IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

RECENT ADVANCES IN TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS)

Dipali A. Chavan*, Pravin B. Suruse, Lokesh G. Barde

Department of Pharmaceutics, S.N.D. College of Pharmacy, Babhulgaon

Abstract

Transdermal drug delivery system (TDDDS), commonly referred to as "patches", are medication dosage forms intended to disperse a therapeutically adequate dose of medication across the skin of patient. It is necessary to consider the complete morphological, biophysical, and physicochemical characteristics of the skin in order to transfer medical substance through the skin of humans for systemic effects. By improving patient compliance and avoiding first pass metabolism, respectively, transdermal administration offers a competitive advantage over injectables and oral methods. Transdermal delivery not only allows for continuous infusion of medication with brief biological half-lives but also avoids pulsed entrance into the systemic circulation, which frequently results in unfavourable side effects. The TDDS review papers offer insightful data on the assessment of transdermal drug delivery system. A transdermal drug delivery system stands out among the new non-invasive administration methods that have recently emerged as alternatives to traditional needle injection because of its low rate of patient rejection, exceptional ease of administration, and exceptional patient convenience and adherence. The skin care sector, including cosmetics, as well as the pharmaceutical industry may be able to use TDDS. This strategy can prevent local drug concentration builds up and non-specific drug delivery to tissue that are not the drugs target tissues because it primarily involves local administration. Nevertheless, despite countless studies being done to find a way around this bottleneck, the physicochemical characteristics of the skin translate to several challenges and limitations in transdermal distribution.

Keywords: Transdermal drug delivery system (TDDS), First-generation TDS, Second-generation TDS, Polymer Matrix, skin, active or passive method, characterization

INTRODUCTION

The concept of a "drug delivery system" (DDS) encompasses a variety of advanced physicochemical methodologies designed to control the distribution and release of pharmacologically active compounds within cells, tissues, and organs, maximizing their therapeutic potential. To enhance treatment effectiveness and minimize adverse effects, DDS focuses on the formulation and administration methods that efficiently

transport medications. Various administration techniques exist, such as oral, transdermal, lung inhalation, mucosal, and intravenous injection, each with its unique delivery pathway.[1]

Among these, the transdermal drug delivery system (TDDS) has gained significant attention as a highly appealing strategy. Unlike conventional direct administration methods, which typically involve needle-based injections, TDDS has emerged as a widely researched non-invasive approach for delivering drugs into the body through the skin. TDDS has had a substantial impact on the distribution of numerous therapeutic substances, particularly in treating cardiovascular and central nervous system disorders, hormone therapy, and pain management. The avoidance of the digestive tract by TDDS ensures that no loss occurs from first-pass metabolism, and drugs can be administered without interference from pH, enzymes, or intestinal flora. TDDS's popularity is also attributed to its capacity to control drug release according to usage constraints and its non-invasive nature.[2]

However, TDDS has yet to reach its full potential due to the inherent skin barrier. The skin, a multi-layered organ that forms the body's outermost defense, serves to protect us from external threats such as toxins, heat, and chemicals. Each skin layer, including the epidermis and the dermis, has components that impede transdermal delivery. In TDDS, it is widely accepted that the intracellular pathway is employed for the delivery of drugs with low molecular weights. However, for high molecular weight compounds, alternative techniques and mechanisms incorporating both intracellular and intercellular pathways have been explored. The skin's structure results in an irregular distribution of lipids, which consist of cells and a mix of hydrophilic and hydrophobic substances. These structural features can be explained by the concept of physicochemical properties, which aim to enhance drug administration through the skin. The skin's endothelium functions similarly to the body's overall endothelium, actively responding to pressure, heat, and cytokines by altering permeability and inducing vasodilation or vasoconstriction. To deliver drugs to the skin tissue and traverse cellular and vascular structures to reach the target tissue, the stratum corneum barrier must be overcome. However, only a small amount of medication can be administered through the skin tissue, posing a challenge. To address this limitation, innovative TDDS solutions have been extensively developed and have gained traction as popular administration methods.[3,4]

Advantages of Transdermal Drug Delivery Systems [5,6]

- **Sustained drug release:** Transdermal drug delivery systems facilitate continuous administration of medications to the body over an extended period. This helps avoid fluctuations in drug levels and the adverse effects typically associated with intermittent dosing.
- **Enhanced therapeutic efficacy:** By bypassing issues such as gastrointestinal discomfort and reduced absorption due to the hepatic "first-pass" effect, transdermal administration can improve the therapeutic effectiveness of many drugs.
- **Improved patient compliance:** A simplified medication regimen leads to better adherence and less variability between and within patients, ensuring more consistent treatment outcomes.

- **Optimal pharmacological effects:** The application and removal of a transdermal patch enable precise control of drug levels in the body, resulting in the most effective sequence of pharmacological effects.
- **Self-administration:** Transdermal drug delivery systems allow patients to self-administer their medications, providing convenience and flexibility.
- **Adjustable drug input:** The transdermal patch can be removed at any time to cease drug delivery, allowing for easy adjustments to dosage or discontinuation of treatment when necessary. [14]

Disadvantages of Transdermal Drug Delivery System:[7-9]

- **Physicochemical limitations:** The drug must possess specific physicochemical properties to penetrate the stratum corneum effectively. Transdermal delivery becomes challenging if the required therapeutic dose exceeds 10mg/day.
- **Skin impermeability:** Due to the natural barrier function of the skin, only relatively potent drugs are suitable candidates for TDDS. The skin's impermeability imposes limitations on the types and quantities of drugs that can be effectively delivered.
- **Contact dermatitis:** Some patients may experience contact dermatitis at the application site due to one or more components of the transdermal system. This allergic reaction can necessitate discontinuation of the treatment.
- **Clinical need assessment:** Before developing a transdermal product, it is crucial to carefully evaluate the clinical necessity and ensure that the benefits outweigh the potential drawbacks.
- **Variability in skin barrier function:** The skin's barrier function varies from one site to another on the same individual, between different individuals, and with aging. This variability can result in inconsistent drug absorption and treatment outcomes.[25]

