



Transdermal Drug Delivery System: A Recent Review

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ABSTRACT

Transdermal patches are a painless drug delivery approach. It is an adhesive patch which made to allow a precise medicine dose to be absorbed into the body's systemic circulation through the skin. In comparison to other routes of administration, transdermal drug delivery gives a number of benefits, including being less invasive, patient- friendly and having the ability to avoid hepatic first- pass metabolism and the harmful acidic environment of stomach that results from oral drug absorption. Since many years ago, transdermal patches have drawn interest and have been used to deliver medications including nicotine, clonidine, fentanyl, and nitroglycerin to treat a variety of illness or disorders. Small, lipophilic, low dosage medicines have been administered using first- generation transdermal administration. Iontophoresis, ultrasound, and chemical enhancers are all used in second- generation transdermal medication delivery. Microneedles, electroporation, thermal ablation, and microdermabrasion have all been employed in third- generation transdermal delivery to deliver the medicine. Transdermal drug delivery devices were created as a workaround for the issues with oral medication administration. Since 1981, these systems have served as trustworthy and safe means of delivering medications.

Keywords: Transdermal drug delivery system; Patch; Skin; Systemic circulation.

1. INTRODUCTION

Transdermal drug delivery system is a controlled delivery system which releases the pharmacologically active substance into the body i.e., cells and tissues and organs which gives optimal effects. It gives maximize therapeutic efficacy and reduces the side- effects. TDDS is painless method of administration which involves minimal pain. It does not involve the passage of drug through the GI tract, so there is no loss of drug due to hepatic first pass metabolism and avoids the interference from enzymes, pH, or intestinal bacteria.

TDDS is topically administered medication that allow delivery of pharmaceuticals across the barrier of skin into systemic circulation at predetermined and controlled rate in the form of patches, considered as device which may be of active or passive and providing alternative method of administration.

Theoretically, it works very simple. Relatively, high dosage of drug is applied onto the inside of patch and worn on skin for extended period of time. The drug enters into the systemic circulation directly through skin by diffusion process. In the patch, there is high concentration of drug while low concentration in bloodstream, the drug diffuses into the blood for a larger period of time and maintains the drug constant concentration in the blood flow.

Transdermal drug delivery system was first used in 1981 for motion sickness when ciba- Geigy marketed TransdermV which currently marketed as Transdermal scope.

1.1 Advantages

1. This delivery system avoids the GI absorption which involves enzymatic and pH deactivation.
2. Reduced pharmacological dosaging.
3. This system has ability to terminate the therapy by removing patch.
4. Avoid first pass metabolism and hepatic metabolism.
5. Minimize the side- effects.
6. It is painless administration and non- invasive.
7. Good patient compliance.
8. Maximizing the therapeutic efficacy.
9. Easily removable system if any side- effect occurs.

10. Useful of those drugs which have narrow therapeutic window and have short half- life.
11. Controlled delivery system.
12. Lesser exposure to unwanted metabolites.
13. Removal and application of this system is very easy.
14. In comparison with buccal cavity and nasal, it has large area of application.

1.2 Limitations

1. Allergic reactions may occur.
2. It is not possible to attain therapeutic level by high molecular drugs.
3. Significant lag time is required.
4. Delivery of ionic drugs.
5. Uncomfortable to wear and adhesives may not attach well to all types of skin.
6. High cost is also a drawback for the acceptance of product.
7. Those drugs which require high blood level cannot be administered by this route and also cause irritation to the skin.

2. ANATOMY AND PHYSIOLOGY OF SKIN

2.1 Skin: The Largest Organ

The skin, which has surface area of around 2 square metres and receives nearly one third of the blood circulation through the body, is the largest organ in the human body. It acts as a permeability barrier to stop different chemical and biological substances from entering the skin through the transdermal route.

Human skin is made up of three different but interdependent tissues:

1. Epidermis, the stratified, vascular and cellular layer.
2. Dermis
3. Hypodermis, the layer of connective tissue beneath the dermis.

Epidermis

The outermost layer of the skin consists of a stratified squamous epithelium, which is mainly made up of two types of cells: Keratinocytes & dendritic cells. It consists of four layers –

- Stratum basal
- Stratum spinosum
- Stratum granulosum
- Stratum corneum

Dermis

A network of interconnected fibrous and filamentous structures serves as the dermis. The stimulus results in the activation of nerves and blood vessels. Appendages, macrophages, mast cells and fibroblasts derived from the epidermis of the skin, cells producing connective tissue, and cells engulfing and digesting foreign objects.

The majority of the skin is made up of dermis, which gives the skin its pliability, elasticity, and tensile strength. It shields the body from mechanical harm, holds water, helps regulate body temperature, and has sensory stimulation receptors.

In order to retain the characteristics of both tissues, the dermis interacts with the epidermis.

Hypodermis

Also known as subcutaneous. The body's subcutaneous tissue serves as an energy reserve and buoyancy system.

Androstenedione is converted into estrone by aromatase in the panniculus during a hormonal process. Leptin is a hormone produced by lipocytes that controls body weight by way of brain.

