REVIEW ARTICLE

FUTURE JOURNAL OF PHARMACEUTICALS AND HEALTH SCIENCES

Published by Pharma Springs Publication Journal Home Page: https://pharmasprings.com/fjphs

Transdermal Drug Delivery System – A Review

Ayesha T[1], Kishore Bandarapalle*[1], Rajasekhar K K[2], Tholla Bhagyamma[3], Mohit Ragavendra M R[1], Pathakota Bhuvan Kumar Reddy[1], Sindhu P[1]

[1]Department of Pharmaceutics, Sri Padmavathi School of Pharmacy, Tiruchanoor, Tirupati-517503, Andhra Pradesh, India
[2]Department of Pharmaceutical Analysis, Sri Padmavathi School of Pharmacy, Tiruchanoor, Tirupati-517503, Andhra Pradesh, India
[3]Department of Pharmacology, Sri Padmavathi School of Pharmacy, Tiruchanoor, Tirupati-517503, Andhra Pradesh, India

Article History:

Received on: 02 Dec 2022
Revised on: 23 Dec 2022
Accepted on: 24 Dec 2022

Keywords:

Transdermal Patch, Controlled Release, Adhesive

ABSTRACT

A transdermal patch is an adhesive patch which carries medicine and is placed on the skin to deliver drug to the bloodstream transdermally. This generally encourages recovery of an injured body part of your body. A transdermal patch facilitates for a controlled release of the drug into the patient, often by the body's heat melting thin layers of the medication incorporated in the adhesive or through a porous membrane concealing a depot of medication. Transdermal drug delivery has this benefit over other drug delivery methods, such as intramuscular, intravenous, topical, oral, etc. Transdermal medication delivery allows for a constant blood level profile, a regulated drug release into the patient and fewer systemic side effects.

*Corresponding Author

Name: Kishore Bandarapalle
Phone: 7995536331
Email: kishore.brr89@gmail.com

eISSN: 2583-116X pISSN:

DOI: https://doi.org/10.26452/fjphs.v3i1.340

Production and Hosted by

Pharmasprings.com

INTRODUCTION

Recently, there has been a rise in interest in creating new methods for delivering current medicinal compounds. For current pharmacological molecules, creating a novel drug delivery method significantly increases not only the efficacy and safety of the drug but also patient compliance and the therapeutic benefit as a whole [1]. The term "patches" refers to discrete, self-contained dosage forms used in transdermal drug delivery systems (TDDS). When patches are put to healthy skin, the medicine is delivered to the systemic circulation through the skin at a controlled rate. To administer a therapeutically effective dose of medication across the patient's skin, TDDS are dosage forms. TDDS are dosage forms created to distribute a therapeutically effective dose of medication across the skin of the patient [2].

The main objective of TDDS is to administer drugs into the body's circulation through the skin at a steady rate with scanty fluctuation between and within patients. Currently, one of the most promising approaches to administering drugs is transdermal administration. It reduces the stress that taking medication orally frequently places on the liver and digestive system. It improves patient compliance, reduces negative drug side effects caused by transient overdoses, and is convenient for transdermal treatments that only require a single weakly application.

This will amplify Due to the retention of plasma concentrations throughout the dosing period, there will be a rise of bioavailability, better constant plasma levels, as well as a prolonged period of action as contrasted to a decline in plasma levels with con-

ventional oral dosage forms. As a result, the therapy will be enhanced, side effects will be decreased, and the frequency of dosing will be reduced. Transdermal delivery short physiological half-lives to also be constantly supplied, preventing pulsed entrance through into circulatory system and provides controlled, constant drug administration [3].

Prospects for Medication Administration via the Transdermal Route

Skin

The skin, which has a surface area of roughly 2 square metres and receives around. The greatest organ within human body, a cardiac, transports one-third among all plasma. This provides as being a permeability barrier to prevent different chemical and biological substances from being absorbed transdermally. It is one of the body's most easily accessible organs and only has a thin (2.97 0.28 mm) thickness [4].

1. Distinct supply of blood system's inner workings from the outer world.
2. Acts as a deterrent against biological, chemical, and physical attacks.
3. By serving as a thermostat, regulates bodily temperature.
4. Has a significant impact on hypertension management.
5. Preventspreventing skin-penetrating UV rays.

Skin has a significant role in defining many elements of delivery of medicines, including such drug penetrating of the dermis and permeation.

In anatomy and ultrastructure of the skin have a significant impact onthe skin's diffusive resistance. There are four primary layers to the formation of human skin (Figure 1).

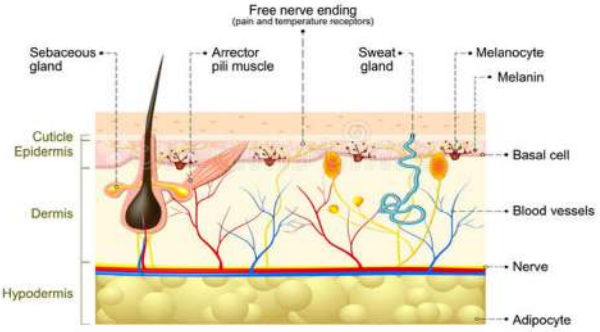

Figure 1: Epidermis as well as its Extensions as seen on a Schematic

Epidermis

The epidermis, which covers the entire outer surface of the body, is such a continuously layered, self-renewing columnar epithelial which is primarily made up of two types of cells: dead cells of a stratum corneum as well as the living cells of a malpighian layer (vital epidermis), also known a slippery slab.

As seen in Figure 2, the functional epidermal was split into four distinct layers:

1. Stratum lucidum
2. Stratum granulosum
3. Stratum spinosum
4. Stratum basale.

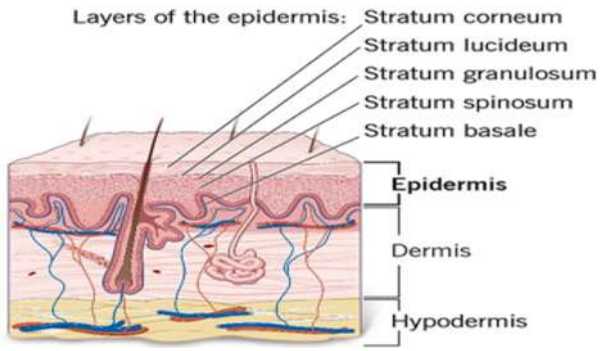

Figure 2: Schematic Representation of Layers of Epidermis

Stratum Corneum

This is the skin's outermost layer, commonly known as a slippery slab. The percentage barriers which restrict the movement for chemical substances both inward and outside. The horny layer's contents, which consist of 5–10% orally administered materials, estimated as dry weight, 5–15% lipids, and 75–80% proteins, are crucial to the barrier nature the layer's. While moist, an epithelial tissue was roughly 10 mm thick, whereas it enlarges significantly when completely moistened. Although flexible, it is largely impermeable. It is conceivable to model the Figure 3 shows the design of a horny layer as just a ceiling construction made from proteins block with lipids cement. This comprises of corneocytes, slippery slab cellulars joined by desmosomes. The lipid matrix in which the corneocytes are embedded has a big impact on how permeable the skin is to substances [5].