Anatomy of skin

Mammalian skin, including human skin, covers an area of approximately 2 square meters and constitutes a significant portion of the body. It receives nearly one-third of the human plasma circulation. The skin serves as the body's primary barrier against the external environment, protecting it from pathogens, physical damage, and environmental factors. It also plays a crucial role in temperature regulation, sensation, and excretion.[10-12]

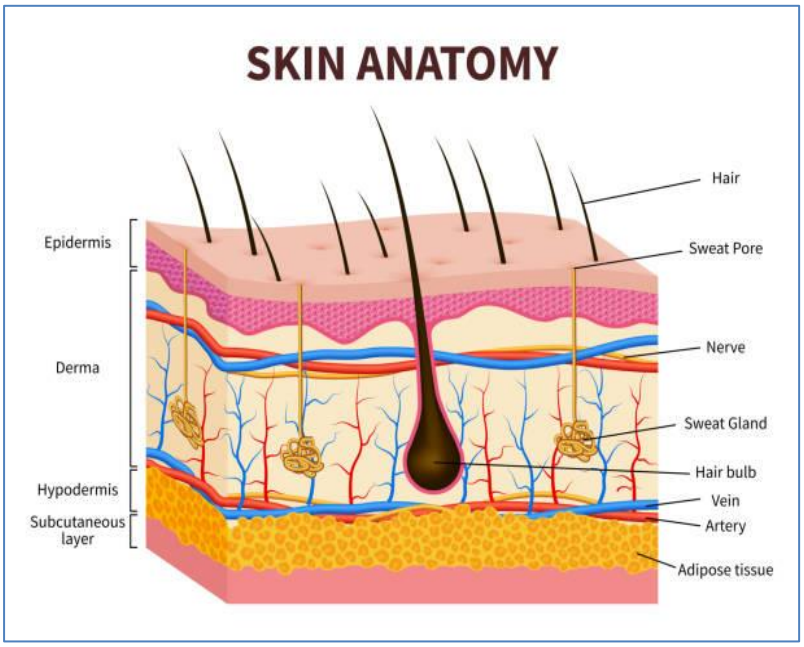

Figure 1: Skin Anatomy

The skin is composed of three primary layers:

- **Epidermis:** The outermost layer of the skin, the epidermis, is composed mainly of keratinocytes, which produce the protein keratin. This layer provides a waterproof barrier and creates our skin tone. The epidermis itself is divided into sub-layers, including the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale.
- **Dermis:** The dermis is the middle layer of the skin, lying beneath the epidermis. It consists of connective tissue, blood vessels, hair follicles, sweat glands, and nerve endings. The dermis provides structural support, nourishment, and elasticity to the skin. Two sub-layers make up the dermis: the papillary dermis and the reticular dermis.
- **Hypodermis (subcutaneous layer):** The innermost layer, the hypodermis, is composed of adipose tissue (fat) and connective tissue. This layer provides insulation, energy storage, and cushioning to the body. It also anchors the skin to the underlying muscles and bones.

In addition to these primary layers, various specialized cells and structures are present in the skin, such as melanocytes (responsible for skin pigmentation), Langerhans cells (immune response), and Merkel cells (sensation). The complex structure of the skin enables it to effectively protect the body while maintaining its essential functions.[13,14]

Structure of the Skin

The morphology of the mammalian skin may possibly classify into 4 major layers, which are-

- The practical epidermis
- An overlying dermis
- The epidermis
- A non-practical epidermis

The structure of mammalian skin, including human skin, can be broadly categorized into four primary layers. Each layer plays a crucial role in the overall function and protection of the skin:

1. **Functional Epidermis:** The functional epidermis is the outermost layer of the skin and is composed mainly of keratinocytes, which produce the protein keratin. This layer serves as a protective barrier against external factors, such as pathogens, physical damage, and moisture loss. The functional epidermis is divided into several sub-layers, including the stratum corneum, stratum lucidum (only in thick skin areas such as the palms and soles), stratum granulosum, stratum spinosum, and stratum basale. Each sub-layer has a specific role in the process of keratinocyte maturation, skin renewal, and barrier function maintenance.[15]
2. **Dermis:** The dermis lies beneath the functional epidermis and consists of connective tissue, blood vessels, hair follicles, sweat glands, and nerve endings. This layer provides structural support, nourishment, and elasticity to the skin. The dermis is further divided into two sub-layers: the papillary dermis and the reticular dermis. The papillary dermis is the thinner, upper layer that forms finger-like projections called dermal papillae, which interlock with the epidermis to increase surface area and facilitate the exchange of nutrients and waste products. The reticular dermis, on the other hand, is the thicker, deeper layer that contains dense connective tissue, collagen, and elastin fibers, providing strength and resilience to the skin.[16]
3. **Epidermis:** Although the term "epidermis" is often used to refer to the entire outer layer of the skin, it can also be considered as a separate layer in some contexts. The epidermis, in this case, refers to the entire stratified squamous epithelium that makes up the outer layer of the skin, including both the functional epidermis (with its sub-layers) and the non-functional epidermis (also known as the stratum corneum). The epidermis serves as the primary barrier between the body and the external environment.
4. **Non-functional Epidermis (Stratum Corneum):** The non-functional epidermis, also known as the stratum corneum, is the outermost sub-layer of the functional epidermis. This layer consists of dead, flattened keratinocytes that are filled with keratin and surrounded by lipids. The cells in the stratum corneum, called corneocytes, are constantly shed and replaced by new cells from the underlying layers. The non-functional epidermis plays a vital role in maintaining the skin's barrier function, preventing water loss, and providing protection against external factors.[17]

In summary, the structure of the skin is complex, with multiple layers and sub-layers working together to provide protection, sensation, and regulation for the body. Understanding the intricacies of the skin's structure can aid in the development of advanced skincare and therapeutic strategies for various skin conditions.