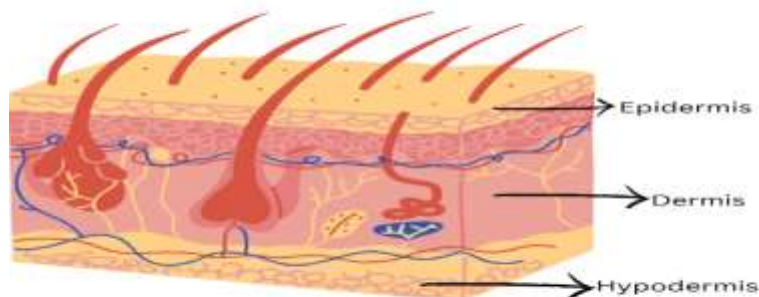


Fig.-1: Structure of Skin

First- generation transdermal delivery systems

The majority of transdermal patches that have been used in clinical settings so far are from the first generation of transdermal delivery methods. Candidates for first- generation delivery must have low molecular weight, be lipophilic, and be effective at low dosages. Due to characteristics including low oral bioavailability, the requirement or desire for less frequent dosing or stable delivery patterns, or other considerations, their transdermal delivery should typically be more desirable than oral delivery.

The stratum corneum, which is the skin's outermost layer and is 10-20 m thick, acts as a barrier for the first- generation transdermal delivery method.

Instead of using a patch, a metered liquid spray, gel or other topical formulation is applied to the skin in a variation of the traditional transdermal patch of first-generation delivery system. This can drive small lipophilic drugs into the stratum corneum, which then act as drug reservoir for hours-long extended release into the viable epidermis.

For instance, transdermal sprays for the delivery of estradiol have just received approval, whereas testosterone gels have been in use for a while.

Second- generation transdermal delivery systems

The second generation of transdermal delivery systems is aware that improving skin permeability is necessary to increase the range of transdermal medications. The ideal enhancers should:

1. Boost skin permeability by reversibly altering stratum corneum structure.
2. Offer an additional driving force for delivery into the skin.
3. Prevent damage to deeper, living tissue.

Chemical enhancers can make the skin more permeable and add a driving force to transport by boosting drug partitioning into the skin (and consequently the concentration gradient that drives diffusion). As chemical enhancers with supramolecular structure, liposomes, dendrimers, and microemulsions have also been utilized to boost skin permeability as well as drug solubilization in the formulation and drug partitioning into the skin.

Third- generation transdermal delivery systems

The third generation of transdermal delivery devices is anticipated to have a significant impact on drug delivery since it concentrates its effects on the stratum corneum. The stratum corneum barrier may be more effectively disrupted because to this targeting, which also protects deeper tissues. Transdermal administration is made more efficient. We have found that in human clinical trials, novel chemical enhancers, electroporation, cavitation ultrasound, and more recently microneedles, thermal ablation, and microdermabrasion have all demonstrated the ability to deliver macromolecules, including therapeutic proteins and vaccines, across the skin.

3. ROUTES OF PENETRATION

1. Transcorneal Penetration

• Intracellular penetration:

The stratum corneum's cells allow the passage of drug molecules. It frequently occurs when using hydrophilic medications. Water builds up close to the exterior of the protein filaments as the stratum corneum hydrates. The immobilized water seems to allow the passage of polar molecules.

• Intercellular penetration:

The path of intercellular penetration is followed by non-polar molecules. The non- aqueous lipid matrix that is ingested between the protein filaments allows these molecules to disperse in and move through it.

2. Appendageal Route

The appendageal route involves transport through sweat glands and hair follicles with accompanying sebaceous glands. They are referred to as "shunt" pathways because they avoid penetrating the stratum corneum. Due to its smallest area- roughly 0.1% of the total skin area- this pathway is referred as minor significance.

4. FORMULATION COMPONENTS**1. Polymer Matrix**

The drug's release from the device is managed by the polymer. A polymer must meet the following requirements in order to be utilized in transdermal patches.

- The polymer's molecular weight and chemical activity should be chosen in a way that will allow the particular medicine to diffuse and be released through it appropriately.
- The polymer ought to be stable.
- The polymer should be simple to produce and harmless.
- It needs to be affordable.
- The degradation product of polymer must be non- toxic to the host.
- The active ingredient is contained in significant proportions.

2. Drug

Drugs that undergo considerable first pass metabolism, have a limited therapeutic window, or have a short half- life that requires frequent dosage and results in non- compliance can all benefit from transdermal patches. The main prerequisite for TDDS is that the drug has the ideal combination of physical, chemical, and biological qualities for transdermal drug delivery. It is widely acknowledged that the best drug candidates for passive adhesive transdermal patches must be non- ionic, have a low molecular weight (less than 500 Daltons), be sufficiently soluble in water and oil (log P in the range of 1-3), have a low melting point (less than 200°C), and be potent (dose in mg per day).

Furthermore, medications including rivastigmine for Alzheimer's and Parkinson's dementia, rotigotine for Parkinson, methylphenidate for attention deficit hyperactivity disorder, and selegiline for depression have recently received TDDS approval.

3. Permeation Enhancers

For therapeutic purposes, the majority of medicines won't penetrate skin. Some enhancers, such as tetrahydrofuryl alcohol, dimethyl sulphoxide, acetone, and propylene glycol, are employed for synergistic effect without displaying their qualities.