Viable Epidermis

The viable epidermis, which is located seems to have a thickness approximately 0.06 mm upon that eyelid but also 0.8 mm upon this palm underneath a

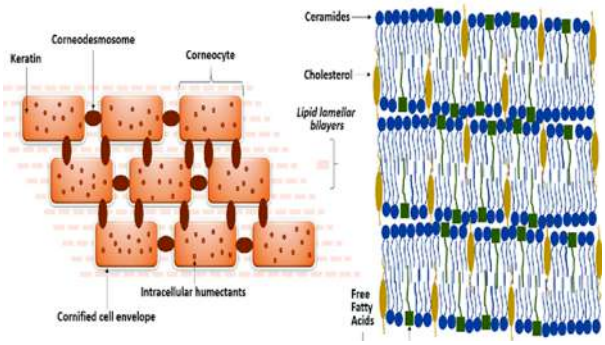

Figure 3: Schematic Representation of Stratum Corneum

cell membrane. A few of the sections which make it up a stratum lucidum include stratum granulosum, stratum spinosum, or epithelial basale interior. Mitosis, which occurs continuouslywhile in epidermis's basal cells, replaces a natural skin surface-lost hairy dead layers. A basale layer's cells to change in morphology as well as histochemistry as they proliferate outward and keratinize to form the stratum corneum's top layer [Figure 4].

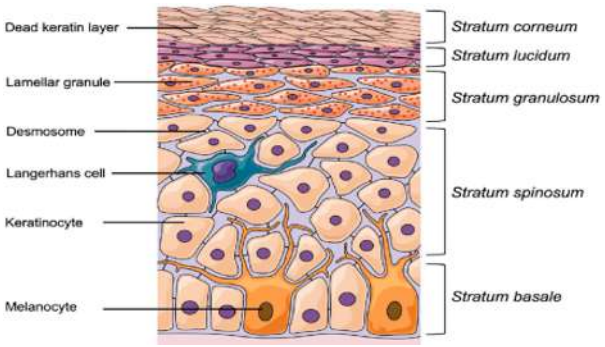

Figure 4: Schematic Representation of Anatomy of Epidermis

Dermis

The dermis is a 3 to 5 mm thick layer of skin that lies directly beneath the epidermis. It is made up of a matrix of connective tissues that houses nerves, blood vessels, and lymphatic vessels. The control of body temperature relies heavily on the cutaneous blood supply. While removing pollutants and waste, it also gives the skin nutrition and oxygen. Most molecules that penetrate the skin barrier sink in capillaries, which are located 0.2 mm from the skin's surface. Therefore, the blood supply maintains a very low epidermal penetrate composition as well as the resulting difference throughout composition across the epidermis acts as a primary driving factor to transdermal permeation [6].

Hypodermis

A endometrium, as well as transcutaneous visceral fat, nourishes the dermis as well as epidermal. This functions as a place to store fat. This layer offers mechanical protection, nutrient support, and assistance with temperature regulation. Principal blood arteries, nerves, and possibly pressure-sensing organs are carried there to the skin. For transdermal medication delivery, the drug must cross all three layers and enter the bloodstream [7].

Percutaneous Absorption

Prior to a drug's action when given topically, It must permeate deeply, either locally or systemically stratum corneum skin-to-skin absorbance is just as the infiltration of chemicals into various skin's layers and the penetration of such a skin within systemic vascular flow. Percutaneous absorption of Drug compounds are particularly significant in medication is delivered via a transdermal method, so must be absorbed at a sufficient rate and level must attain as well as sustain uniformity, systematic. Typically, when a medication molecules reaches inner epidermal regions, penetrates a stratum corneal barriers, and also is drawn into the body happens rather fast and effortlessly [8].

It takes several steps for a medicinal substance to be released a composition that has been implemented towards the surface of skin, as well as transported towards the systemic vascular system. which comprises:

1. Internal and external formulations dissolution.
2. Separating enters its skin's stratum corneum (SC), which serves as its topmost part.
3. Dispersion predominantly through the SC's lipophilic intercellular route.
4. The SC divides within watery healthy skin, a healthy skin diffuses within a upper dermis, such upper dermis is absorbed into the papillary dermis (capillary system), as well as at this point such microcirculation is impacted.

Possible Routes of Drug Penetration Through Skin

A drug molecule may pass through the epidermis during percutaneous permeation or may diffuse through shunts, particularly those provided by the more widely dispersed. Figure 5 demonstrates epidermis gland as well as hair follicles. During the earliest transitory diffusion process, drugs might penetrate its dermis via sweaty duct and hair follicles before even being ingested through to the epithelial tissue as well as sweat glands. Once this steady state has now been attained, diffusing through the intact

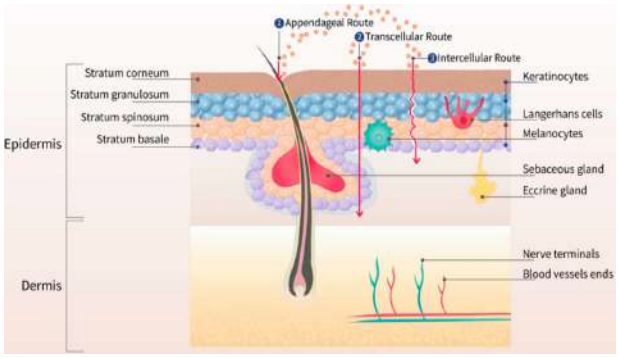

Figure 5: Possible Macro Routes for Drug Penetration

endothelium is becoming the primary route of epidermal permeation reached [9].