Transdermal patches

Transdermal patches, also known as skin patches, are adhesive patches applied to the skin that contain medication intended to be absorbed through the skin into the bloodstream. These patches often promote the healing of an injured body part. The controlled release of medication into the patient is an advantage of transdermal drug administration compared to other forms, such as oral and topical. However, the skin's effectiveness as a barrier poses a challenge to development. Transdermal patches can deliver a wide range of medications.[18]

The main components of a transdermal patch are:

- Liner - protects the patch during storage and is removed before use.
- Drug – drug solution in direct contact with the release liner.
- Adhesive – adheres the components of the patch together and secures the patch to the skin.
- Membrane – controls drug release from the reservoir and multi-layer patches.
- Backing – protects the patch from the external environment.[19,20]

Types of Transdermal Patches

1. Single layer drug in adhesive:

In this type, the adhesive layer contains the drug. The adhesive layer serves not only to adhere the various layers together but is also responsible for releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.[21]

Figure 2: Single layer drug in adhesive

2. Multi-layer drug in adhesive:

This type is similar to the single-layer patch but contains an immediate drug release layer and a controlled release layer along with the adhesive layer. The adhesive layer is responsible for the release of the drug. This patch also has a temporary liner and a permanent backing. [22]

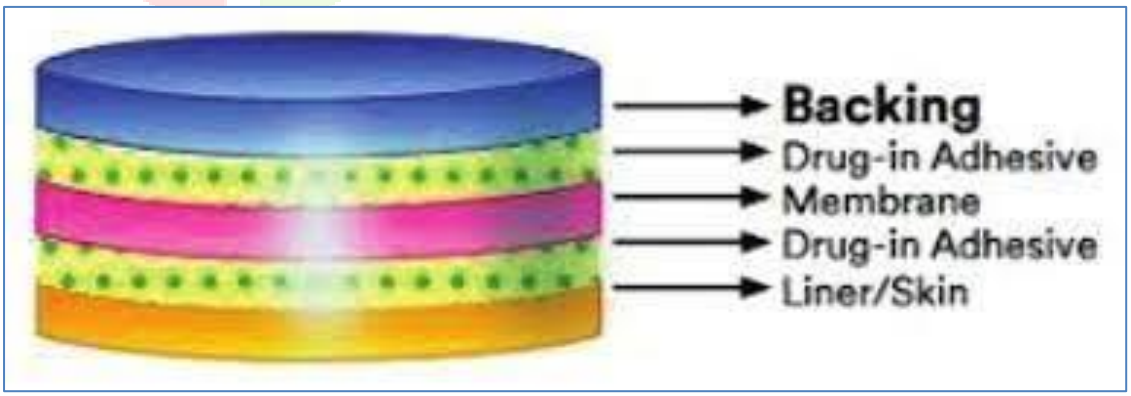

Figure 3. Multi-Layer Drug in Adhesive [22]

3. Drug Reservoir-in-Adhesive:

In this system, the drug reservoir is embedded between an impervious backing layer and a rate-controlling membrane. The drug release occurs only through the rate-controlling membrane, which can be microporous or non-porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel, or

dispersed in a solid polymer matrix. A hypoallergenic adhesive polymer can be applied as an outer surface polymeric membrane compatible with the drug. [23]

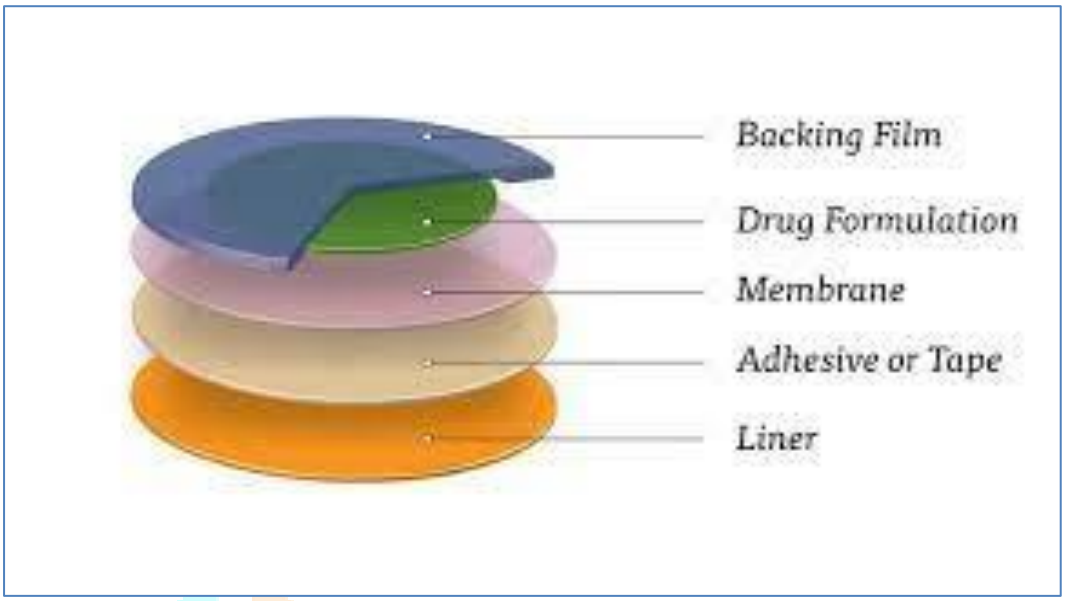

Figure 4: Drug Reservoir in Adhesive [23]