4. Backing Laminates

Backings are chosen for their appearance, flexibility, and necessity for occlusion; as a result, the material's chemical resistance must be taken into account while creating a backing layer. Excipient compatibility should also be taken into account because extended contact between the backing layer and the excipients could result in additives leaching out of the layer or excipient, medication or penetration enhancer diffusion. The backing with the lowest modulus or high flexibility, good oxygen transfer, and a high moisture vapour transmission rate will be the most comfortable.

Vinyl, polyethylene, polyester films, aluminium, and polyolefin films are a few examples of backing materials.

5. Adhesives

In addition to sticking the patch to the skin, it acts to bind the patch's components together. For instance, silicone, polyisobutylene (PIB), and acrylic are three adhesives with several medical uses. The choice of a PSA (Pressure Sensitive Adhesives) is more difficult for applications (such as matrix designs) where the adhesive, medication, and may be enhancers are compounded.

6. Release Liner

A protective liner covers the patch while it is in storage; this liner is taken off and discarded before the patch is applied to the skin. Since the liner and TDDS are in close proximity, it should be chemically inert.

5. FACTORS AFFECTING TRANSDERMAL PERMEABILITY

The following are the primary factors that have an impact on the stratum corneum of the skin's permeability:

- a. The physicochemical characteristics of medication.
- b. The drug delivery system's physicochemical characteristics.
- c. Physicochemical and pathological conditions of the skin.

Physicochemical properties of the drug molecule

1. Partition co-efficient: Drugs that are soluble in both water and lipids are more readily absorbed via the skin. The partition co-efficient has a linear relationship with the transdermal permeability co-efficient. A medicinal molecule's lipid/water partition co-efficient may change when the vehicle is changed. Chemical alteration of a drug's molecule can change its partition co-efficient without changing the drug's pharmacological activity.

2. pH condition: Acidic and basic medications are absorbed at different rates depending on pH. Pharmaceuticals in their unmodified form penetrate more effectively. Ionizable species transport from aqueous solutions exhibits a significant pH dependence.

3. Drug concentration: The concentration of penetrant molecules in the skin's surface layer determines the transdermal permeability through mammalian skin, which is a passive diffusion process.

Physicochemical Properties of the drug delivery system

The drug delivery system vehicle acts as a carrier for the medicine rather than speeding up how quickly it enters the epidermis.

1. Release characteristics: The drug's solubility in the transport medium affects the rate of release. The following variables affect the drug release mechanism:

- a. In the delivery method, the medication molecule is either suspended or dissolved.
- b. The drug's interfacial partition coefficient between the skin tissues and the delivery device.
- c. Vehicle's pH level.

2. Composition of the drug delivery system: The boundary layer, thickness, polymers, and vehicle in a drug delivery system, not only affect the rate of drug release but also the permeability of the stratum corneum by hydrating it with skin lipids or by having other sorption-promoting effects.

For example, PEG with a low molecular weight inhibits the penetration of benzocaine.

3. Enhancement of transdermal permeation: The majority of medications won't enter skin at rates high enough for therapeutic effectiveness. The penetration can be enhanced by adding a permeation promoter into the drug delivery systems to provide clinically meaningful transdermal permeation of the majority of medicines.

Physicochemical and pathological conditions of the skin

1. Skin temperature: A temperature differential of about 37°C to about 32°C at the skin's outer surface is maintained by the human body. Elevating the skin's temperature can cause structural changes in the stratum corneum, which can then accelerate diffusion into the tissues since stratum corneum diffusion is a passive process.

2. Skin condition: Acids, alkalis, and several solvents, including methanol and chloroform, harm skin cells and encourage penetration. Patient illness affects their skin's condition. Although the skin is a better barrier when it is intact, the aforementioned factors affect penetration.

3. Skin metabolism: Steroids, hormones, chemical carcinogens, and some medicines are all processed by the skin. The effectiveness of a medicine absorbed through the skin is determined by skin metabolism.

4. Blood Supply: Transdermal absorption may be impacted by changes in peripheral circulation.

5. Race: Despite the paucity of available information, there are racial distinctions between skin types with black and white skin in some anatomical and physiological functions. Increased intracellular cohesiveness, higher lipid content, and higher electrical skin resistance levels have all been found in black skin compared to white skin.

6. Body site: It is obvious that the structure of skin differs somewhat on different parts of the human body. However, stratum is not the only factor affecting the relative permeability of various skin locations. It is clear that vaginal tissue often has the maximum permeability for transdermal medication delivery. The skin of head and neck is also more permeable than the skin on other parts of the body, such as the arms and legs.

6. FORMULATION APPROACHES USED IN DEVELOPMENT OF TDDS

1. Membrane Permeation Controlled Systems:

In this method, a metallic plastic lamination that is impermeable to drugs and a polymeric membrane that regulates flow rate surround the drug reservoir. The substance molecules are release is only authorized through the polymeric membrane that regulates rates. The rate- controlling membrane may be a microporous or nonporous polymeric membrane having drug permeability, such as an ethylene- vinyl acetate copolymer. To ensure close contact between the TDDS and the skin surface, a thin film of pressure- sensitive adhesive polymer that is drug- compatible and hypoallergenic, such as silicone adhesive, may be placed to the outside of the polymeric membrane.