There are two main ways whereby substances put on the skin can permeate through epidermis: Transfollicular as well as transepidermal route.

Transepidermal Route

In transepidermal transport, molecules cross the intact horny layer. The intercellular pathway and transcellular (or intracellular) pathway are two potential micro-routes of entrance is as shown in Figure 6. By various mechanisms, both polar and non-polar chemicals diffuse through transcellular and intercellular pathways. primarily disperse the polar molecules while non-polar molecules dissolve and diffuse through the stratum corneum's non-aqueous lipid matrix, through the polar channel made up of "binding water" within the hydrated stratum corneum.

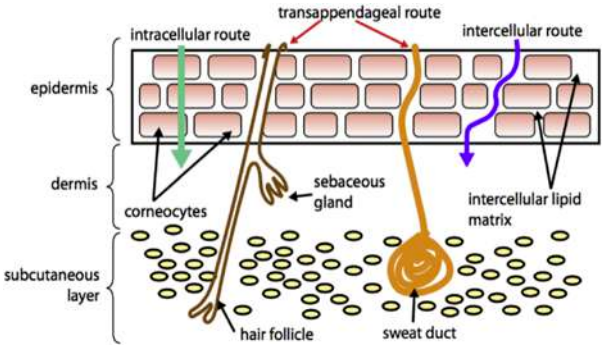

Figure 6: Schematic Representation of Transepidermal Route

Transfollicular/Transappendeageal Route

This route includes passage through the sweat glands and the hair follicles and sebaceous glands that are connected to them. These channels have high permeability, but due to their modest size—roughly 0.1% of the total skin—they are thought to be of secondary importance. For ions and big polar molecules, which barely pass through the stratum corneum, this pathway appears to be particularly important.

Barrier Functions of the Skin

The most crucial component in maintaining the barrier's efficacy is the top layer of skin. The skin's ability to retain water is preserved because the individual cells are closely packed and overlie one another in this area. In contrast to the other skin components, the stratum corneum mostly consists of keratinized dead cells and has a lower water content. From the skin's deepest layers to its surface, cells release lipids. In essence, these lipid molecules combine to form a strong connective network that serves as the mortar between a wall's bricks [10, 11].

Basic Principal of Transdermal Permeation

Passive diffusion is the basis for transdermal permeation. Given that only a few hundredths a millimetre thick tissues distinguishes its outer layer of skin as from network of capillaries beneath it, the skin is the most active as well as quickly acquirable organ in the body. It takes several steps for a medicinal substance to release from a formulation applied to the skin surface and go to the systemic circulation, which includes:

1. Drug diffusion from the medication applied to the rate-regulating membranes.
2. Internal and external composition dissolution.
3. Permeation via healthy epidermal as well as absorption even by stratum corneum.
4. Drug absorption even by dermis papillary layer's network of capillaries.
5. Result on the intended organ.
6. Dividing through into stratum corneum, an uppermost skin layer.
7. Dispersion mostly by a lipophilic interstitial pathway through to the stratum corneum.

Advantages of Transdermal Drug Delivery

Transdermal medication delivery makes it possible to avoid gastrointestinal absorption and all of its potential difficulties, including enzymatic and pH-related inactivation.

1. Preventing first-pass metabolites.
2. Transdermal medication delivery is a particularly good option for treatments that need generally constant plasma levels since the absence of peaks in concentration can lower the risk of side effects.

3. Acts as a substitute for oral route.
4. The patch also enables continuous dosing as opposed to the medicine levels' peaks and valleys that are common with orally administered drugs.
5. The ability to quickly stop medicine effects by removing the patch, as well as quick notifications of medication in an emergency.
6. Reducing harmful side effects to a minimum.
7. Provide access to medications with limited therapeutic windows and short biological half-lives.
8. Variation between and among patients [12].

Disadvantages of Transdermal Drug Delivery

1. A transdermal drug delivery system might administer ionic medicines device.
2. It is unable to raise blood drug levels to high levels.
3. It is unable to develop for medicines with big molecular weights.
4. Pulsatile medication delivery is not possible.
5. If a medicine or formulation irritates the skin, it cannot develop.
6. May produce an allergic reaction.
7. Potential for local irritation at the application site.

Factors Affecting Transdermal Permeation

Biological Factors

Skin Conditions

The intact skin serves as a barrier, but many substances such as acids and alkalis can pass through the barrier cells and infiltrate the skin. In addition, many solvents can access the intricate structure of the horny layer. Lipid fraction is removed by solvents like methanol and chloroform, creating artificial shunts that make it easy for drug molecules to pass through.

Skin Age

Although there is no obvious difference, it is observed that adults and young children's skin is more porous than that of elderly people. Children have harmful effects due to their larger surface area relative to their body weight. Strong steroids, boric acid, and hexachlorophene have therefore resulted in undesirable side effects.

Blood Supply

Variations with transdermal absorption were influenced through peripheral circulations.

Physicochemical Factors

Skin Hydration

Skin's permeability dramatically increases whenever it comes in contact with water. A majority crucial aspect in promoting skin permeability is hydration. So humectant usage occurs during transdermal administration.

Temperature and pH

With temperature change, drug permeability multiplies ten times. As temperature drops, the diffusion coefficient lowers.

Diffusion Coefficient

Drug diffusion coefficient affects drug penetration. The features of the drug, the diffusion medium, and their interactions determine the drug's coefficient of diffusion at a constant temperature.

Drug Concentration

The flux is inversely correlated with the gradient of concentration across the barrier, and the gradient will be bigger if the drug concentration is higher across the barrier.

Partition Coefficient

For effective action, the ideal partition coefficient (K) is needed. High K drugs are not yet ready to leave the lipid layer of skin. Additionally, medications with low K levels won't permeate.

Molecular Size and Shape

Drug absorption is inversely proportional to tiny molecules penetrate relatively more quickly than large ones due to molecular weight [13].

Environmental Factors

Sunlight

When areas which have been exposed to the sun, bruising occurs as a result of the thinning of blood vessel walls caused by direct sunlight just mild stress.

Also Pigmentation

A freckle or solar lentigo is the most obvious pigment change brought on by the sun.

Cold Season

Frequently cause dry, itchy skin. To fight the drying effects of the weather, skin reacts by producing more oil. The signs of dry skin can be relieved

with a decent moisturizer. Furthermore, consuming plenty of water can keep your skin hydrated and radiant.

