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Transdermal Drug Delivery System – A Brief Review

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1. INTRODUCTION

Traditional medication delivery methods, such as parenteral and oral administration face challenges including gastrointestinal degradation, hepatic first-pass metabolism and limited control over drug biodistribution. Transdermal drug delivery (TDD) provides a viable alternative allowing medications to penetrate the epidermis by treating the stratum corneum (SC) and layers of the dermis for both systemic and local effects. Research on TDD began in the 1960s when the SC was recognized as a barrier to skin penetration and water loss.[1,2] In 1975, researchers discovered that various compounds exhibited differing penetrability across the SC which could be optimized through improved formulations.[3] Over the subsequent decades numerous TDD formulations have been developed, enhancing medication bioavailability, patient compliance and wearability (Fig. 1).

TDD systems can be classified into two main categories: passive and active delivery methods.[4,5] Passive delivery relies on diffusion-based medication release or the spontaneous degradation of the drug reservoir. Conversely, active delivery refers to the release of medicationdriven by internal or external environmental factors, including pH, enzymes, electrical stimuli,[6] mechanical forces, ultrasound and optical fields. Unlike passive delivery, active systems allow for targeted drug delivery with precise control over dose and timing.[7,8]

Examples of active delivery systems include insulin-releasing microneedles (MNs) and glucose-responsive patches, as well as smartphone-controlled glucose management solutions. These innovations underscore the potential of TDD to improve therapeutic efficacy and patientexperience. By addressing the limitations of traditional methods, TDD represents a significantadvancement in drug delivery systems enhancing both safety and effectiveness.[9,10]

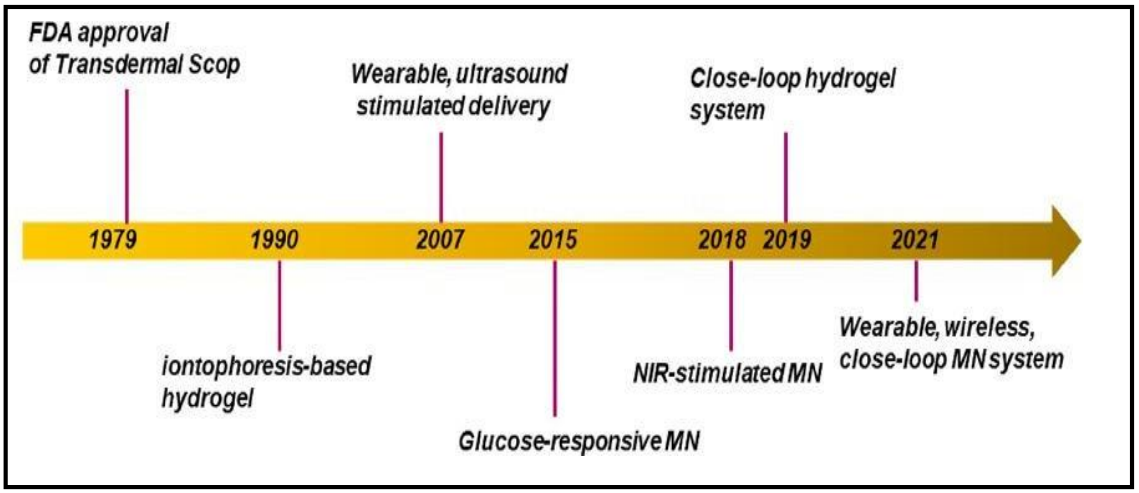
These active and passive TDD systems can be categorized into patches, semi-solid formulations(such as creams, gels and ointments) and liquid formulations (including sprays and lotions). Liquid and semi-solid formulations are relatively straightforward to apply and can cover largeareas without being constrained by skin surface area or curvature. However, they can be messywith ingredients easily transferring to unintended areas of the skin making precise dosage application challenging. In contrast, patches are designed to act specifically on the area in contact allowing for precise control over the dosage delivered. The first TDD patch TransdermScop received approval from the U.S. Food and Drug Administration (FDA) in 1979 for the delivery of scopolamine to treat motion sickness.[11] Since then numerous TDD patches have been approved for various applications including vaccination, pain relief and skinmanagement.[12,13]

Recently, wearability has become a pivotal trend in the development of transdermal drug delivery (TDD) patches. The term "wearability" encompasses the factors that influence the comfort experienced by wearers or patients including physical, psychological and socialdimensions. This focus on comfort has led to the use of innovative materials and designs aimedat enhancing the overall wearability of TDD systems.

This review highlights the latest advancements in various formats including adhesive hydrogelpatches, microneedles (MNs) and wearable electronics. Beyond their primary function of drugdelivery these patches are increasingly capable of sensing physiological parameters such as body temperature, blood sugar levels, lactic acid, pH and ion concentrations.