For example, Transderm – Scop system, Transderm- Nitro system, the Estraderm system, the Duragesic system and the catapres system.

2. Adhesive Dispersion Type System:

Forming a thin drug reservoir layer by solvent casting or hot melting the medicated adhesive onto a flat sheet of drug- impermeable metallic plastic backing. An adhesive diffusion-controlled drug delivery system is created by layering non-medicated adhesive polymers with a particular permeability and consistent thickness on top of the drug reservoir layer.

Example, Poly acrylate or Poly isobutylene adhesive.

3. Matrix- dispersion system:

The medication is uniformly distributed in a hydrophilic or lipophilic polymer matrix in this type. This drug- containing polymer disc is mounted on an occlusive base plate in a compartment made from a backing layer that is impermeable to drugs. The adhesive is placed around the outside of the drug reservoir rather than on the face to create a strip of adhesive rim.

4. Microreservoir system:

This kind of drug delivery system combines a matrix- dispersion mechanism with a reservoir. The process for creating a drug reservoir involves first suspending the drug in an aqueous solution of a water-soluble polymer before homogenously dispersing the solution in a lipophilic polymer to create millions of tiny, inaccessible drug reservoir spheres. Cross- linking the polymer in situ as soon as possible with cross- linking agents stabilizes this thermodynamically unstable dispersion.

5. Microneedle-Based Patches:

There are various varieties of microneedles, each having special traits and qualities. In total, four different kinds of microneedle-based patches have been created: coated, hollow, dissolving, and solid microneedles. The particular application and the user's requirements will determine which type of microneedle is best.

a. Solid Microneedles: These are the most basic kind of microneedles, with solid needles that pierce the skin to form tiny channels. For aesthetic procedures and medicine delivery, solid microneedles are frequently employed.

b. Hollow Microneedles: These tiny needles feature a hollow core that makes it possible to inject liquids or medications beneath the epidermis. Transdermal medication delivery and interstitial fluid collection frequently involve hollow microneedles.

c. Coated Microneedles: The coating on these microneedles breaks when they penetrate the skin, allowing medicines or other substances to be released. For the transdermal delivery of drugs, coated microneedles are frequently utilized.

d. Dissolving Microneedles: The regulated release of medications or other substances is made possible by the dissolving ingredients used to make these microneedles. Dissolving microneedles are frequently utilized for the delivery of drugs and vaccinations.

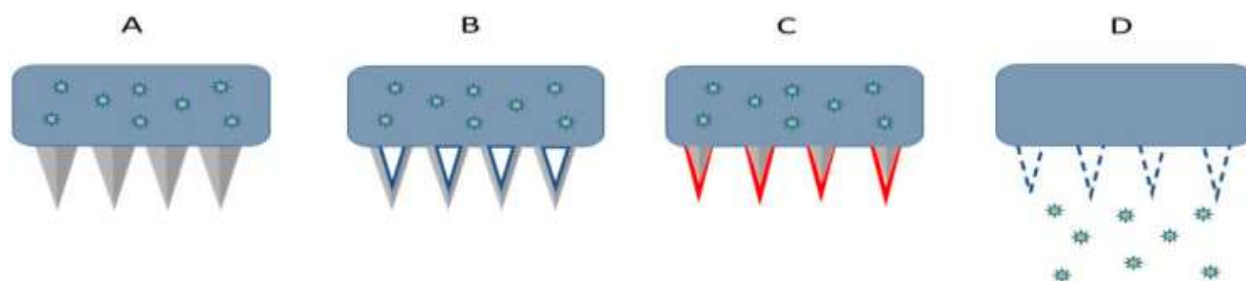


Fig.- 2: Microneedles-based Patches

7. RECENT TECHNIQUES USE TO ENHANCE TDDS

A. Structure- Based Enhancement Techniques

1. Microfabricated Microneedles: In order to deliver the medicine over the membrane, this kind of device utilizes both the hypodermic needle and transdermal patch principles. This device consists of a drug reservoir and a few microneedles. The medicine is delivered via the stratum corneum with the aid of microneedles.

2. Metered- Dose Transdermal Spray: The medication is totally dissolved in the liquid preparation in this solution technique, which also uses a volatile or non- volatile vehicle. Consequently, the medicine is delivered via the skin more effectively and continuously.

3. Macroflux: In such devices, an area of around 8 cm² is covered by 300 micro needles. Three different types of macro flux systems are typically employed.

a. Dry-Coated Macroflux system

b. D-TRANS Macroflux system

c. E-TRANS Macroflux system

B. Electrically-Based Enhancement Techniques

1. Iontophoresis: Drug is applied to the skin beneath the active electrode in iontophoretic delivery system, and a current of around 0.5 mA is transmitted between the two electrodes to efficiently repel the drug away from the active electrode and into the skin.

For example, the delivery of pilocarpine can be used to induce perspiration in the detection of cystic fibrosis, and the delivery of lidocaine using iontophoretic means is regarded as a pleasant method for achieving a speedy onset of anesthesia.