Air Pollution

Acne or spots can result from dust clogging pores and causing an increase in germs on the skin's surface and on the face.

Types of tdds Patch

Reservoir System

In reservoir systems, a rate-regulating microporous or nonporous membrane and an impermeable backing laminate surround the medicament (Figure 7). In order to create a paste, the medication is uniformly dispersed in a viscous liquid medium suspended inside a solid polymer matrices. The speed at which medication was delivered was controlled either by membrane's thicknesses, penetration, diffusing, as well as abrasion rate. A reservoir system's release rate is a zero-order process. The impermeable metallic backing supports the whole system [14].

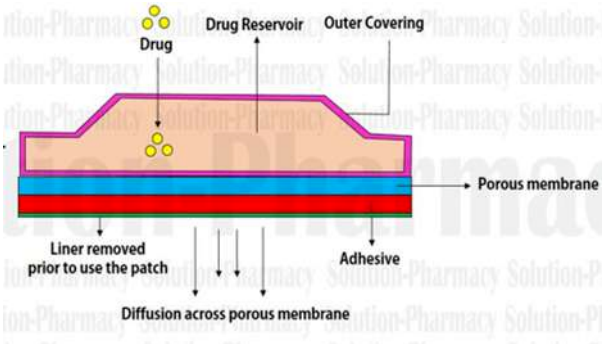

Figure 7: Reservoir System of Drug Delivery

Matrix Diffusion System

Drug is equally diffused in hydrophilic or lipophilic polymeric material in the matrix diffusion system (Figure 8). The amount of drug released depends on the rate at which the polymer is eroding, the thickness of the layer, and the surface area of the film. In the matrix system, there is no additional membrane that controls rate. These are additionally referred to as monolithic systems. Instead of spreading on the patch's surface, the adhesive layer is dispersed throughout the polymer disc's perimeter [15].

Drug in Adhesive System

The patch's sticky layer is where the medicine is dispersed in this method (Figure 9). The adhesive layer controls the rate of drug distribution to the skin in addition to adhering the patch's components to the skin. The liner encloses the sticky layer. In a single-layer patch, there is only one medication In contrast, a multilayer patch includes 2 layers:

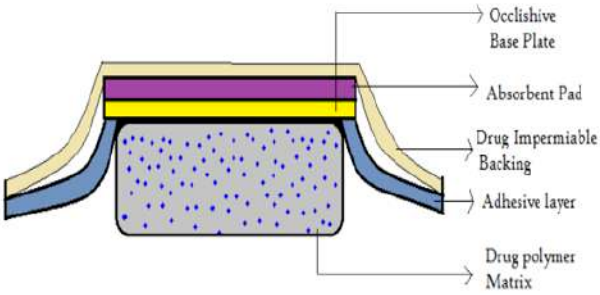

Figure 8: Matrix Diffusion System of Drug Delivery

one is for instant release and another for sustained release [16].

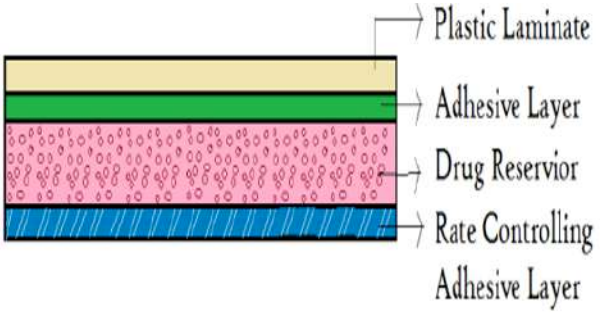

Figure 9: Drug in Adhesive Layer System

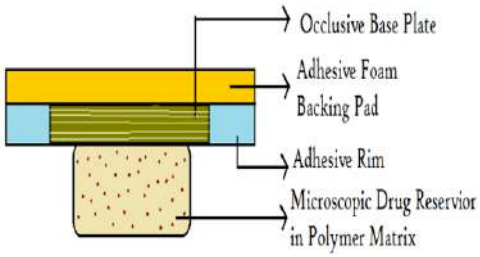

Figure 10: Drug Delivery in Micro Reservoir System

Micro Reservoir System

The matrix and reservoir system are combined to form the micro reservoir system (Figure 10). The medicine is first suspended in an aqueous solution of a hydrophilic polymer (such as PEG) in the micro reservoir system before being combined with a lipophilic polymer (such as silicon) using a high-shear mechanical stirrer. A medicated polymer disc with a specified area and thickness is formed as a result of the cross-linking of the polymer chains created in situ, which stabilises the micro reservoir system [17].

Formulation of Transdermal Drug Delivery System

Various components of a transdermal drug delivery system are:

Backing Layer

It provides support, protects the polymeric drug reservoir from the outside environment, and receives printings. To stop drug loss, the backing membrane needs to be as elastic, flexible, and impermeable to drug diffusion as possible. It shouldn't create any reactions and should be compatible with the polymer, excipients, and medicine. It is made of polyethylene, polyester, polyvinyl chloride, heat-sealed layers of polyurethane, adhesive foam pad, and aluminium foil.

Polymer

Polymer is the main ingredient in transdermal delivery systems. The properties of the polymer determine and regulate drug loading, rate of drug release, and appropriate adhesion of the patch to the skin. Thus, polymer selection is a key stage in TDDS. A polymer matrix is produced when drug-loaded polymer is placed between a backing layer and laminate. The polymer would need to enable both widespread drug absorption and the distribution of a variety of medications over the skin. The formulation's other excipients should be biocompatible, and the polymer used must be both skin- and drug-compatible [18].

Polymers employed to prepare TDDS systems are:

Natural polymers: e.g shellac, zein, natural rubber, waxes, gelatin, chitosan and cellulose derivatives.

Synthetic polymers: e.g polypropylene, polyacrylate, PMMA, polyethylene, PVA, PVC.

Synthetic elastomers:e.g silicon rubber, acrylonitrile

Biopolymers: collagen, pullulane, gellan, xanthane, polylylactic acid.

Permeation Enhancers

These substances serve to increase skin permeability by changing skin acts as a barrier to the flow of a desired penetrant.