4. Drug Matrix-in-Adhesive:

The matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension in direct contact with the release liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix.[24]

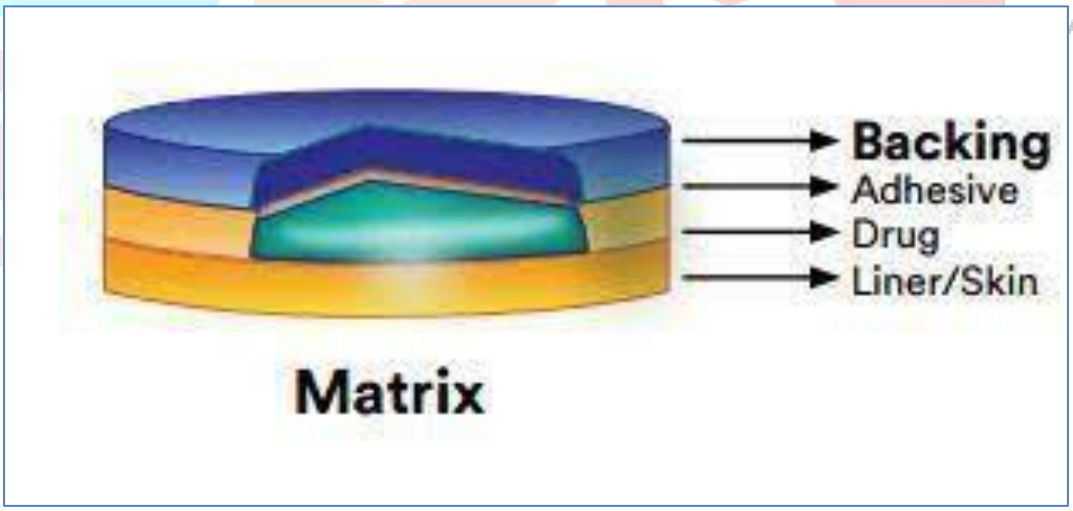

Figure 5: Drug Matrix in Adhesive [24]

Various methods for the preparation of TDDS:[25-27]

1. Asymmetric TPX membrane method:

In this method, a prototype patch is created using a heat-sealable polyester film with a backing membrane featuring a 1 cm-diameter concave. The concave membrane is covered with a poly asymmetric membrane made of TPX, which is adhered to the asymmetric TPX membrane preparation. Dry/wet inversion is employed for the preparation of the asymmetric TPX membrane. TPX is dissolved in cyclohexane, a solvent, along with non-solvent additives to create a polymer solution. After being kept at 40°C for 24 hours, the polymer solution

is cast on a glass plate using a garden knife. Once the casting film has evaporated, the glass plate is immediately immersed in the coagulation bath.

2. Circular Teflon mold method:

In this method, solutions containing polymers in varying ratios are used in an organic solvent. A calculated amount of the drug is dissolved in half the quantity of the same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butylphthalate is added as a plasticizer into the drug-polymer solution. The solution is stirred and poured into a circular Teflon mold.

3. Mercury substrate method:

In this method, the drug is dissolved in a polymer solution along with a plasticizer. The solution is stirred for 10-15 minutes to create a homogeneous dispersion and poured onto a leveled mercury surface, covered with an inverted funnel to control solvent evaporation.

4. Aluminum-backed adhesive film method:

Transdermal drug delivery may produce unstable matrices if the loading dose is greater than 10 mg. Chloroform is the solvent of choice for this preparation. The drug is dissolved in chloroform, and the adhesive material is added to the drug solution and dissolved.

5. Free film method:

In this method, film formation is observed by examining the mercury surface after complete solvent evaporation. The dry film is separated and stored between sheets of wax paper in a desiccator until use. Free films of different thicknesses can be prepared by altering the volume of the polymer solution.[28]

Evaluation parameters [29-32]

- **Interaction studies:** To ensure the stability and bioavailability of the drug, it is crucial to evaluate potential physical or chemical interactions between the drug and excipients. Interaction studies can be carried out using thermal analysis, FT-IR, and UV spectroscopy.
- **Thickness of the patch:** The thickness of the drug-loaded patch is measured at various points using a digital micrometer. The average thickness and standard deviation are determined to ensure the uniformity of the prepared patch.
- **Folding endurance:** A strip of a specific area is cut evenly and repeatedly folded at the same place until it breaks. The number of times the film can be folded at the same place without breaking indicates the folding endurance of the patch.
- **Percentage moisture uptake:** The weighted films are placed in a desiccator at room temperature containing a saturated solution of potassium chloride to maintain 84% relative humidity (RH). The films are then reweighed, and the percentage moisture uptake is determined.

- **Drug content:** A specified area of the patch is dissolved in an appropriate solvent. The solution is filtered and analysed for drug content using suitable analytical methods such as UV or HPLC techniques.