2. Ultrasound: The process of phonophoresis or sonophoresis- the transdermal delivery of medications through the skin system- is considerably improved by the application of ultrasound at the right frequency. To achieve therapeutic medication concentrations at specific skin areas, a combination of topical drug therapy and ultrasound therapy is used. In this method, the medicine is combined with a coupling agent- typically a gel, although occasionally a cream or ointment is used- that allows ultrasonic energy from the device to be transmitted to the skin. In order for the medication to pass through the biological barrier, this involves rupturing the lipids present in the stratum cornea. It uses ultrasonic waves with frequencies ranging from 20 KHz to 10 MHz and intensities up to 3Wcm⁻² to reduce the stratum corneum barrier property.

3. Electroporation: Aqueous holes are created in the lipid bilayers with this technique by applying brief electrical pulses of around 100-1000 volts per cm. It might work in conjunction with iontophoresis to improve peptide permeability.

4. Photomechanical waves: It was discovered that the photochemical wave's method of action involves altering the lacunar system, which causes a permeabilization mechanism to produce transitory channels through the stratum corneum.

C. Velocity-Based Enhancement Techniques

1. Intraject

2. Jet syringe

3. Mini-Ject

4. Powder-Ject Device: Drug solid particles that are driven through skin barriers by high- speed gas flow. Here, helium gas is used; the gas enters compartment containing medication powder that is sandwiched between two polycarbonate membranes. Immediately following the release, solid drug particles rupture through the epidermal barrier layers at a speed of 600-900 m/s and pass the barrier.

D. Other Enhancement Techniques

1. Magnetophoresis

2. Medicated Tattoos

3. Liposomes

4. Skin Abrasion

5. Transferosomes

6. Laser Radiation

7. Super Saturation.

8. EVALUATION METHODS

The following types of transdermal dosage form evaluation techniques can be identified:

1. Physicochemical type of evaluation.

2. In- Vitro evaluation.

3. In- Vivo evaluation.

Physicochemical Evaluation:

1. Interaction studies: To form a stable product, the medicine and the excipients must be compatible with one another. The bioavailability and stability of the medicine are impacted by the interaction between the excipients and the drug. Thermal analysis, FTIR, UV, and chromatographic procedures are used to conduct interaction investigations by contrasting their physicochemical characteristics, such as assay, melting point, wave numbers, and absorption maxima.

2. Thickness of the patch: Digital micrometer is used to measure the thickness of the patch at different points which determines the average thickness.

3. Film thickness: This is measured with a micrometer, electronic Vernier calipers, dial gauge, or screw gauge. Five distinct locations on the film are used to assess thickness, and the average of the five readings is used.

4. Folding endurance: It is discovered by continuously folding a short (2×2 cm) strip of film until it breaks. The folding endurance value is the number of times the film could be folded in the same position without breaking.

5. Elongation Break test: It can be calculated by taking note of the length shortly before the break point.

Elongation break= Final length – Initial length/ Initial length

6. Weight Uniformity: This test is conducting by choosing patches randomly which are 10 in number. A predetermined patch area must be divided into several pieces and weighed on a digital scale. Using the individual weights, compute the average weight and standard deviation.

7. Drug content determination: A precisely measured quantity of film weighing about 100 mg is dissolved in 100 ml of an appropriate solvent in which the medication is soluble, and the mixture is then continuously shaken for 24 hours in a shaker incubator. Then the entire remedy is sonicated. Drug in solution is determined spectrophotometrically by suitable dilution after sonication and subsequent filtration.

8. Content Uniformity test: 10 patches are chosen, and each patch's content is decided. Transdermal patches pass the content uniformity test if out of ten patches, nine have content that ranges from 85% to 115% of the given value and one has content that is atleast 75% to 125% of the specified value. However, a further 20 patches are examined for drug content if 3 of them have content between 75% and 125%. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

9. Moisture Content: The produced films are weighed separately and maintained at room temperature in dessiccators with calcium chloride for 24 hours. After a predetermined amount of time, the films are weighed once more until they reach a constant weight. The percent moisture content is calculated using following formula:

% Moisture Content= Initial weight – Final weight/ Initial Weight× 100

10. Shear Adhesion test: The cohesive strength of adhesive polymers was governed by this method. On the stainless-steel plate, an adhesive film is applied. Moreover, the length of time it takes to remove the film off the plate allows for the evaluation of shear adhesion strength. The shear strength will increase as the time required increases.

11. Rolling ball tack test: It involves measuring how far a stainless- steel ball travels with an upward- facing adhesive; the less adhesive, the further the ball travels. This test is used to evaluate a polymers softness.

12. Quick stick test (peel tack test): In this test, the peel strength is required to break down the bond between a substrate and an adhesive at a speed of 12 inches per minute and a 90- degree angle. The tack value is expressed in units of force (ounces per inch width).

13. Probe Tack test: In this test, an adhesive is brought into contact with a clean probe tip with a predetermined surface roughness, and a connection is created between the probe and the adhesive. The probe is mechanically broken when it is later removed. Tack, which is measured in gram, is the force needed to pull the probe away from the adhesive at a constant rate.

14. Stability studies: Stability is an important factor in developing transdermal drug delivery system as it influences the therapeutic effectiveness as well as patient compliance. After 30 days, the transdermal films were investigated on the skin of rats for their drug release profile.