Solvents

These substances could improve permeability by depleting the polar route or liquefying fats. Example comprise 2-methyl formamide, 2-methyl 2-purrolidone, as well as alkyl homologs like methyl sulfoxide dimethyl acetamide, alkyl methyl sulfoxides – dimethyl sulfoxide and water alcohols – methanol and ethanol; laurocapram (Azone), miscellaneous solventsisopropyl palmitate, silicone fluids, glycerol, propylene glycol.

Surfactants

These substances are suggested to improve the transport of hydrophilic medicines, in particular, through polar pathways. The polar head group and the length of the hydrocarbon chain affect a surfactant's capacity to change penetration.

Anionic Surfactants: e.g.Decodecylmethylsulphoxide, Sodium lauryl sulphate, Dioctylsulphosuccinateetc. Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc. Bile Salts: e.g. Sodium tauroglycocholate, Sodium deoxycholate, Sodium taurocholate. Binary system: These systems reportedly enable both the continuous paths and the heterogeneous multilaminate pathway. e.g. 1, 4-butane diol linoleic acid and Propylene glycol-oleic acid [16].

Miscellaneous Chemicals

Which include calcium thioglycolate, anticholinergic drugs, as well as urea, a moisturising as well as keratolytic substance.

Drug

The drug must possess some desired physicochemical characteristics that facilitate drug absorption through skin. Drugs should be effective, non-irritating, and have low molecular weights (up to 1000 dalton), low melting points, brief half-lives, affinities for lipophilic and hydrophilic compounds.

Adhesive

The patch's adhesive keeps it in constant touch with the skin. With finger pressure, it should stick to the skin and keep the patch in place for an extended amount of time. The type of patch, its design, and its adhesive qualities are among the selecting factors. It should be non-irritating, acceptable to the skin and other formulation ingredients, and simple to remove.E.g., silicon based adhesive polymer, polyacrylate and polyisobutadiene.

Plasticizers

It provide the polymer flexibility and modify the polymer's physical and mechanical properties. By coming together between the molecules of the polymer chains, these weaken the rigid polymer connection.

The polymer's elongation at break, toughness, and flexibility are increased while its tensile stress, hardness, electrostatic chargeability, and glass transition temperature are decreased e.g., alcohols, phthalic acid esters, and glycerol derivatives.

Rate Controlling Membrane

The rate at which the medicine is to be given from the dosage form is decided by rate regulating membranes.

To create a rate-regulating membrane, many polymers of natural and synthetic origin are used. E.g., chitosan, poly2-hydroxyethyl methacrylate.

Release Liner

It is a component of primary packaging, protects against drug evaporation from the polymer matrix and outside environmental contamination of the patch during storage and transportation. At the moment of use, it is peeled off. It depends on the release liner whether it is occlusive (like polyethylene or PVC) or not (paper fabric). For release liners, polyester foil and metallic foil are also employed [17].

Evaluation of TDDS

Physicochemical Evaluation

Thickness

At numerous locations along the transdermal film, the thickness is screw gauge, dial gauge, as well as micrometre are utilized to analyse.

Uniformity of Weight

Weighing 10 randomly chosen patches individually and finding out the average weight, weight variation is studied. The weight of a person shouldn't differ greatly from the average weight.

Drug Content

In a shaker incubator, an measured quantity of film (about 100 mg) is solubilized in 100 mL of a suitable solvent. The solution is then agitated continuously for 24 hours. The entire solution is then sonicated after that. Following sonication and filtering, the amount of drug in the solution is determined spectrophotometrically by the proper dilution.

Moisture Content

The manufactured films are weighed individually and kept in desiccators with calcium chloride at room temperature for 24 hours. After a predetermined amount of time, the films are weighed once more until they display a steady weight. Using a formula, the percentage of moisture content is determined.

Folding Endurance

In order to evaluate folding endurance, it is necessary to determine the folding capacity of the films that are frequently folded under extreme conditions. The test for folding endurance involves folding the film repeatedly until it breaks. Folding endurance value is the maximum number of folds a film can sustain without breaking [18].

Tack Properties

It is the polymer's capacity to stick to a surface with minimum contact pressure. The usage of tackifying resins in polymers as well as the molecular weight and makeup of the polymer have an impact on tack.

Rolling Ball Tack Test

This test measures how long a stainless steel ball travels over the adhesive's upper face. The ball has a 7/16" diameter and is released on an inclined track with a 22 degree inclination. Therefore, the sticky polymer is reduced the further it travels. Inches are used to measure the ball's distance travelled, which affects how tacky the polymer is. It establishes the sticky polymer's softness [Figure 11].

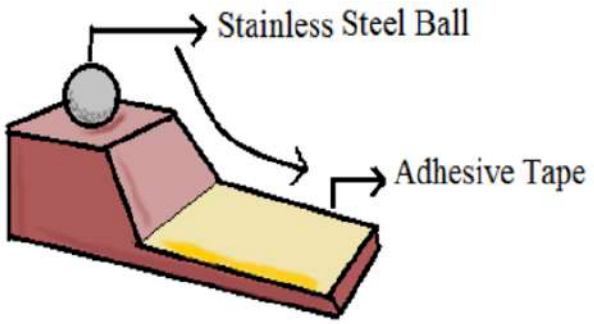

Figure 11: Rolling Ball Tack Test

Peel Tack or Quick Stick Test

The force necessary to break the link between the adhesive and the test substrate is known as the peel force. At a speed of 12 inches per minute, the patch is dragged 90 degrees away from the substrate. Inches or grammes per inch are used to measure force [Figure 12].

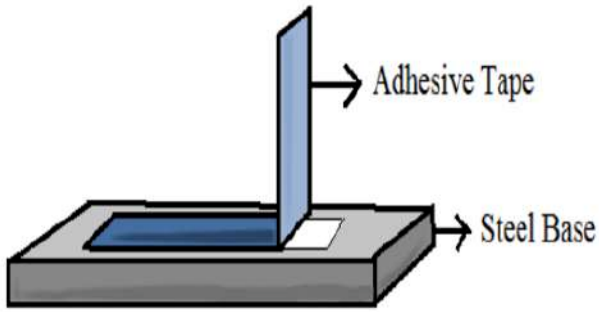

Figure 12: Peel Tack Test /Quick Stick Test

Probe Tack Test

In this, an adhesive is brought into touch with a probe tip with a specified level of surface roughness. Once a bond is formed between the adhesive and probe, the probe is removed at a set rate away from the glue, breaking the bond. Tack, which is measured in grams, is the amount of force needed to rupture the bond [Figure 13] [19].