This multi-functionality makes them not only therapeutic devices but also valuable tools for health monitoring. We begin with a brief overview of the skin's anatomical structure laying thefoundation for understanding how TDD systems interact with the body. Following this, we explore the various release mechanisms utilized in TDD detailing how these mechanisms facilitate effective drug absorption and delivery.

Subsequently, we delve into the design concepts of different wearable patches emphasizing how recent innovations have improved comfort and usability. We provide a comprehensive examination of current achievements in the field showcasing examples of successful implementations and their clinical implications. Additionally, we discuss the challenges that remain including issues related to skin compatibility, long-term wear and patient adherence.



By addressing both the advancements and the obstacles in TDD patch development, this reviewaims to shed light on the future of wearable drug delivery systems and their potential to transform patient care. The integration of comfort and functionality in these devices is essential for enhancing user experience and therapeutic outcomes.[14-17]

Figure No. 1- The timeline of transdermal drug delivery (TDD) systems development.[18]

2. SKIN'S ANATOMICAL STRUCTURE

From top to bottom the skin may be generally divided into the SC and layers of epidermis, dermis and hypodermis (Fig. 2). On top of the epidermis the thick SC layer (10-20 mm) is madeup of a lipid matrix and corneocytes. Corne desmosomes which bind the corneocytes together securely create a mechanically robust barrier that shields the inner side from moisture loss, UVrays and pathogen invasion. The vascularized matrix that makes up the epidermis (50–100 mm)is mostly made up of keratinocytes, merkel cells and langerhans cells.[19]

The dermis (2 mm) is the initial site of drug absorption because it has a rich capillary network that connects to the systemic circulation. The hypodermis or lowermost layer of skin is made up of adipose tissue and loose areolar vascularized connective tissue. Trans epidermal and transappendageal channels are the primary routes via which a non-formulated medication given topically penetrates the skin.[20] Drugs can infiltrate via the intercellular lipid matrix (intercellular pathway) or the corneocytes which are followed by the intercellular lipid matrix (intracellular and transcellular pathway) via the trans epidermal route.[21] Nevertheless, researchindicates that the primary barrier to medication absorption is the intercellular lipid matrix whichmakes it particularly difficult for those big hydrophilic molecules to penetrate the skin. The transappendageal routes are designed to traverse the skin's appendages including hair follicles and sebaceous glands. It avoids the lipid matrix in contrast to transepidermal routes.[22]

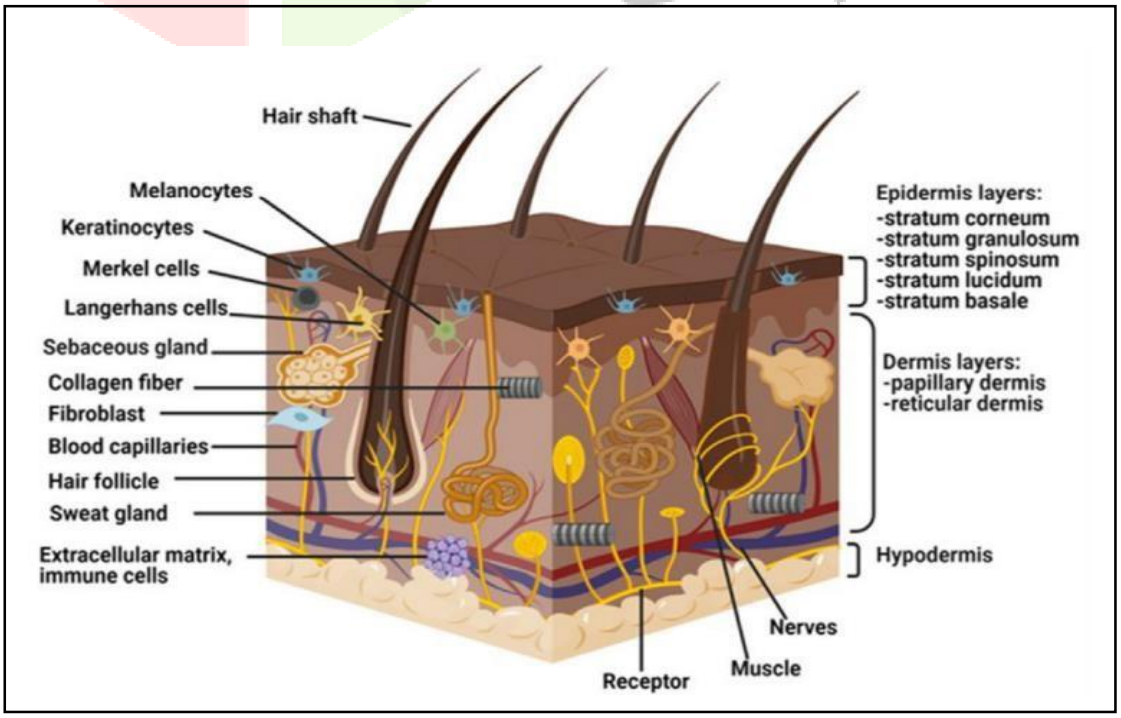


Figure No. 2 - Anatomical structure of the skin[19]

Skin appendages account for only about 0.1% of the skin's surface are and their numbers varyacross different body parts and individuals. This variability complicates efforts to measure and predict the amount of substances entering the body through the skin. To enhance medication penetration and maximize bioavailability scientists and engineers have developed a range of chemical, physical and biological techniques.

