side effects from oral administration.
- Patches can be applied on one's own.

DISADVANTAGES:

- Difficulty in delivering high dosages (10 mg/day and above).(8-10)
- Ionic medicines are challenging to administer using a Transdermal medication delivery method.
- .High plasma drug concentrations are difficult to obtain; high concentrations of medicines may irritate the skin.
- Long-term adherence causes patients to feel uncomfortable.

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- Transdermal medicine administration is not tolerable for drugs having a molar ratio of 500 Dalton or more.
- Drugs with incredibly high or low partition coefficients have a hard time entering the bloodstream.

PHYSIOLOGY ANDANATOMYOF SKIN:
Three major tissue types make up the human skin.(11)

EPIDERMIS :
The surface area of the multilayered epidermis varies depending on the system on cell size and the number of cell layers, spanning from 0.8 mm on the palms and soles to 0.06 mm on the eyelids. The top layer of the skin is the stratum corneum, also called the horny layer. It swells to a thickness that is several percent greater than its dry thickness of around 10 mm when wholly saturated. It consists of 10 to 25 layers of keratinized, dead cells called corneocytes. It is able to adapt and mostly impermeable. The stratum corneum layer is the main impediment to drug admittance. The structure of the horny layer can be compared to a wall.

DERMIS:
Blood arteries, lymphatic vessels, and nerves may all be found in the 3 to 5 mm thick layer of connective tissue identified as the dermis. The cutaneous blood supply is a crucial factor in regulating body temperature. It cleanses the body of waste and toxins while nourishing and oxygenating the skin.Capillaries are 0.2 mm away from the skin's surface, allowing the majority of molecules that get through the skin barrier to sink.(12)

THE HYPODERMIS:
It supports the epidermis and dermis. It functions as a container for fat. This layer supports food needs, regulates body temperature, and offers mechanical safety. There may be significant blood arteries and pressure-sensing organs.Transdermal drug administration often refers to the penetration of the medication through all three layers and into the blood circulation, in conversely to topical medicine delivery, which only really includes penetration through the stratum corneum and then requires drug retention in the skin layers.

DRUG ABSORPTION :
Depending on the drug's physiochemical properties drug, there are a number of ways it can be absorbed via the skin. Drugs that are hydrophilic and those that are lipophilic are absorbed via various techniques. The presence of numerous absorption channels, which avoid the top stratum corneum of the epidermis and facilitates drug entry and delivery to the systemic circulation.(13-15)
The three primary medication absorption mechanisms are listed below.

1. TRANS-FOLLICULAR PATHWAY:
The fastest approach for a medicine to enter the systemic circulation is by this strategy, which contains a significant space for drug diffusion. Numerous pores, sweat and oil glands, hair follicles, and ducts that allow them to penetrate the skin's surface are present on the skin. Despite being influenced by a wide variety of factors, such as gland secretion, the sort and amount of secretion, among others, drug transport through these ducts is consistent across the stratum corneum. The trans appendageal route, however, makes a smaller contribution because it only uses 0.1% of the skin's surface.

2. ROUTE OF TRANSCELLULAR:
Medication is handed by this mechanism to corneocytes, which have a hydrophilic channel and may store highly concentrated medications.

3. INTER-CELLULAR PATHWAY:
Medication is infused into the platform through the prolonged lipid matrix that exists between the cells. This route has a barrier nature as a result of further into extended and painful form that corneocytes have created, and in order for medicine to switch for both alternating phospholipids. andwater realm, it must diffuse to inner surface and partition Since it has been established that current travels along this path 50 times more quickly, the following is provided: - for lipophilic drugs that are not charged. .(16)

DRUG ABSORPTION KINETICS:
The major method of medication absorption via the skin is passive diffusion of the drug molecules. Drug molecules permeate through the skin from the reservoir to the circulation. showing that the medicine is absorbed in sequence with the large percentage gradient since there is a of the drug on the skin than in it. The rate of medication absorption by passive diffusion is governed by