In- Vitro Evaluation:

1. In vitro drug release studies: It is possible to evaluate the drug release from the produced patches using the paddle over disc method (USP equipment V). A glass plate must be covered with dry films of defined thickness that have been cut into a specific form, weighed, and applied with an adhesive. The apparatus was then brought to an equilibrium temperature of $32 \pm 0.5^\circ\text{C}$ before the glass plate was submerged in 500 ml of the dissolving liquid or phosphate buffer (pH 7.4). The paddle was then turned on at a speed of 50 rpm while being placed 2.5 cm away from the glass plate. At suitable intervals upto 24 hours, samples (5 ml aliquots) can be taken out and analysed using a UV- spectrophotometer or HPLC. The experiment must be carried out three times, and the mean value can be determined.

2. In vitro skin permeation studies: Diffusion cells can be used to conduct an in vitro permeation research. Male wistar rats weighing 200-250 gm have full thickness abdomen skin. The dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment, and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the test substance. Using a thermostatically controlled heater, the temperature of the compartment was kept at $37 \pm 0.5^\circ\text{C}$. The isolated rat skin piece needs to be put in the diffusion cell between the compartments, with the epidermis facing up into the donor compartment. At regular intervals, a sample volume of a specific volume has to be taken out of the receptor compartment and replaced with an equal volume of fresh medium. The analysis of samples can be done using HPLC or UV spectrophotometry after they have been filtered through a filtering medium. As the slope of the curve between the steady – state values of the amount of drug penetrated (mg cm^2) vs time in hours, flux can be calculated directly. Permeability coefficients were then derived by dividing the flux by the initial drug load (mg cm^2).

In- Vivo evaluation: The most accurate representation of a drug's performance comes from in-vivo tests. In vivo- investigations can completely examine the characteristics that cannot be taken into consideration during in- vitro experiments. Human volunteers, animal models, or both may be used in the in-vivo evaluation of TDDS.

1. Animal models: Research on humans need a lot of time and resources, hence small-scale animal research is preferable. The most popular animal species for testing TDDS are the mouse, hairless rat, hairless rhesus monkey, Hairless dog, rabbit and guinea pig, among others. According to the results of the current studies, hairless animals are preferred over hairy ones in both in-vitro and in-vivo experiments. One of the best models for in-vivo testing of transdermal medication administration is the rhesus monkey.

2. Human models: Gathering pharmacokinetic and pharmacodynamic data after applying the patch to human volunteers is the last step in the development of a transdermal device. Clinical trials are carried out to evaluate the transdermal systems effectiveness, risk level, side-effects, and patient compliance. Phase-1 clinical trials are done to assess safety mostly in volunteers, while phase-2 clinical trials assess safety primarily in patients over the short term and safety primarily in the long term. Phase-3 trials demonstrate the safety and efficacy in a wide patient population. For approved patches, phase-4 trials at post- marketing surveillance are conducted to identify adverse medication reactions. Although they demand significant resources, but human studies are the most effective way to evaluate a drug's effectiveness.

9. APPLICATIONS OF TRANSDERMAL PATCHES

1. Invisible ink could be used to label individuals with transdermal patches in order to retain medical information subcutaneously. This method was created and patented by Robert S. Langer and his team in December 2019. This was promoted as a benefit for “developing nations” because a lack of infrastructure results in a lack of medical facilities. The procedure involves administering a vaccination combined with a quantum dot dye.
2. Patches with caffeine that are intended to be applied to the skin to give caffeine to the body.
3. Rivastigmine, a drug used to treat Alzheimer's disease, was first made available as a patch in 2007 under brand name Exelon.
4. Nitro glycerin (Deponit) is used as a patch for Angina Pectoris.
5. Hokumalin for bronchial asthma under name Tolobuterol.
6. The nicotine patch, which distributes nicotine in controlled dosages to aid in quitting smoking, is the most popular transdermal patch in the US.
7. Menopausal symptoms and post- menopausal osteoporosis may both be treated with oestrigen patches. The contraceptive patch (also known as Ortho Evra or Evra) is another transdermal patch for hormone delivery.
8. Scopolamine used topically is frequently used to cure motion sickness.
9. In March 2006, Emsam, a transdermal formulation of the MAOI selegiline, was authorized for use in the United States as the first transdermal delivery system for an antidepressant.
10. Clonidine is an anti- hypertensive medication that comes in transdermal patch form.
11. In April 2006, the FDA authorized Daytrana, the first methylphenidate transdermal delivery system for the treatment of attention deficit hyperactivity disorder (ADHD).
12. A transdermal patch may also be used to deliver vitamin B12. Transdermal patching is compatible with the high stable form of vitamin B12 known as cyanocobalamin.
13. In October 2019, the FDA approved Secuado, a transdermal formulation of the atypical antipsychotic asenapine.
14. Fentanyl CII (marketed as Duragesic) and buprenorphine CIII (marketed as BuTrans) are two opioid drugs that are frequently prescribed in patch form to provide 24- hour relief from severe pain.
15. A transdermal patch that was introduced in the UK in early 2014 allows for the administration of 5- hydroxytryptophan (5- HTP).