Adhesive Studies

Shear Adhesion Test

This test evaluates an adhesive polymer's cohesive strength. The strength value can be affected by the

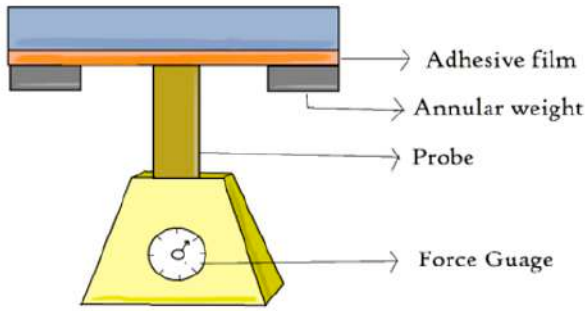

Figure 13: Probe Tack Test

degree of cross-linking, the molecular weight, the composition of the polymer, and the amount of tackifiers utilized. A stainless steel plate is positioned on top of an adhesive-coated patch, and a certain weight is suspended from the patch in a straight line across the plate. The time it takes to remove the patch from the plate gives an indication of the cohesive strength [Figure 14].

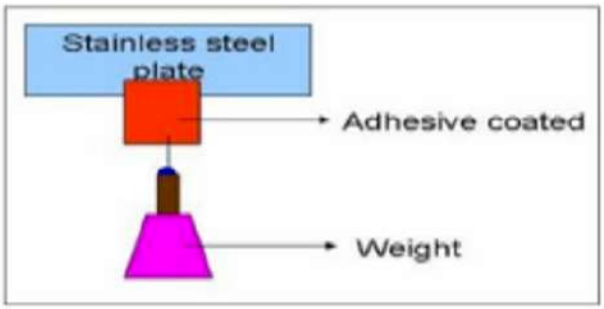

Figure 14: Shear Adhesion Test

Peel Adhesion Test

The strength of the bond between an adhesive and a substrate is measured in terms of adhesion. The sticky characteristics of a polymer depend on the type, quantity, molecular weight, and content of the polymer. A steel test surface had a single patch attached to it, and it was moved away from it at an 180^0-degree angle [Figure 15] [20].

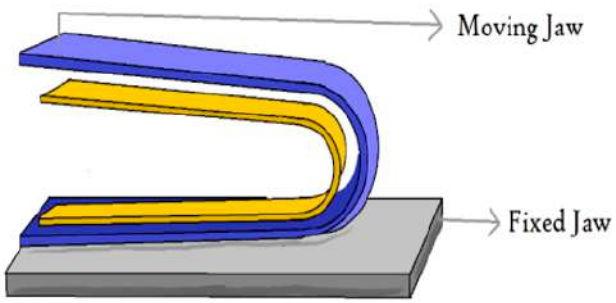

Figure 15: Peel Adhesion Test

In Vitro Release Studies

Franz diffusion cells, which have two compartments—donor and receptor—can be used in vitro to test transdermal patches. The receptor compartment has an effective surface area of 1–5 cm^2 and a capacity of 5–12 ml. A magnetic bar continuously stirs the diffusion buffer at 600 rpm. A water jacket that envelops the receptor compartment is circulated with thermostated water to maintain the temperature in the rest of the solution. A suitable method is used to analyse the drug content, and maintaining the state of the sink is essential.

Animal Models

Since conducting research on humans requires a lot of time and resources, small-scale animal experiments are favoured. The most often utilised animal species for testing transdermal drug delivery systems include the guinea pig, hairless rhesus monkey, hairless dog, hairless rat, rabbit, and mouse. Numerous studies demonstrate that hairless animals outmatch hairy animals in both in vitro and in vivo investigations rhesus monkey is one of the most reliable animal models for assessing transdermal drug delivery in humans in vivo.

Human Model

After applying the patch to human volunteers, the transdermal device's final stage of development involves collecting pharmacokinetic and pharmacodynamic data. 39 Clinical studies have been carried out to evaluate the effectiveness, risks, side effects, patient compliance, etc. of a treatment. Phase I clinical studies are conducted largely to assess volunteer safety, whereas phase II clinical trials are undertaken primarily to evaluate patient short-term safety and efficacy. Phase III studies demonstrate safety and efficacy in a wide patient population, while phase IV studies are conducted for marketed patches during post-marketing surveillance to identify adverse medication reactions. Though it is better to evaluate the effectiveness of the drug through human studies, which involve large resources [21].

Approaches/Technologies Used in TDDS

Electroporation

Iontophoresis and electroporation are the two main methods of electrically facilitating TDD. In electroporation, cells are briefly exposed to strong electric pulses that cause the lipid bilayers of the stratum corneum to generate aqueous pores, allowing medicines to diffuse over the skin. Neumann et al. provided the initial description of the method. It has been demonstrated that applying high voltage pulses(50–500 V) for brief periods of time—as little as one second—can improve the transport of various medicines with a range of molecular weights

across the skin. e.g., orcalcein, timolol, fentanyl, to pharmaceuticals containing high viscosity, including such FITC-dextran as well as heparin, possessing molecular mass upwards over 40 kDa, calcitonin. The primary downsides, include the inadequacy of quantitative delivery, high fields that cause cell death, and potential ruin to labile medicines, such as those having protein origins.

Iontophoresis

By using medically acceptable electrical currents (0.1-1.0 mA/cm2), this procedure forces charged permeants into the skin through electrostatic impacts and causes ionic medications to permeate through the skin and into the body by its potential gradient [Figure 16] [22].

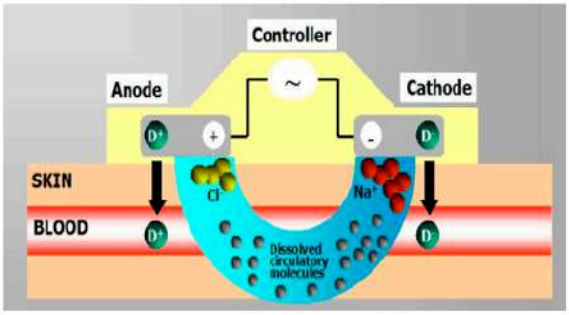

Figure 16: Schematic Representation of an Iontophoresis Patch

Velocity Based Devices

Velocity-based devices, such as powder or liquid jet injections, employ a power source include compressed gas or spring to create a high-velocity jet with speeds between 100 and 200 m/s to pierce the skin and deliver drugs. Around the beginning of the 1930s, Arnold Sutermesiter investigated the use of jet injectors for the delivery of drugs. Since then, there has been a major increase in interest in this form of drug delivery, leading to the development of two different types of liquid jet injectors single-dose jet injectors (also known as disposable cartridge jet injectors) and multi-use-nozzle jet injectors (MUNJIs). For more than 50 years, jet injections have been used for the parenteral delivery of vaccinations and other small molecules, such as anaesthetics and antibiotics. A needle-free device called a jet injector can provide electronically regulated dosages of medication, improving uniformity of delivery and decreasing patient pain [Figure 17] [23].