These evaluation parameters help ensure the quality, stability, and efficacy of the transdermal patch, making it suitable for therapeutic use.[33]

Application of nanotechnology based transdermal and topical delivery systems [34-38]

- **Microneedles:** Microneedle-based drug delivery systems have gained significant attention due to their ability to bypass the first-pass metabolism in the gastrointestinal tract and liver, as well as avoiding the invasive and painful approach of intravenous drug delivery. Microneedles offer higher drug bioavailability compared to creams and transdermal patches, as they pierce the stratum corneum (SC) and deliver the active ingredients directly to the viable epidermis. Despite some drawbacks, such as compatibility, loading capacity, and potential inflammatory immune response, microneedles have become a preferred delivery method for vaccines and medications due to their numerous advantages.
- **Vesicular nanocarriers:** Vesicular nanocarriers are composed of active ingredients enclosed in an aqueous core. Liposomes were the first vesicular nanocarriers developed, but they demonstrated poor transdermal permeation. This led to the development of other vesicular carriers, such as niosomes and transferosomes. These carriers enhance the permeation of active ingredients by incorporating a permeation enhancer into the phospholipid vesicle.
- **Polymeric nanocarriers:** Polymeric micelles have emerged as an innovative approach to overcome the poor solubility and permeability of drugs across the skin. These self-assembling nanocarriers are composed of amphiphilic, biocompatible, and biodegradable copolymers. Examples of natural polymers include gelatin and albumin, while synthetic polymers include polylactic acid and polyglycolic acid. Polymeric nanocarriers form a hydrophobic core and hydrophilic shell when self-assembling in an aqueous environment above the critical micelle concentration.
- **Nano-emulsions:** Nano-emulsions have been developed to enhance the penetration and absorption of active molecules and achieve controlled release. These lipid-based, colloidal oil-in-water dispersions consist of finely dispersed droplets with hydrophilic and lipophilic phases. They are biodegradable and increase the solubility of both polar and non-polar compounds. Nano-emulsions offer greater thermodynamic and kinetic stability and increased bioavailability of lipophilic compounds.
- **Microfibers:** Microfibers provide a high surface area that enhances drug dissolution. The drug molecules are entrapped in the polymer structure, allowing for a more controlled drug delivery system and increased drug concentration in a carrier. This results in an increased flux of the drug into the skin, making microfibers a promising approach for transdermal drug delivery. [17,25]

Enhancement of transdermal delivery by equipment (active delivery): [39-41]

1. **Iontophoresis:** Iontophoresis enhances skin penetration and increases the release rate of various drugs with poor absorption/permeation profiles by facilitating the movement of ions across the membrane under the influence of a small externally applied potential difference. This method has been applied to the in vivo transport of ionic or non-ionic pharmaceuticals using an electrochemical potential gradient. The efficacy

of iontophoresis depends on factors such as the polarity, valency, mobility of the therapeutic molecule, the type of electrical cycle used, and the drug formulation.

2. **Sonophoresis:** Sonophoresis utilizes ultrasound frequencies generated by an ultrasound device to improve transdermal drug delivery. Low-frequency ultrasound is more effective as it facilitates drug movement by creating an aqueous path in the perturbed bilayer through cavitation. The drug is mixed with a specific coupler, such as gel or cream, which transmits the ultrasonic waves to the skin, creating an aqueous path for the drug to be administered. Ultrasound waves with energy levels between 20 kHz and 16 MHz often allow drugs to permeate through. Additionally, ultrasound raises local skin temperature and produces a thermal effect, both of which enhance drug penetration.
3. **Electroporation:** Electroporation involves applying a high-voltage electric pulse to the skin for brief periods (5 to 500 V), creating tiny pores that increase permeability and facilitate drug diffusion. Electrodes are placed close together to introduce an electric pulse for the safe, painless administration of drugs. This painless and safe method of permeabilizing the skin has been demonstrated to successfully deliver both high and low molecular weight medications.
4. **Photomechanical waves:** Photodynamic waves applied to the skin can penetrate the stratum corneum, allowing drugs to travel through the channels created. Low radiation exposure of about 5-7 J/cm is used to achieve the restricted ablation caused by the incident waves, maximizing the depth of successful transmission. Compared to previous direct ablation, this method shows a longer rise and duration, necessitating the regulation of photodynamic wave characteristics to ensure drug delivery to the desired depth in the skin.
5. **Thermal ablation:** Thermal ablation, also known as thermophoresis, selectively disrupts the stratum corneum structure using localized heat to enable improved drug delivery through skin microchannels. Laser thermal ablation techniques use a laser to create micropores in the skin and enhance skin diffusivity. This method allows for better penetration of medications through the skin by bypassing the barrier provided by the stratum corneum.[5,9,14]

Enhancement of transdermal delivery by equipment (passive delivery): [42-45]

1. **Vesicles:** Vesicles are colloidal water-filled particles composed of amphiphilic molecules arranged in bilayers. They can transport drugs that are soluble in both fat and water for transdermal absorption. Vesicles can also be used in TDDS to regulate the rate of absorption through a multi-layered structure. Depending on the characteristics of the constituent substances, vesicles are classified into several categories including liposomes, transferosomes, and ethosomes. These vesicles can improve the bioavailability and stability of the encapsulated drug while providing controlled release.
2. **Polymeric nanoparticles:** Polymeric nanoparticles (NPs) can enhance drug delivery by altering the in vivo dynamics of the drug and prolonging the drug's residence time in the circulation. Drug administration in the form of NPs results in targeted and controlled drug release behavior, which further improves drug bioavailability and reduces toxicity and adverse effects. These nanoparticles can encapsulate both

hydrophilic and hydrophobic drugs and provide a sustained release profile for improved therapeutic outcomes.

3. **Nano-emulsion:** Nano-emulsions are characterized by low viscosity, isotropy, thermodynamic stability, and dynamic stability as a mixture. They have exceptional wettability, which ensures close contact with the skin due to their small particle size, large specific surface area, and low surface tension. Nano-emulsions provide a shorter transdermal time and better transdermal absorption compared to commonly used topical skin preparations. They can be used to enhance the delivery of both lipophilic and hydrophilic compounds, improving the drug's permeability across the skin and increasing its bioavailability.