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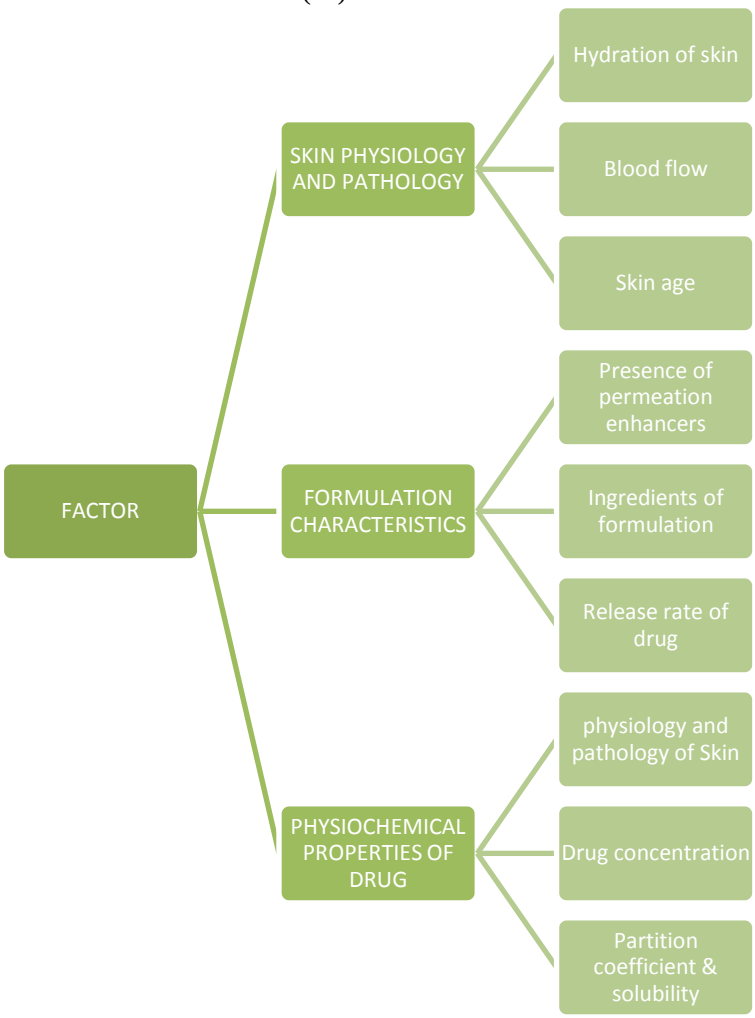
Fick's law of diffusion,permeation rate is given by:
Ps [Cd-Cr] =dt/dQ -------(1)
where
Cd stands for the donor phase drug's concentration.
Cr stands for the receptor phase drug's concentration
The following equation may be used to get Pr, the total permeability constant:

(Ks Dss / hs) = Pr --
-----(2)

Ks stands for partition coefficient,
Dssstands apparent diffusivity.
Diffusion occurs at a steady pace if Cd > Cr.
Results
The diffusion rate dQ/dt in equation 1 being changed to

Ps. Ce =(dt/dQ)m-------(3). (17)

CONTRIBUTING TO PERMEABILITY : (18)



TYPES:
RESERVOIR SYSTEM:

In reservoir systems, the drug is protected by an impermeable backing laminate and a rate-regulating microporous or nonporous membrane.To generate a paste, the medication is uniformly dispersed in a solid polymer matrix and suspended in a viscous liquid medium. The membrane's thickness, diffusion, and permeability all affect how quickly the drug is issued.

SYSTEM OF MATRIX DIFFUSION:

The medicine is evenly distributed in a lipophilic orhydrophilic polymeric material in a matrix diffusion system. The rate of polymer degradation, film surface area andlayer thickness

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all affect how quickly drugs are released. There are no extra rate-regulating membranes in the matrix system. Matrix diffusion systems are often referred to as monolithic systems. Instead of the patch's surface, the adhesive layer is put to the edge of the polymer disc.20-21 The Matrix drug delivery technique may be changed by injecting the medication directly into the sticky layer. For usage with this, it is possible to In an adhesive system, generate both a single-layer drug and a multi-layer drug.

ADHESIVE SYSTEM OF DRUG:

In this method, the patch's sticky layer is where the drug is distributed. In addition to sticking the patch's components to the skin, the adhesive layer regulates how quickly drugs are distributed to the skin. The liner surrounds the sticky layer. Unlike a multilayer patchA single drug is housed in the adhesive layer of a single-layer patch, which contains two layers, one of which is for immediate drug release and the other of which is for regulated drug release.

SYSTEM OF MICRO RESERVOIRS:

It consists of a matrix reservoir system and amatrix. The medicine is initially an aqueous solution of a hydrophilic polymer suspended in (like plasticizer) in the micro reservoir system. A mechanical stirrer with a high shear rate then combines the added suspension combined with a lipophilic polymer (like silicon). A medicated polymer disc with a certain area and texture is produced polymer chains are in-situ cross-linked, which stabilizes the micro reservoir system. **(**19-22)

COMPONENTS OF TTDS

DRUG:

Direct contact between the medication solution and the desired release liner is.