Chemical penetration enhancers include fatty acids, surfactants, organic solvents and nanoparticles;[23] these substances can facilitate the absorption of drugs. Physical methods, suchas heating, laser ablation, ultrasound, electrical fields and microneedles (MNs) also play a crucial role in enhancing skin permeability;[24] additionally, biological agents like peptides canassist in delivering medications through the skin barrier more effectively.

2.1. Epidermis Layer

The thickness of the epidermis, which is the skin's outermost layer varies measuring around 0.8 mm on the palms of hands and the soles of feet.[25] The viable epidermis is sometimes referred to as the epidermal layers underneath the stratum corneum and is composed of multi- layered areas of epithelial cells.[25,26] Approximately 95% of the cells of the epidermis are keratinocytes, melanocytes, langerhans cells and merkel cells make up the remaining cells inthe epidermal layers.[27] The outermost layer of the epidermis is called the stratum corneum.[25,28,29] It has direct touch with the outside world and its extremely high density (1.4g/cm3) may contribute to some of its barrier qualities in the arid condition and its minimal 15%–20% hydration. The majority of the cells of the stratum corneum are made up of 20% lipid and 70% insoluble keratins.[30] keratin in the corneocytes is linked to water in the stratum corneum.[25,31]

2.2. Dermis Layer

The dermis is a critical layer of the skin situated beneath the epidermis and plays a vital role in providing strength and flexibility. Typically measuring around 2-3 mm in thickness, the dermis is primarily composed of collagenous and elastin fibers which make up approximately70% of its structure. These fibers are essential for maintaining the skin's resilience and elasticity, allowing it to withstand various forms of stress while remaining pliable.[32]

This vascular network is crucial for sustaining the health of the skin facilitating not only nutrient delivery but also waste removal. Furthermore, the dermis houses lymphatic vessels, which play a significant role in immune function and fluid balance.[28]

2.3. Hypodermis Layer

The innermost layer of the skin known as the hypodermis or subcutaneous layer is made up of a network of fat cells.[32] It serves as the layer of contact between the skin and the body's deepertissues including the bones and muscles. Thus, the primary roles of the hypodermis are defencefrom physical shock, heat insulation, skin conductivity and support for vascular and neurological signals.[33] About half of the body's fat is made up of

fat cells that dwell in the hypodermis; the other main hypodermis cells are made up of macrophages and fibroblasts.[34]

2.4. Drug Penetration Routes

A diagrammatic representation of the trans epidermal and transappendegeal pathways, which are the two potential mechanisms via which drugs might permeate intact skin. The molecules go through the stratum corneum as part of the transepidermal route, an multilayered, multicellular and diversely architecturally designed barrier. One might refer to transepidermalpenetration as intra- or intercellular as shown in Figure 3.[35] Hydrophilic or polar solutes can be transported intracellularly by corneocytes, which are terminally differentiated keratinocytes.Molecules go via sweat glands and across hair follicles via the transappendegeal pathway.[36,37]

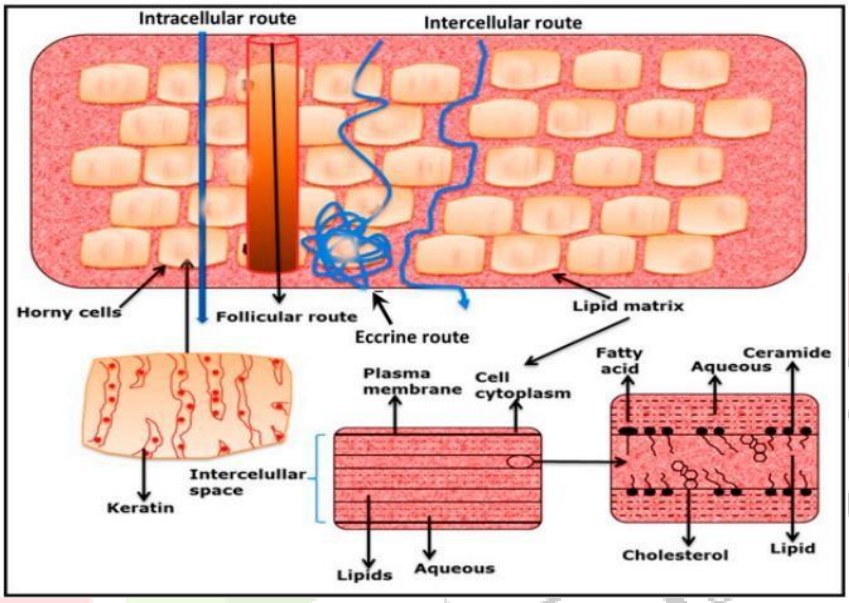


Figure No. 3 - Possible drug penetration routes across human skin.[37]