10. ADVERSE EVENTS

1. The FDA released a public health statement in 2009 warning of the possibility of burns during MRI scans from transdermal medication patches with metallic backings. Before having an MRI scan, patients should be instructed to remove any medicinal patches, and then when the scan is finished, to replace them with fresh ones.
2. A report published in the *Europace* journal in 2009 described cases of skin burns brought on by shock therapy from both external and internal cardioverter defibrillators (ICD) and transdermal patches containing metal (typically as a supporting material).
3. The FDA reported in 2005 that it was looking into reports of narcotic overdose deaths and other significant adverse events in patients using Duragesic, a fentanyl transdermal patch for pain management. Later, in June 2005, the Duragesic product label was revised to include safety information.
4. The Daytrana ADHD patch's producers, Shire and Noven Pharmaceuticals, announced a voluntary recall of various lots of the medication in 2007 due to issues with the patch's ability to release from its protective release liner. Since that time, no new issues with the patch or its protective packaging have been reported.

11. CONCLUSION AND FUTURE CHALLENGES

Compared to other delivery methods, transdermal patch technology is a useful drug administration mechanism with several benefits. Patches can deliver continuous drug doses for a long time by skipping the digestive system and first-pass metabolism. They are frequently employed to deliver medications for a variety of conditions, including hormone replacement therapy, motion sickness, and chronic pain. Transdermal patch technology has made tremendous strides in recent years, including the creation of smart, biodegradable/ dissolving, high-loading/ release, and 3D-printed patches. Transdermal patches have the potential to be an easy and efficient way to deliver medication for a variety of conditions, but there is still some obstacle to overcome, including the risk of self-inflicted toxicity from improper dosage, poor adhesion, poor drug penetration, the potential for skin irritation, and patch failure. All of this calls for additional study and development to enhance the safety and effectiveness of this distribution system.

REFERENCES

- Jeong W. Y., Kwon M, Choi H. E. and Kim K. S., Recent advances in transdermal drug delivery system: a review, *Biomaterials Research*, 2021, 25:24.
- Yadav V, Transdermal Drug Delivery System: Review, Department of Pharmaceutics, MB University, Solan, H.P., *International Journal of Pharmaceutical sciences and Research*, vol. 3(2), 2012, 376-382.
- Sahu K, Transdermal Drug Delivery System: A Review Article, BN University, Udaipur, *Pharmatutor*, 2021.
- Chaudhary N, Singh A.P., Singh A.P., Transdermal drug delivery system: A Review, St. Soldier Institute of Pharmacy, Punjab, *Indian Journal of Pharmacy and Pharmacology*, vol. 8(1), 2021, 5-9.
- Tanwar H, Sachdeva R, Transdermal drug delivery system: A Review, Guru Jambheshwar University of Science and Technology, Haryana, India, *International Journal of Pharmaceutical Sciences and Research*, vol. 7(6), 2016, 2274- 2290.
- Digambar Mali A, Bathe R, Patil M, An Updated review on transdermal drug delivery system, Department of Pharmaceutics, Sahyadri College of Pharmacy, Maharashtra, India, *International Journal of Advances in Scientific Research*, vol. 1(06), 2015, 244-254.
- Kolarsick Paul A.J., Goodwin C, *Anatomy and Physiology of the skin*, 10th ed., 2006.
- Prausnitz M.R. & Langer R, Transdermal drug delivery, Department of Chemical Engineering, USA, *Nature Biotechnology*, vol. 26, 2008, 1261-1268.
- Gaikwad A.K., Transdermal drug delivery system: Formulation aspects and evaluation, Maharashtra India, *Comprehensive Journal of Pharmaceutical sciences*, Vol. 1(1), 2013, 1-10.
- Sharma N, Agarwal G, Rana A.C., Bhat Z.A., & Kumar D, A review: Transdermal Drug Delivery System: A Tool for Novel Drug Delivery System, *International Journal of Drug Development and Research*, vol. 3(3), 2011, 70-84.
- Shinde N, Manikpuriya S, Sanap G, Review of Transdermal drug delivery system, *World Journal of Pharmaceutical Research*, Vol. 13(1), 2024, 835-857.
- Mali A.D., Bathe R and Patil M, An updated review on transdermal drug delivery systems, Department of Pharmaceutics, Maharashtra, India, *International Journal of Advances in Scientific Research*, vol. 1(06), 2015, 244-254.
- Arunachalam A, Karthikeyan M, Kumar D.V., Prathap M, Sethuraman S, Ashutoshkumar S, Manidipa S, Transdermal Drug Delivery System: A Review, Department of Pharmaceutics, India, *Current Pharma Research*, vol. 1(1), 2010, 70-81.
- Marwah H, Garg T, Goyal A.K., & Rath G, Permeation enhancer strategies in transdermal drug delivery, Department of Pharmaceutics, ISF College of Pharmacy, Punjab, India, *Informa healthcare*, vol. 23(2), 2016, 564-578.