- **Physical properties**
  The molecular weight of the medication must be less than 1000 Daltons.The drug must be capable of attaching to both the lipophilic and hydrophilic phases.
- **Biological properties-**
  Only a few mg of the drug must be taken daily for it to be effective.The drug's half-life must be minor. It must not be possible for the drug to cause an anaphylaxis.

THE POLYMER:

The following qualities of the polymer used in transdermal patches should be present.

- For effective drug diffusion and easy drug release via the polymer, it must have a specified molecular weight and chemical activity. The polymer needs to satisfy the following requirements: cost, nontoxicity, and stability.
- The host must not be harmed by the by product of polymer breakdown.

BACKING LAYER:

The transdermal patches are supported and shielded from the environment by it. The backing membrane must be elastic, impermeable,flexible to drug absorption in order to prevent drug loss. It must to work well with the medicine, excipients, and polymer. (23)

MEMBRANE THAT CONTROLS RATE:

Rate controlling membranes regulate how quickly a medicine is released from a dose form. A range of organic and man-made polymers are used to create rate-controlling membranes. Chitosan and poly2-hydroxyethyl methacrylate are two examples.

ADHESIVE:

In transdermal patches, the adhesive's primary function is to sustain long-term contact with the skin. Patch selection criteria include patch type, patch design, and adhesive properties. It must be easy to remove, non-irritating, and safe for skin and excipients. Polyacrylate, polyisobutadiene, and silicon-based adhesive polymers are a few examples of adhesives.

RELEASE LINER:

The primary packaging's release liner protects the patch during storage and delivery from both external environment contamination and medication loss from the polymer matrix. It is peeled off when it is ready to utilise it. For instance, occlusive materials like polyethene or polyvinyl chlorideMetallic and polyester foil non-occlusive (paper fabric)

PLASTICIZERS:

Plasticizers make the polymer more brittle and flexible. These are added, which changes the polymer's mechanical and physical properties. For instance, sebacic acid esters,flexibility , alcohols, oleic acid esters, and derivatives of glycerol.Boost the toughness, phthalic acid esters, and elongation

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at break of polymers.decreases tensile stress, hardness, ability to conduct an electric charge, and glass transition temperature.

OTHER EXCIPIENTS:

Drug and polymer dissolution is accomplished through permeation enhancers. propylene glycol ,polyethene glycol , triethyl citrate, chloroform, and Methanol are among examples. (24)

EVALUATION :

PHYSICAL-CHEMICAL EVALUATION

Thickness:

A efficient travel microscope, dial gauge, screw gauge, or micrometer can be used to measure. At three different locations on the patch, gauge the thickness of transdermal patches. After averaging the three readings, the patch's thickness is determined with consistent thickness will be thick throughout. It is possible to calculate the thickness variation both within and between patches

Weight stability:

Before the patches are weighed, they are dried at 60 °C. The weight homogeneity of a transdermal patch is evaluated by cutting weighing and cutting a 1 cm2 portion of three patches, and the weight deviation is then calculated. By averaging the three results, the weight of the patch is calculated. An individual's weight cannot deviate from the average weight in a substantial way.

Folding Endurance:

A strips of patch or film is gently inverted in the exact direction and folded a total of 300 times to measure the strength of the folds.The number of folds a patch may endure before breaking is what is known as its folding endurance. Flexibility of the transdermal patch is influenced by folding endurance.

Drug Content:

An appropriate solvent, such as methanol phosphate or methanol buffers pH 7.4, is initially used to dissolve a film of the right area and weight., before being filtered. Following the correct dilutions, a standard curve is used to calculate the drug content using the HPLC or UV method.

Stability :

A stability analysis is done to figure out how long the patch will remain functional and usable. According to international conference of Harmonization (ICH) criteria; stability is tested for six months at a relative humidity of 75% at 40 OC. Since the medication rapidly degrades in unstable patch formulations. Stability tests are performed on samples at 0, 30, 60, 90, and 180 days.

Percentage Moisture Content:

To calculate the % moisture content, weighted patches for individual sections are kept in desiccators with fused cacl2 at 24 hours at room temperature..48,47 After 24 hours, the patch are re - weighed to calculate their % moisture content using the formula below.

PMC is equal to 100 times (Actual weight - Final weight/Final weight).