3. ADVANTAGES AND DISADVANTAGES OF TDDS

3.1. Advantages

- Bypasses first-pass metabolism and enzymatic degradation by the gastrointestinal tract.
- Transdermal medications can be self-administered. Topical patches provide sustained release of medication into the bloodstream.
- Patches are generally less painful than alternative delivery methods.
- Transdermal patches tend to have fewer adverse effects compared to oral methods. Avoids issues related to gastrointestinal incompatibilities.

- Dosage and therapeutic effects are predictable.
- This treatment provides extended duration of action.[38]

3.2. Disadvantages

- Transdermal drug delivery systems (TDDS) are not suitable for high-dose medications.
- Drugs with large molecular sizes are challenging to absorb through the skin.
- There is a potential for skin irritation and hypersensitive reactions may occur.
- It is difficult to produce drugs with a long half-life for transdermal use.
- TDDS cannot achieve high concentrations of drugs in the bloodstream.
- Ionic medications cannot be effectively delivered via transdermal methods.[39]

TYPES OF TDDS

Transdermal drug delivery systems (TDDS) are classified into three types:

3.3. Reservoir System

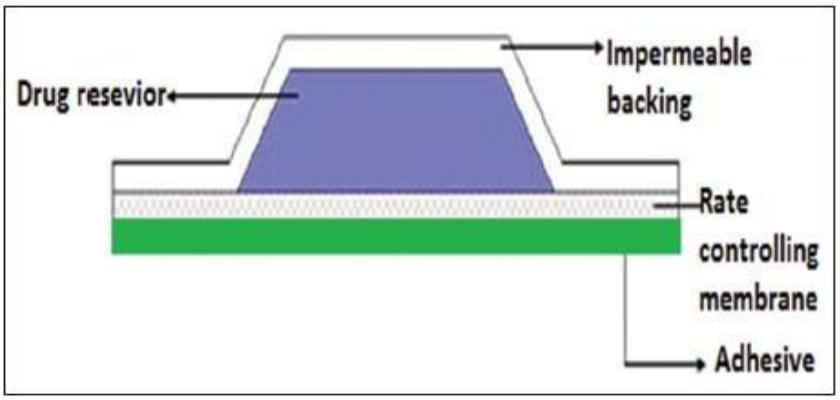
3.4. Matrix System

3.5. Microreservoir System

4.1. Reservoir System

In this system, the drug reservoir is strategically located between the backing layer and the rate-controlling membrane, enabling controlled and consistent release of the drug into the skin. Thedrug can be formulated as a suspension, gel or solution and is dispersed within a solid polymeric matrix. This configuration ensures a steady release rate enhancing the drug's bioavailability and maintaining therapeutic levels over time. By effectively regulating the movement of the drug through the membrane, this design optimizes the delivery process, improving patient compliance and overall treatment effectiveness.[40]

Figure No. 4 - Reservoir System[40]



4.2. Matrix System

The matrix system is classified into two types (Fig. 5):

- Drug Adhesive System: In this system, the drug reservoir is created by dispersing the drug in an adhesive polymer. This mixture is then applied to a medicated adhesive layer or melted on to the backing layer.
- Matrix Dispersion System: Here, the drugs are homogeneously dispersed within a lipophilic or hydrophilic polymer matrix. The polymer-drug combination is placed on a specific base plate.Instead of using an adhesive layer or a separate drug reservoir, the drug spreads from a drug- impermeable backing layer to form an adhesive rim.[40]

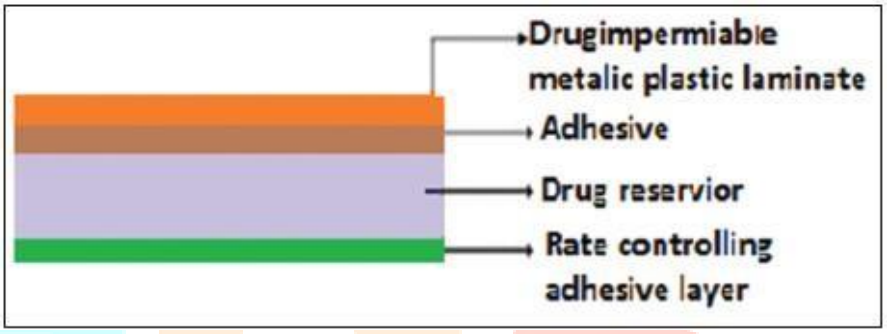


Figure No. 5 - Matrix System[40]