Prospective advancements in transdermal delivery system:[46,47]

Nanotechnology has demonstrated significant potential in the evolution of topical and transdermal drug delivery, with biologics being a notable example. Biologics are gaining popularity in transdermal administration due to the presence of biological barriers that restrict drug absorption. Novel therapies, such as the anti-IL-13 inhibitor tralokinumab, janus kinase (JAK) inhibitors like baricitinib, and the anti-IL-4R antibody, are being used to treat inflammatory diseases. The Food and Drug Administration has approved the first topical JAK inhibitor, ruxolitinib cream, for the treatment of mild to severe atopic dermatitis that is not sufficiently manageable with prescribed topical medications.

Hyaluronic acid-based systems are also gaining popularity in the pharmaceutical sector due to their increased permeability and biocompatibility. These systems are typically used in the treatment of anti-inflammatory diseases such as atopic dermatitis and psoriasis by incorporating hyaluronic acid into nanoparticles, ethosomes, and liposomal transdermal systems. In addition to microneedles, other physical penetration techniques in transdermal administration, such as sonophoresis, iontophoresis, and electroporation, are being researched. These methods are generally regarded as effective, safe, and providing high drug bioavailability. Electroporation employs small electrical impulses to deliver medication, enhancing the penetration of hydrophilic drugs through the stratum corneum. Sonophoresis utilizes ultrasonic waves of varying frequencies to drive drug diffusion across the skin by disrupting the skin barrier, thereby improving drug penetration. In comparison, iontophoresis uses an electric field to push molecules into the skin, providing rapid drug release for both charged and uncharged molecules. Low-frequency ultrasound increases drug penetration to a greater extent than high-frequency ultrasound. However, many of these prospective strategies face challenges such as cost and large-scale feasibility due to the patient-specific nature of the models. As these techniques continue to be developed, they hold the potential to revolutionize the field of transdermal drug delivery, offering improved treatment options for patients.

Advanced Development in TDDS:

Drug-in-adhesive technology has emerged as the preferred system for passive transdermal delivery, with two main areas of formulation research focusing on adhesives and excipients. Adhesive research aims to improve skin adhesion over the wear period, enhance drug stability and solubility, reduce lag time, and increase the rate of delivery. Customizing the adhesive chemistry allows for the development of patches tailored to specific

drug and formulation chemistries, as there is no one-size-fits-all adhesive that can accommodate all variations.[48]

Innovations in adhesive technology have led to the creation of adhesives with improved biocompatibility, reduced irritation potential, and increased drug permeation. Some of the advanced adhesives include silicone-based adhesives, polyisobutylene adhesives, and acrylate-based adhesives, each offering unique benefits for specific transdermal drug delivery applications. Excipient research, on the other hand, focuses on the development of novel penetration enhancers, solubilizers, and stabilizers to optimize drug delivery across the skin. These excipients play a crucial role in modulating the drug's physicochemical properties, enhancing solubility, and improving skin permeation, ultimately leading to more effective and targeted delivery. Recent advancements in nanotechnology have also opened up new possibilities for TDDS, such as the development of nanocarriers like liposomes, niosomes, and polymeric nanoparticles. These nanocarriers offer several advantages, such as increased solubility, improved stability, and targeted drug release, thereby enhancing the overall performance of transdermal drug delivery systems. In conclusion, advanced developments in TDDS, particularly in adhesive and excipient research, are paving the way for more effective, targeted, and patient-friendly transdermal drug delivery systems. These innovations have the potential to revolutionize the field and provide improved treatment options for various medical conditions.[49]

Conclusion:

The widespread acceptance of TDDS technology as a mainstream delivery method has established it as a preferred mode of drug administration for transdermal delivery across various skin types, circumventing first-pass metabolism and other sensitivities associated with alternative drug administration routes. TDDS's controlled-release approach allows for the uniform distribution of medication in a non-allergic and non-invasive manner. The presence of TDDS in the domestic and international drug delivery system market has grown considerably, as evidenced by the surge in research studies, patents, and commercially available products from various industry and research institutions. The advancement of TDDS could serve as a catalyst for improving vaccination and supporting patient preferences for self-administering medications for long-term therapy. Additionally, it could act as a driving force for reducing the prevalence of cardiovascular and central nervous system diseases, diabetes, and hereditary diseases.

Future prospective

The market for transdermal devices has been estimated at U.S. $2 billion. Transdermal drug delivery has experienced a healthy annual growth rate of 25%, which outpaces the oral drug delivery system at 2% and the inhalation market. This figure is expected to rise in the future as novel devices emerge and the list of marketed transdermal drugs increases. The devices in development are more costly and complex compared to conventional transdermal patch therapies.

Regulatory bodies will also require data to substantiate the safety of the device on the skin for either short- or long-term use. Thus, for any of these novel drug delivery technologies to succeed and compete with those already on the market, they must demonstrate safety, efficacy, portability, cost-effectiveness, and potential for

broad application. As the field of transdermal drug delivery continues to evolve, addressing these challenges will be crucial to the development and commercialization of innovative, patient-centered solutions that have the potential to revolutionize drug administration and improve patient outcomes.