- Rastogi V, Yadav P, Transdermal drug delivery system: An overview, Department of Pharmaceutics, IFTM University, UP, India, Asian Journal of Pharmaceutics, vol. 6(3), 2012, 161-170.
- Shingade G.M., Quazi A, Sabale P.M., Grampurohit N.D., Gadhave M.V., Jadhav S.L., Gaikwad D.D., Review On: Recent Trend on Transdermal Drug Delivery System, Department of Pharmaceutics, India, Journal of Drug Delivery & Therapeutics, Vol. 2(1), 2012, 66-75.
- Wokovich A.M., Prodduturi S, Doub W.H., Hussain A.S., Buhse L.F., Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute, Food and Drug Administration, USA, European Journal of Pharmaceutics and Biopharmaceutics, Vol. 64(1), 2006, 1-8.
- Ramteke K.H., Dhole S.N., Patil S.V. Transdermal Drug Delivery System: A Review, Modern college of pharmacy, Maharashtra, Department of Pharmacy, Orissa, Journal of Advanced Scientific Research, Vol. 3(1), 2012, 22-35.
- Sharma A, Garg R, Raju L, Goyal S, Transdermal Drug Delivery System: A Review, Abhilashi college of Pharmacy, Tanda, World Journal of Pharmaceutical Research, Vol. 7(7), 2018, 260-288.
- Malvey S, Rao J.V. & Arumugam K.M., Transdermal drug delivery system: A mini review, Talla Padmavathi College of Pharmacy, Telangana, India, The Pharma Innovation Journal, Vol. 8(1), 2019, 181-197.
- Prabhakar D, Sreekanth J, Jayaveera K.N., Transdermal Drug Delivery Patches: A Review, A.P, India, Journal of Drug Delivery & Therapeutics, Vol. 3(4), 2013, 213-221.
- Bhowmik D, Pusupoleti K.R., Duraivel S, Kumar Sampath K.P., Recent Approaches in Transdermal Drug Delivery System, India, The Pharma Innovation- Journal, Vol. 2(3), 2013, 99-108.
- Newaz N, Transdermal Drug Delivery System.: An Overview, A project report submitted to the Department of Pharmacy, University of Asia Pacific, 2013, 1-49.
- Kumar A.J., Pullakandam N, Prabu S.L., Gopal V, Transdermal Drug Delivery System: An Overview, India, International Journal of Pharmaceutical Sciences Review and Research, Vol. 3(2), 2010, 49-54.
- Bose P, Jana A, Mandal S, Chandra S, Transdermal Drug Delivery System: Review and Future, India, Annals of R.S.C.B., Vol. 25(2), 2021, 3420-3436.
- Deshwal S & Verma N, Optimization Techniques in Transdermal Drug Delivery System, Department of Pharmaceutics, Uttar Pradesh, India, International Journal of Pharmaceutical Sciences and Research, Vol. 3(8), 2012, 2362-2370.
- Hanumanaik M, Patil U, Kumar G, Kumar Patel S, Singh I, & Jadatkar K, Design, Evaluation and Recent Trends In Transdermal Drug Delivery System, A Review, Department of Pharmaceutics, Karnataka, India, International Journal of Pharmaceutical Sciences and Research, Vol. 3(8), 2012, 2393-2406.
- Pawar P.M., Solanki K.P., Mandali V.A., Recent Advancements in Transdermal Drug Delivery System, Gujarat, India, International Journal of Pharmaceutical and Clinical Research, Vol. 10(3), 2018, 65-73.
- Sarooha K, Yadav B, Sharma B, Transdermal patch: A Discrete Dosage Form, Institute of Pharmaceutical Sciences, Kurukshetra University, International Journal of Current Pharmaceutical Research, Vol. 3(3), 2011, 98-108.
- Kajal, Sharma D.V., Pandit V, Ashawat M.S., Review Article: Recent Advancements in Transdermal Drug Delivery System (TDDS), Department of Pharmaceutics, Himachal Pradesh, India, Journal of Positive School Psychology. Vol. 6(8),2022, 8882-8892.
- Patel D.M., Kavitha K, Formulation and Evaluation of Transdermal Drug Delivery System, Department of Pharmaceutics, Karnataka, India, International Journal of Pharmaceutical Sciences Review and Research, Vol. 6(2), 2011, 83-90.
- Alam M.I., Alam N, Singh V, Alam M.S., Anwer T, Safhi M.M., Type, Preparation and Evaluation of Transdermal Patch: A Review, College of Pharmacy, Punjab, India, World Journal of Pharmacy and Pharmaceutical Sciences, Vo. 2(4), 2013, 2199-2233.
- Purushotham K and Vijetha K.A., A review on transdermal drug delivery system, Department of Pharmaceutics, Centre for Pharmaceutical sciences, Telangana, India, GCS Biological and Pharmaceutical Sciences, Vol. 22(02), 2023, 245- 255.
- Ghulaxe C, Verma R, A review on transdermal drug delivery system, G. R. Y. Institute of Pharmacy, M.P., India, The Pharma Innovation Journal, Vol. 4(1), 2015, 37-43.
- Wong F.W., Ang K.P., Sethi G, and Looi C.Y., Recent Advancement of Medical Patch for Transdermal Drug Delivery, Malaysia, Medicina, Vol. 59(4), 2023.
- Deulkar D.A., Kubde A.J., Hatwar P.R. & Bakal R.L., A review on transdermal drug delivery system, GSC Advanced Research and Reviews, Vol. 18(02), 2024, 347-361.
- Dr. Vigneswaran L.V., Chaithanya A.P., Dr. Ajit Babu K.T., Dr. Sebastian V.M. & Farha A.A., Review of Transdermal Patches, International Journal of Research Publication and Reviews, Vol. 5, 2024, 1008-1016.