4.3. Microreservoir System

This system effectively combines elements of both matrix dispersion and reservoir systems. Initially, the drug is dissolved in an aqueous solution of a water-soluble polymer, which ensuresuniformity. This solution is then dispersed in lipophilic polymers to form microscopic spheresthat serve as the drug reservoir. This innovative approach allows for controlled release of the medication, ensuring that it is delivered steadily over time. Additionally, by enhancing the drug's bioavailability, the system improves the overall effectiveness of the treatment, optimizingpatient outcomes and therapeutic benefits.[40]

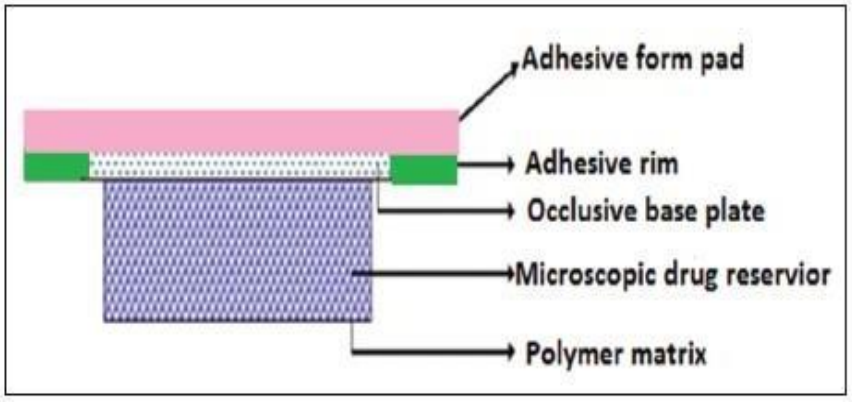


Figure No. 6 - Microreservoir System[40]

5. EVALUATION PARAMETERS

5.1. Thickness

The thickness of the matrix patches was measured using a screw gauge, a precise instrument designed for accurate measurements. This method involves placing the patch between the gauge's jaws and adjusting the screw until a snug fit is achieved. The scale on the gauge providesa direct reading of the thickness. This technique ensures high precision and consistency in measuring the patches, which is crucial for evaluating their performance and efficacy in drug delivery systems. Accurate thickness measurements help in understanding the release characteristics and overall effectiveness of the patches.[41]

5.2. Weight uniformity

The made patches need to dry for around four hours at 60°C before testing. It's necessary to divide a specified patch area into separate portions and weigh each one on a digital balance. Wewill calculate the standard deviation and average weight using individual data.[42]

5.3. Folding endurance

To evaluate the foldable endurance of a strip with a specified area, the strip is cut uniformly into manageable lengths. Once prepared, the strip is folded repeatedly at a designated spot, which serves as the focal point for the test. Each fold applies stress to the material at that location and the process continues until the strip ultimately breaks.

During the folding process, several factors influence the foldable endurance including the material properties, thickness and the angle of the fold. Each fold generates additional strain and the cumulative effect of these repeated bends tests the structural integrity of the material.

The number of times the film can be folded at that specific location without breaking is recordedas its foldable endurance. This measurement is significant in applications where flexibility anddurability are critical such as in packaging electronics or textiles. By understanding the foldable endurance, manufacturers can assess the material's performance and suitability for various applications, ensuring that it meets the required standards for durability and reliability under repeated stress.[42]

5.4. Drug content

It is necessary to dissolve a specific patch area in a predetermined amount of solvent. After passing the solutions through a filter medium, the drug content is ascertained using the suitabletechnique (UV or HPLC). Each number displays the average of three samples.[43]

5.5. WVTR (Water Vap. Transmission Rate)

The same-sized vials as the cells were used, washed and allowed to dry. The cells were supplemented with 1.0 gm of CaCl2 and 2.076 cm^2 patches were put at the brim. The cells were weighed and then kept in a desiccator with KCl and an 80–90% humidity level. For a period of seven days, cells were removed and

weighed each day. The WVTR was calculated using an equation.[44]

$$\text{WVTR} = \frac{WF - WI}{TXA} \times 100$$

Where, WI=Weight Initial, WF= Weight Final, T=Time, A=Area

5.6. Flatness

After cutting 1.5cm-long matrix patches from the generated film, the length differencesresulting from uniformity of flatness were computed using the following formula.

$$CONSTRICTION(\%) = \frac{LF - LI}{LI} \times 100$$

Where LF stands for final length and LI stands for initial length.