Moisture Uptake as a Percentage:

After being desiccated for 24 hours, weighted films are subjected to 84 percent humidity levels using potassium chloride. Once the films' weight has stabilised, they are once again weighed.

moisture uptake percentage = (Final weight - Initial weight/Initial weight) x 100

Test for Shear Adhesion:

This test evaluates the sticking polymer's cohesive strength. The patches with adhesive is placed upon a flat surface, and the required weight is then suspended directly from the patch. We can assess how well-adhered a patch is to the surface by how long it takes to remove it. (25)

B. IN-VITRO EVALUATION:

STUDY ON IN-VITRO RELEASE:

Mice, rabbits, or albino rats are employed for skin irritation testing in an in vitro skin permeation examination. Each of the five animal categories contains six different species. The control group is Group I, while Group II is given commercially available.

SKIN PERMEATION STUDY IN-VITRO:

In a vertically diffusion cell with two compartments split by the skin of a male Wistar rat, in vitro skin permeation studies are conducted. The rat's skin is wrapped with the transmembrane film, which is attached to the compartment that is situated between both the receptor and do norcompartments. Samples are gathered on a regular basis, and a fresh medium containing the exact volume is switched out. Spectrophotometric examination of the material yields the flux calculation. (26)

C. IN-VIVO EVALUATION:

Animal Model:

Small-scale animal experiments are preferred because conducting human research is time- and cost. The hairless dog, hairless rat, hairless dog, rabbit, mouse and hairless rhesus monkey guinea pig are the species of animal that are most frequently used to evaluate transdermal drug administration systems. Numerous studies

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have demonstrated that in both in in vivo and in vitro examinations, hairless animals are favoured over hairy ones. One of the greatest models for studying transdermal medication administration in humans is the Macaque monkey.

Human Model:

Human volunteers were given the patch at the extreme of the transdermal device development phase, It led to the assembling of pharmacodynamic and pharmacokinetic information. Clinical studies have been carried out to evaluate the efficacy, patient compliance dangers, adverse effects, dangers, and other factors.Phase II clinical studies are designed to evaluate safety and efficacy in patients over the short term, while phase One clinical trials are used to study safety mostly in volunteers. Phase III trials show the safety and effectiveness of marketed patches in a variety of patient demographics, while phase IV trials are carried out during post-marketing surveillance to identify adverse medication reactions. (27)

THERAPEUTIC APPLICATIONS

S.no	Name of the drug	TDDS Application
1	celecoxib and Diclofenac sodium	Developed in TDDScould be able to prevent the stomach lesions brought on by oral dosage.
2	Captopril, verapamil, terbutaline sulfate, and propranolol	When TDDS formulations in membrane control, the medicine is delivered in enough quantity to sustain the MEC without causing hypotension, which is a side effect of high initial oral dose.
3	Indomethacin	With polyvinylpyrrolidone polymer, greater anti-inflammatory action can be provided together with decreased ulcer indices.

Advancement In Transdermal Drug Delivery System

Chemicals have been used by human civilization for thousands of years for beauty and therapeutic purposes. The skin was, however, recognized as a medication delivery channel in the 20th century. When it comes to medication distribution, skin has some restrictions and cannot be employed for all drug candidates. the transdermal administration of drugs technique is becoming more popular and useful for the majority of drugs as science and technology advance. Three generations of transdermal drug delivery systems have been identified based on system advances.(28)

THE PROSPECTS OF THE TRANSDERMAL DELIVERY SYSTEM FOR DRUGS

Transdermal medication delivery will eventually be the preferred option due to controlled dosages, decreased dosing frequency, and improved patient compliance. Twenty years ago, transdermal nicotine patches for quitting smoking were developed. Following that, a number of drugs including nitroglycerin for angina, fentanyl for pain were, and estradiol for estrogen deficiency fentanyl for pain were created as transdermal patches. Due to patent expiration, researchers have been motivated to develop pharmaceuticals in fresh and tasty dosage forms. As technology and design progress, transdermal delivery techniques are becoming more and more wide spread. There are several transdermal delivery methods that have been trademarked and are being actively explored for use,and the biggest pharmaceutical firms are working on transdermal drug delivery systems. Liposomes, Niosomes, nanoparticles, microspheres, and other cutting-edge delivery.(29-30)

II. CONCLUSION:

The safest and most efficient route of medicine administration is transdermal. To prevent gastrointestinal tract side effects and first-pass metabolism, several medications, including hormone treatment, a variety of analgesics, and medications for heart disease, have been designed in transdermal drug delivery systems. Researchers are becoming more interested in transdermal drug delivery methods, and many novel medications may soon be formulated in this manner. It is important to keep in mind that the formulation of a transdermal medication delivery system may not change the physiology of the skin. We might develop transdermal patches in the future with a greater understanding of the physiology and architecture of skin. However, a complete comprehension of the relationships between numerous

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