The continued advancement of transdermal drug delivery systems (TDDS) hinges on the development of innovative technologies that can overcome the limitations of existing systems, such as poor drug permeability and limited applicability to a narrow range of therapeutic molecules. As research and development efforts in this area progress, new opportunities for TDDS are emerging, particularly in the context of personalized medicine, biologics, and the administration of complex therapeutics. One potential area of growth for TDDS is the integration of advanced materials, such as nanotechnology and smart polymers, to enhance drug delivery efficiency and patient compliance. For example, responsive polymers that respond to changes in environmental factors like pH, temperature, or light can provide more precise and controlled drug release profiles. Nanotechnology-based carriers, such as polymeric nanoparticles and liposomes, can also be tailored to improve drug encapsulation, stability, and permeability across the skin barrier. Another promising avenue for TDDS development is the incorporation of biosensors and digital health technologies into drug delivery platforms. These systems can provide real-time monitoring of drug levels, physiological parameters, or disease biomarkers, enabling personalized dosing regimens and better therapeutic outcomes. Moreover, the integration of digital health tools with TDDS can facilitate patient engagement and adherence, which are critical factors in the overall effectiveness of treatment plans.

As the demand for biologics and other large-molecule drugs continues to rise, there is a growing need for TDDS that can effectively deliver these therapeutics across the skin barrier. The development of novel strategies, such as microneedle arrays, electroporation, and sonophoresis, holds great potential in addressing this challenge, as they have shown success in enhancing the delivery of macromolecules and improving bioavailability. Finally, the future of TDDS also lies in the expansion of its applications beyond traditional therapeutic areas. As research into the skin microbiome advances, new opportunities for transdermal drug delivery may arise in the context of microbiome-based therapies, such as topical probiotics or prebiotics. Furthermore, TDDS could play a role in the delivery of gene therapies or CRISPR-based treatments, which require targeted, efficient, and non-invasive methods of administration. [50]

Acknowledgment:

The authors would like to acknowledge S.N.D. college of pharmacy, babhulgaon for providing the necessary infrastructure and resources for this study.

References:

1. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008 Nov;26(11):1261-8.
2. Ita K. Transdermal drug delivery: progress and challenges. J Drug Deliv Sci Technol. 2014 Aug;24(4):245-50.
3. Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci. 2001 Sep;14(2):101-14.

4. Benson HAE. Transdermal drug delivery: penetration enhancement techniques. Curr Drug Deliv. 2005 Jan;2(1):23-33.
5. Williams AC, Barry BW. Penetration enhancers. Adv Drug Deliv Rev. 2012 Apr;64:128-37.
6. Cevc G, Blume G. Lipid vesicles penetrate into intact skin owing to the transdermal osmotic gradients and hydration force. Biochim Biophys Acta. 1992 Jun;1104(1):226-32.
7. Verma P, Pathak K. Therapeutic and cosmeceutical potential of ethosomes: an overview. J Adv Pharm Technol Res. 2010 Jul;1(3):274-82.
8. Kogan A, Garti N. Microemulsions as transdermal drug delivery vehicles. Adv Colloid Interface Sci. 2006 Jun;123-126:369-85.
9. Banga AK, Chien YW. Iontophoretic delivery of drugs: fundamentals, developments and biomedical applications. J Control Release. 1993 Jun;25(1-2):1-25.
10. Kost J, Mitragotri S, Gabbay RA, Pishko M, Langer R. Transdermal monitoring of glucose and other analytes using ultrasound. Nat Med. 2000 Mar;6(3):347-50.
11. Denet AR, Vanbever R, Preat V. Skin electroporation for transdermal and topical delivery. Adv Drug Deliv Rev. 2004 Feb;56(5):659-74.
12. Sintov AC, Krymberk I, Daniel D, Hannan T, Sohn Z, Levin G. Radiofrequency-driven skin microchanneling as a new way for electrically assisted transdermal delivery of hydrophilic drugs. J Control Release. 2003 Apr;89(2):311-20.
13. Dragicevic N, Maibach HI, editors. Percutaneous penetration enhancers: chemical methods in penetration enhancement. Berlin: Springer; 2015.
14. Mitragotri S, Kost J. Low-frequency sonophoresis: a review. Adv Drug Deliv Rev. 2004 Feb;56(5):589-601.
15. Park JH, Allen MG, Prausnitz MR. Biodegradable polymer microneedles: fabrication, mechanics and transdermal drug delivery. J Control Release. 2005 May;104(1):51-66
16. Donnelly RF, Singh TRR, Woolfson AD. Microneedle-based drug delivery systems: microfabrication, drug delivery, and safety. Drug Deliv. 2010 May;17(4):187-207.
17. Pillai O, Panchagnula R. Polymers in drug delivery. Curr Opin Chem Biol. 2001 Oct;5(4):447-51.
18. Lv F, Xu T, Wu Y, Huang X, Yang M, Gu G. Applications of PLGA-based electrosprayed nanoparticles in drug delivery and biomedical research. J Drug Deliv Sci Technol. 2020 Oct;60:102077.
19. Gupta A, Aggarwal G, Singla S, Arora R. Transdermal drug delivery system: a review. Asian J Pharm. 2013 Oct;3(3):161-7.
20. Zhang YT, Shen LN, Wu ZH, Zhao JH, Feng NP. Comparison of ethosomes and liposomes for skin delivery of psoralen for psoriasis therapy. Int J Pharm. 2014 Aug;471(1-2):449-52.
21. Balakrishnan P, Shanmugam S, Lee WS, Lee WM, Kim JO, Oh DH, et al. Formulation and in vitro assessment of minoxidil niosomes for enhanced skin delivery. Int J Pharm. 2009 Sep;377(1-2):1-8.
22. El Maghraby GM, Williams AC, Barry BW. Oestradiol skin delivery from ultradeformable liposomes: refinement of surfactant concentration. Int J Pharm. 2000 Aug;196(1):63-74.