Liquid Jet Injectors

The aperture diameter of a liquid-jet injector's nozzle, which can range from 50 to 360 m, is substantially smaller than a typical hypodermic nee-

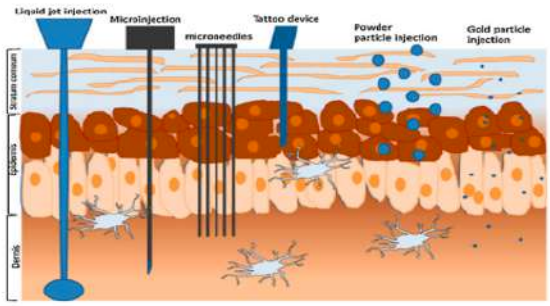

Figure 17: Schematic Representation of Methods of Intradermal Injections

dle's (810 m for a 21G needle) outer diameter. By adjusting the jet's velocity and orifice size, the medicine can be delivered into various layers of skin, such as the intradermal (i.d.), subcutaneous (s.c.), or intramuscular (i.m.). The main benefit of utilising needle-free devices is the reduction of worries about accidental needle stick injuries and proper needle disposal. The risk of cross-contamination is not entirely eliminated, though, as the nozzle may become contaminated by interstitial liquid that bounces back from the skin. Multiple-use nozzle jet injectors are no longer used, and these devices are now only used to administer multiple doses of medication to the same person, such as the Tjet®device that distributes somatropin (human growth hormone (hGH)) [Figure 18].

Figure 18: Commercially Available Jet Injector

Laser Thermal Ablation

Clinical therapies for the treatment of dermatological problems like pigmented lesions have utilised laser methods. The removal of the stratum corneum selectively, without harming deeper tissues, is the basic mechanism of laser thermal ablation of the skin, which improves drug administration of lipophilic and hydrophilic substances into skin layers. By depositing optical energy on the stratum corneum, lasers remove it, which evaporates water and creates microchannels in the skin. These techniques have also been used to remove interstitial fluid from diabetic patients in order to assess their

blood glucose levels afterwards. However, the pulse repetition rate, exposure time, pulse number, pulse energy, tissue absorption coefficient, tissue thickness, pulse length, and wavelength all affect how much of a barrier is disrupted. The commencement of lidocaine action in human volunteers was shown to be shortened to 3-5 min by pre-treatment with the laser and then lidocaine cream by Baron et al. in 2003. However, it is important to assess the structural changes in the skin, especially when utilising stronger laser energies that could be necessary to enhance the transport of therapies with heavy molecular weights.

Radiofrequency (RF) Thermal Ablation

A tiny, needle-like electrode is inserted into the skin during radiofrequency (RF) thermal ablation, and high frequency alternating current (100 kHz) is then applied to make tiny openings inside the endothelium because then medication may permeate over. After being subjected with higher frequency, epithelial cells (between 100 and 500 kHz), the tissue's ionic vibrations try to localise the heating to a particular area of the skin and subsequently ablate the cells in that area, resulting in drug transport across the skin. Using a low-cost, entirely disposable device, this approach may enable the transdermal distribution of a wide range of hydrophilic medicines and macromolecules [Figure 19] [24].

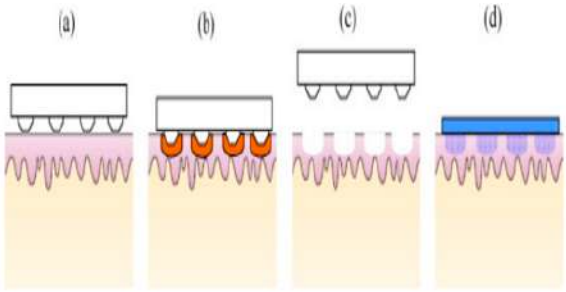

Figure 19: Schematic Diagram of Drug Delivery Using Thermal Ablation

Microneedle Arrays

(MNMinimally intrusive drug delivery systems, also known as MN arrays, were developed to address and improve patient compliance as well as to address some of the issues that are usually associated with the use of hypodermic needles. MN arrays could be used in place of hypodermic and subcutaneous needle technology. While some devices are now undergoing clinical testing and others are waiting for FDA clearance, MN technologies have been the subject of majorAcademic and industry researchers both are engaged with study and development. Additionally, there has been a significant rise in recent years in the number of articles characterising MN as novel minimally invasive drug delivery methods. MN continues to combine the ease of a transdermal patch with the effective delivery made possible by a conventional hypodermic needle and syringes [Figure 20] [25].

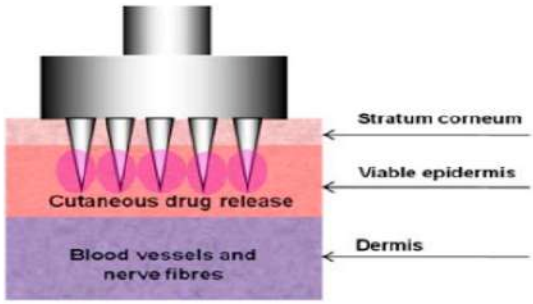

Figure 20: Schematic Representation of the Mechanism of Action of a Microneedle Array Device

The tool penetrates the stratum corneum (SC), giving medications direct access to the dermis' blood vessels and nerve fibres while leaving the overlying, viable epidermis unharmed.

Tape Stripping

Tape stripping is an easy removal technique for such stratum corneum layers through applying adhesive tapes repeatedly. The power with which the tape is pulled away from the skin and how long the skin is under pressure also have an impact on how much stratum corneum is lost during tape stripping. Tape peeling is a reliable and easy technique. To remove the stratum corneum uniformly, numerous factors, such as the time spent applying pressure to the skin, should be taken into account both before and after this treatment [5].