100% flat patches were those that had zero percent constrictions.[45]

5.7. In Vitro Release Tests

For this investigation, a Franz cell was manufactured locally. A donor compartment and a receptor compartment make up this cell. A sampling port in the receptor compartment is used to gather samples for analysis. The two portions are connected by rubber bands. The pH 7.4 buffer-filled receptor compartment was rotated by means of a magnetic bead. A patch was madeout of aluminium foil. Every seven hours, a one millilitre sample was collected and measured at 232 nm using a UV spectrophotometer. A fresh buffer was added to replace the removed sample each time.[46]

5.8. Drug Release Kinetic Data Analysis

Release data for kinetic models was analysed using PCP Disso software, with a focus on Zero,Higuchi and Peppas models. These models were used to evaluate the drug release behaviour of the tested formulations.[47]

5.9. Stability Studies

Based on a number of assessment criteria, matrix patches including two batches were determined to be the optimal formulations. These two formulations were put through an expedited three-month trial. experiment with different temps. Two sets of formulations were kept for three months at 40°C (75 percent relative humidity) in air-tight packaging. 232 nm wasthe wavelength at which a UV spectrophotometer was used to test the samples' absorbance. Thecalibration curve was used to compute the quantity.[48]

5.10. Thumbtack Test

This qualitative test evaluates the tackiness of the glue. To assess its relative tack property, pressyour thumb onto the adhesive surface. The ease with which your thumb sticks indicate the glue'stackiness. This simple method provides a clear indication of the adhesive's effectiveness, helping to determine its suitability for various applications. A stronger stick suggests higher tackiness, which is crucial for applications requiring reliable bonding and adhesion. Overall, this test helps in understanding the adhesive's performance in practical uses.[49]

5.11. Shear Adhesion Test

The cohesive strength of the sticky polymer is determined by this test. The amount of cross- linking, molecular weight, kind of polymer and quantity of tackifiers impact the strength measurement. An adhesive-coated patch is used to cover a stainless-steel plate and a specifiedweight is suspended from the patch parallel to the plate. The amount of time it takes to removethe patch from the plate indicates the cohesive strength. It takes longer the bigger the shear strength.[50]

5.12. Peel Adhesion Test

Adhesion refers to the strength of the bond formed between an adhesive patch and a substrate,which is crucial in determining the effectiveness of adhesive materials in various applications.To assess this adhesion, a test is conducted using a steel substrate covered with the adhesive patch. The key measurement is the force required to remove the adhesive from the steel surface.

In the adhesion test, the patch is affixed to the steel substrate and then pulled away at a 180- degree angle. The force applied during this removal process is carefully measured. If the adhesive fails, it means that the patch comes off cleanly without leaving any residue on the substrate. This result indicates poor adhesion suggesting that the bond between the adhesive and the steel was insufficient.

Conversely, if residue remains on the steel substrate, it implies that the adhesive has successfully adhered, indicating effective bonding properties. This test helps in evaluating the suitability of the adhesive for specific applications ensuring that it meets the necessaryperformance standards for strength and reliability in real-world conditions. By analysing theseresults, manufacturers can refine their adhesive formulations to enhance adhesion for intendeduses.[51]

6. MECHANISM OF ACTION

The most significant obstacle to the effective administration of transdermal drugs is the diffusion of active ingredients via the skin's many layers' barrier function. With many layers ofcorneocytes that are high in

keratin, the stratum corneum, the skin's outermost layer is also thethickest.

When developing transdermal medications, it is also important to take into consideration that the stratum corneum is composed of two chemically distinct areas. For active drugs to be effective, they must be able to permeate through both the lipid matrix between the keratin filaments and the watery area at their outer surface.[52]

Nonetheless, there have been developments recently in the creation of transdermal enhanced delivery techniques for active medications. The following is a list of these techniques:

6.1. Microneedles

Microneedles are extremely tiny, painless needles that can be either solid or hollow, designed to deliver medication effectively. They puncture the stratum corneum without causing discomfort, making the application process user-friendly. One of the primary advantages of thismethod is its ability to deliver larger molecules, which are typically difficult to penetrate through the skin. By utilizing microneedles, medications can be administered more efficientlyand with improved patient compliance, offering a promising alternative to traditional injectionmethods.

6.2. Iontophoresis

In electrophoresis, the movement of charged particles serves as the primary mechanism for transporting materials across the stratum corneum. This process utilizes an electrical driving force allowing chemicals to diffuse through the skin barrier under the influence of a continuouslow-voltage current. The electrical current facilitates the migration of the drug, enhancing its penetration and absorption. Notably, the delivery rate can be precisely regulated by either a microprocessor or the patient, allowing for tailored medication administration. This method notonly improves drug delivery efficiency but also enhances patient comfort and compliance.

6.3. Thermal Poration

When heat is applied to the skin, it triggers the opening of tiny pores, which enhances the flowof molecules across the stratum corneum. This process significantly improves the penetration of various substances, facilitating more efficient and effective drug delivery. By temporarily altering the barrier properties of the skin, the heat enables larger molecules to pass through morereadily, allowing therapeutic agents to reach their target sites with greater ease. Consequently,this enhanced absorption not only increases the bioavailability of the drugs but also leads to improved treatment outcomes for various medical conditions. Whether in transdermal patches or topical formulations, using heat as a method of enhancing permeability offers a promising strategy to optimize drug delivery systems, ultimately benefiting patient care and treatment effectiveness.