23. Taveira SF, Nomizo A, Lopez RFV. Topical delivery of ciclosporin A: an in vitro study using monoolein as a penetration enhancer. Eur J Pharm Biopharm. 2007 May;66(2):260-5.
24. Park JH, Choi SO, Seo S, Choy YB, Prausnitz MR. A microneedle roller for transdermal drug delivery. Eur J Pharm Biopharm. 2010 Oct;76(2):282-9.
25. Zhang H, Zhang J, Streisand JB. Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications. Clin Pharmacokinet. 2002;41(9):661-80.
26. Zhang L, Granick S. How to stabilize phospholipid liposomes (using nanoparticles). Nano Lett. 2006 Mar;6(3):694-8.
27. Patzelt A, Lademann J. Drug delivery to hair follicles. Expert Opin Drug Deliv. 2013 Feb;10(6):787-97.
28. Choi MJ, Maibach HI. Liposomes and niosomes as topical drug delivery systems. Skin Pharmacol Physiol. 2005 Sep-Oct;18(5):209-19.
29. Manconi M, Sinico C, Valenti D, Loy G, Fadda AM. Niosomes as carriers for tretinoin: III. A study into the in vitro cutaneous delivery of vesicle-incorporated tretinoin. Int J Pharm. 2006 Sep;311(1-2):11-9.
30. Rainsford KD, Kean WF, Ehrlich GE. Topical nonsteroidal anti-inflammatory drugs for the treatment of pain due to soft tissue injury: diclofenac epolamine topical patch. J Pain Res. 2011;4:397-406.
31. Lademann J, Richter H, Schanzer S, Patzelt A, Meinke MC, Sterry W, et al. Penetration and storage of particles in human skin: perspectives and safety aspects. Eur J Pharm Biopharm. 2011 Mar;77(3):465-8.
32. Boddé HE. Transdermal drug delivery: status, potentials and limitations. Int J Pharm. 1991 Feb;72(1):89-102.
33. Gratieri T, Alberti I, Lapteva M, Kalia YN. Next generation intra- and transdermal therapeutic systems: using non- and minimally-invasive technologies to increase drug delivery into and across the skin. Eur J Pharm Sci. 2013 Nov;50(5):609-22.
34. Benson HAE. Transdermal drug delivery: penetration enhancement techniques. Curr Drug Deliv. 2005 Jan;2(1):23-33.
35. Hadgraft J, Lane ME. Skin permeation: the years of enlightenment. Int J Pharm. 2005 Oct;305(1-2):2-12.
36. Escobar-Chavez JJ, Díaz-Torres R, Rodríguez-Cruz IM, Domínguez-Delgado CL, Morales RS, Ángeles-Anguiano E, et al. The use of sonophoresis in the administration of drugs throughout the skin. J Pharm Pharm Sci. 2005;8(2):147-66.
37. Bhatnagar S, Dave K, Venuganti VVK. Microneedles in the clinic. J Control Release. 2017 Aug;260:164-82.
38. Chen Y, Shen Y, Guo X, Zhang C, Yang W, Ma M, et al. Transdermal protein delivery by a coadministered peptide identified via phage display. Nat Biotechnol. 2006 Apr;24(4):455-60.
39. Liu Y, Wang J, Zhang R, Lan W, Qi X, Cao Y, et al. Functional graphene oxide as a nanocarrier for controlled loading and targeted delivery of mixed anticancer drugs. Small. 2010 Feb;6(4):537-44.
40. Banga AK. Electrically assisted transdermal drug delivery. Pharm Sci Technolo Today. 1998 Mar;1(3):128-35.
41. Meidan VM, Bonner MC, Michniak BB. Transfollicular drug delivery--is it a reality? Int J Pharm. 2005 Oct;306(1-2):1-14.

42. Pillai O, Nair V, Panchagnula R. Transdermal iontophoresis of insulin: IV. Influence of chemical enhancers. Int J Pharm. 2004 Jan;269(1):109-20.
43. Montenegro L, Carbone C, Puglisi G. From nanoemulsions to nanostructured lipid carriers: a relevant development in dermal delivery of drugs and cosmetics. J Drug Deliv Sci Technol. 2016 Jun;32(Part B):100-12.
44. Zhang YT, Zhao JH, Feng NP. Research progress of in situ gelling ophthalmic drug delivery system. Asian J Pharm Sci. 2013 Sep;8(5):278-86.
45. Zhang YT, Zhao JH, Zhang SJ, Zhu JJ, Feng NP. Optimization of formulation factors in tanshinone IIA submicron emulsion for transdermal delivery. Int J Pharm. 2013 Oct;454(1):86-92.
46. Kim YC, Ludovice PJ, Prausnitz MR. Transdermal delivery enhanced by magainin pore-forming peptide. J Control Release. 2007 Apr;118(1):1-6.
47. Böttiger LE, Svedman P, Gustavsson G, Norman C. Patch testing with corticosteroids: multicentre study of a corticosteroid series. Br J Dermatol. 1986 Nov;115(5):551-8.
48. Lee WR, Shen SC, Wang KH, Hu CH, Fang JY. The human skin barrier is organized as stacked bilayers of fully extended ceramides with cholesterol molecules associated with the ceramide sphingoid moiety. J Invest Dermatol. 2012 Aug;132(8):2215-25.
49. Hao J, Ghosh P, Li SK, Newman B, Kasting GB, Raney SG. Heat effects on drug delivery across human skin. Expert Opin Drug Deliv. 2016 Apr;13(4):501-12.
50. Bala I, Hariharan S, Kumar MN. PLGA nanoparticles in drug delivery: the state of the art. Crit Rev Ther Drug Carrier Syst. 2004;21(5):387-422.