CONCLUSION

The TDDS is a relatively novel strategy to drug administration compared to the traditional methods, such as solid oral dosage form and parenteral. Its ability to avoid metabolism that works too quickly, great endurance, and few adverse effects make it special. Drugs that require frequent doses and irritate the stomach now have a new method of administration with TDDS. The amount of TDDS-related research and development is increasing today compared to the previous two decades. Various current methods, such as improving transdermal medication delivery, are being studied. The TDDS has become a significant research priority since it solves the majority of the problems with conventional dose forms.

ACKNOWLEDGEMENT

The corresponding author desires to explict utmost gratitude to the Management and Prof. Dr. D. Ranganayakulu, M. Pharm., PhD, Principal, Sri Padmavathi school of pharmacy, Tiruchanoor, Andhra Pradesh, India, for presenting all the necessary laboratory demands of the research and constant support.

Funding Support

The authors declare that they have no funding support for this study.

Conflict of Interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] D Bhowmik, Chiranjib, M Chandira, B Jayakar, and K P Sampath. Recent advances in transdermal drug delivery system. *Int. J Pharm Tech Res*, 2(1):68–77, 2010.

[2] A Kumar, N Pullankandam, S L Prabhu, and V Gopal. Transdermal drug delivery system, an overview. *Int. J Pharm Sci. Review Res*, 3(2):49–54, 2010.

[3] A Divya, M K Rao, K Gnanprakash, A Sowjanya, N Vidyasagar, and M Gobinath. A review on current scenario of transdermal drug delivery system. *Int. J Res. Pharm Sci*, 3(4):494–502, 2012.

[4] S Rani, K Saroha, N Syan, and P Mathur. Transdermal patches a successful tool in transdermal drug delivery system. *Plegia Res, Lib*, 2(5):17–29, 2011.

[5] D Patel, S A Chaudhary, B Parmar, and N Bhura. Transdermal drug delivery system: a review. *The Pharm Innovation*, 1(4):66–75, 2014.

[6] D Kumar, N Sharma, A C Rana, G Agarwal, and Z A Bhat. A review: transdermal drug delivery system: a tools for novel drug delivery system. *Int. J Drug Dev. Res*, 3(3):70–84, 2011.

[7] K H Ramteke, S N Dhole, and S V Patil. Transdermal drug delivery system: a review. *Journal of Advanced Scientific Research*, 3(1):22–35, 2012.

[8] G M Shingade. Review on: recent trend on transdermal drug delivery system. *Journal of drug delivery and therapeutics*, 2(1), 2012.

[9] K S Paudel, M Milewski, C L Swadley, N K Brogden, P Ghosh, and A L Stinchcomb. Challenges and opportunities in dermal/transdermal delivery. *Therapeutic delivery*, 1(1):109–131, 2010.

[10] L Z Kaestli, A F Wasilewski-Rasca, P Bonnabry, and N Vogt-Ferrier. Use of transdermal drug formulations in the elderly. *Drugs & aging*, 25(4):269–280, 2008.

[11] M R Prausnitz and R Langer. Transdermal drug delivery. *Nature biotechnology*, 26(11):1261–1268, 2008.

[12] S K Vishwakarma, S K Niranjans, R Irchhaiya, N Kumar, and A A Akhtar. A Novel transdermal drug delivery system. *International Journal of research of pharmacy*, 3(8):39–44, 2012.

[13] K Saroha, B Yadav, and B Sharma. Transdermal patch: A discrete dosage form. *Int J Curr Pharm Res*, 3(3):98–108, 2011.

[14] I K Gupta and M M Chokshi. Transdermal drug delivery system: an overview. *Asian J Pharm Sci. Clinical Res*, 1(1):25–43, 2011.

[15] V S Jatav, J S Saggu, R K Jat, A K Sharma, and R P Singh. Recent advances in development of transdermal patches. *Pharmacophore (An international research journal)*, 2:287–297, 2011.

[16] D S Patel, M V Patel, K N Patel, B A Patel, and P A Patel. Transdermal patches: a complete review on transdermal drug delivery system. *Int. J Pharm Res. Scholars*, 1(1):55–71, 2012.

[17] L K Lende, N D Grampurohit, D D Gaikwad, M V Gadhave, and S L Jadhav. Transdermal patches: a review. *Int. J Pharm Res. Dev*, 4(3):96–103, 2011.

[18] S Parivesh, D Sumeet, and D Abhishek. Design, evaluation, parameters and marketed products of transdermal patches: A review. *Journal of Pharmacy Research*, 3(2):235–240, 2010.

[19] A Adhyapak and B G Desai. Preparation and in vitro characterization of the transdermal drug delivery system containing tamoxifen citrate for breast cancer. *Asian Journal of Pharmaceutics (AJP)*, 5(1), 2011.

[20] K Kavitha and M M Rajendra. Design and evaluation of transdermal films of lornoxicam. *Int J Pharma Bio Sci*, 2(2):54–62, 2011.

[21] G Darwhekar, D K Jain, and V K Patidar. Formulation and evaluation of transdermal drug delivery system of clopidogrel bisulfate. *Asian J. Pharm. Life Sci. ISSN*, 1(3):269–278, 2011.

[22] K Ansari, A K Singhai, G K Saraogi, and S Patil. Transdermal Drug Delivery of Salbutamol Sulphate with Different Concentration of Polymers. *International Journal of Research in Pharmacy and Science*, 1(3), 2011.

[23] E N Hanan, G Fakhry, E G Hanaa, and S Shereen. Effect of various penetration enhancers concentrations on diclafenac sodium release from cellulose acetate phthalate polymeric film. *Asian Journal of Pharmaceutics (AJP)*, 5(1), 2011.

[24] B Sachan and M Bajpai. Transdermal drug delivery system: A review. *Int. J Res. Dev. Pharm and life Sci*, 3(1):748–765, 2013.

[25] R Bathe and R Kapoor. Transdermal drug delivery system: formulation, development and evaluation-An overview. *Drug Deliv*, 6:7–12, 2015.

Cite this article: Ayesha T, Kishore Bandarapalle, Rajasekhar K K, Tholla Bhagyamma, Mohit Ragavendra M R, Pathakota Bhuvan Kumar Reddy, Sindhu P. **Transdermal Drug Delivery System – A Review**. Future J. Pharm. Health. Sci. 2023; 3(1): 52-64.