6.4. Electroporation

Electroporation involves applying a high electrical voltage to the skin, temporarily disrupting the stratum corneum and creating microscopic pores. These tiny openings increase the skin's permeability allowing larger molecules including therapeutic drugs to pass through more easily. By enhancing the skin's ability to absorb drugs, electroporation improves transdermal drug delivery making it more effective for treating a range of medical conditions. This non-invasive method offers significant advantages over traditional drug delivery systems as it enables drugs to bypass the digestive system and liver metabolism potentially increasing bioavailability and improving treatment outcomes. Electroporation is a promising technique for advancing transdermal therapy.

6.5. Conventional Enhancers

A chemical applied to the skin acts as a penetration enhancer, designed to alter the thermodynamics of the active drug or increase the permeability of the stratum corneum. By modifying the skin barrier's structure, this chemical facilitates the improved absorption of the drug, enabling larger molecules to penetrate more easily. This enhancement allows for more effective drug delivery, ensuring that therapeutic agents reach their target sites in the body more efficiently. As a result, the overall efficacy of transdermal therapies is significantly improved, benefiting various medical applications. By optimizing skin penetration, this approach enhances drug bioavailability and supports better treatment outcomes for a range of conditions.

6.6. Ultrasound

The use of sound waves, particularly through a technique known as ultrasound can effectivelybreak up and enhance the permeability of the stratum corneum. By applying ultrasonic waves to the skin the sound energy creates microscopic cavitation bubbles that disrupt the lipid structure of the stratum corneum. This disruption increases the skin's permeability allowing larger molecules and drugs to penetrate more easily. As a result, this method can significantly improve the delivery of therapeutic agents through the skin making transdermal drug administration more efficient. Overall, ultrasound offers a promising approach for enhancing drug absorption, potentially leading to better therapeutic outcomes in various medical applications.[53-56]

7. FORMULATION OF TDDS

7.1. Method Of Asymmetric TPX Membrane

This approach uses a heat-sealable polyester sheet with a 1 cm diameter concave as the backingmembrane for the patch that is manufactured. The drug sample is injected into the concave membrane sealed with an adhesive and covered with an asymmetric TPX {poly (4-methyl-1-pentene)} membrane.[57,58]

7.2. Circular Teflon Mould Method

An organic solvent is employed with solutions that contain polymers in various proportions. Half the volume

of the same organic solvent is used to dissolve the predetermined amount of medication. After dissolving enhancers at different concentrations in the remaining organic solvent, this mixture is combined with the drug-polymer solution along with di-N-butylphthalate as a plasticizer. The mixture is stirred for 12 hours. Subsequently, it is transferred intoa circular Teflon mold. To regulate solvent evaporation, the molds should be placed on a flat surface and covered with an inverted funnel inside a laminar flow hood set to an air speed of

0.5 m/s. The solvent should evaporate for a full day. Before assessment, the dried films need tobe stored for an additional twenty-four hours at 25±0.5°C in a desiccator filled with silica gel to avoid aging effects. The films should be evaluated within a week of their preparation.[57-60]

7.3. Mercury Substrate Method

This approach dissolves the medication in a polymer solution with the plasticizer.To ensure a uniform dispersion, the aforementioned solution should be mixed for ten to fifteenminutes. Then, it should be poured over a flat mercury surface and covered with an inverted funnel to prevent solvent evaporation.[57,58]

7.4. IPM Membranes Method

The required medication is dissolved using a magnetic stirrer in a mixture of water and propylene glycol that contains carbomer 940 polymer with the combination stirred for 12 hours. Triethanolamine is then added to the dispersion to neutralize it and increase its viscosity.If the drug exhibits very low solubility in aqueous solutions, a gel can be formed using a buffer with a pH of 7.4. The resulting gel will be incorporated into the IPM membrane.[57,58]

7.5. EVAC Membrane Method

Rate control membranes, including polyethylene (PE), 1% carbopol reservoir gel and ethylenevinyl acetate copolymer (EVAC) membranes, can be used to develop the desired transdermal delivery system. If the medication is insoluble in water, a gel is prepared using propylene glycol.The drug is dissolved in propylene glycol followed by the addition of carbopol resin, which isthen neutralized with a 5% w/w sodium hydroxide solution. The medication, now in gel form is applied to a backing layer that covers the intended area. To create a leak-proof device, a rate-regulating membrane is placed over the gel and the edges are heated to seal the assembly.[57,58]

7.6. Aluminium Backed Adhesive Film Method

When the loading dose for a transdermal drug delivery system exceeds 10 mg, unstable matricesmay arise. In such cases, the adhesive film method with aluminium backing is suitable. Chloroform is the preferred solvent

for this process, as most medications and adhesives dissolvewell in it. Once the medication is dissolved in chloroform, adhesive materials are added to the drug solution. A specially designed aluminium former is lined with aluminium foil and cork blocks that fit snugly are used to seal the ends.[57,58]

7.7. Proliposomes Method

The film deposition technique is utilized in the carrier approach to create liposomes, ideally with a drug-to-lecithin ratio of 0.1:2.0. To start, 5 mg of mannitol powder is added to a 100 mlround-bottom flask, which is placed in a temperature-controlled environment at 60–70°C. Theflask is then swirled at 80–90 rpm and the mannitol is dried under vacuum for 30 minutes. After drying, the water bath temperature is lowered to 20–30°C. A 0.5 ml aliquot of the organic solution is introduced to the flask at 37°C, after the drug and lecithin have been dissolved in a suitable organic solvent mixture. Once the solution has completely dried, another 0.5 ml aliquotis added. Following the final loading, the flask containing the proliposomes is connected to a lyophilizer. The drug-loaded mannitol powdered proliposomes are then stored in a desiccator overnight before being sieved through a 100-mesh screen. The resulting powder is collected and stored in a glass bottle at freezing temperatures until it is characterized.[61]

7.8. Free Film Method

A free film of cellulose acetate is formed by casting onto a mercury surface. This process beginswith creating a 2% w/w polymer solution in chloroform. Plasticizers are incorporated at a 40%weight-to-weight ratio based on the polymer. Five milliliters of the polymer solution are placedin a glass ring and laid over the mercury surface in a glass petri dish. To control the evaporationrate of the solvent, the Petri dish is covered with an inverted funnel. Once the solvent has completely evaporated the mercury surface is inspected for film formation. The dried film is then removed and stored in a desiccator between sheets of wax paper. Varying film thicknessescan be achieved by adjusting the volume of the polymer solution.[57,58]

8. CONTACT TIME FOR DIFFERENT TYPES OF TDDS

The contact time for transdermal drug delivery systems (TDDS) can vary based on the type ofsystem and formulation. Here are some general guidelines:

8.1. Transdermal Patches

Transdermal patches are designed for continuous wear, providing sustained drug release over extended periods, typically ranging from 24 hours to several days. Some formulations can lastup to a week. The duration of wear depends on factors such as the specific drug, formulation and intended therapeutic effect. These patches allow for a steady absorption of medication through the skin, offering a convenient and effective delivery method that can enhance patientadherence to treatment. By tailoring the patch design to individual patient needs, healthcare providers can optimize therapeutic outcomes while minimizing side effects associated with traditional medication administration routes.[62]

8.2. Transdermal Gels and Creams

Transdermal patches are specifically designed for continuous wear, allowing for sustained drugdelivery over extended periods. Typically, these patches can be worn for durations ranging from24 hours to several days, with some specialized formulations lasting up to 7 days. The specificduration of wear is influenced by various factors, including the properties of the drug, the formulation design and the intended therapeutic effect. For instance, some drugs may require longer contact times to achieve optimal absorption, while others may be effective with shorterdurations. This versatility in wear time ensures that transdermal patches can be tailored to meetindividual patient needs, ultimately enhancing treatment efficacy and improving patient outcomes.[63]

8.3. Transdermal Sprays

Transdermal patches are specifically designed for continuous wear, allowing for sustained drugdelivery over extended periods. Typically, these patches can be worn for durations ranging from24 hours to several days with some specialized formulations lasting up to 7 days. The specificduration of wear is influenced by various factors, including the properties of the drug, the formulation design and the intended therapeutic effect. For instance, some drugs may require longer contact times to achieve optimal absorption, while others may be effective with shorterdurations. This versatility in wear time ensures that transdermal patches can be tailored to meetindividual patient needs, ultimately enhancing treatment efficacy and improving patient outcomes. [64]

9. APPLICATION OF TDDS

- **Pain Management**

Fentanyl patches provide steady chronic pain relief, ensuring consistent analgesic delivery, reducing frequent dosing, and enhancing patient comfort. [65]

- **Hormone Replacement Therapy**

Transdermal patches deliver hormones like estrogen or testosterone, providing a convenient, effective way to maintain steady blood levels.[66]

- **Nicotine Replacement Therapy**

Nicotine patches assist individuals in quitting smoking by providing a controlled release of nicotine, helping to reduce withdrawal symptoms and cravings, ultimately supporting a smoother cessation process.[67]

- **Cardiovascular Medications**

Patches delivering nitroglycerin provide continuous medication, effectively managing angina and relieving chest pain for patients over time. [68]

- **Vaccination**

Research is exploring transdermal vaccine delivery systems, aiming to improve convenience, accessibility,

and acceptance through less invasive administration methods.[69]

- **Antidepressants**

Some patches deliver antidepressants like selegiline, providing an alternative method to oral medications for effective treatment of depression.[70]

- **Local Anesthetics**

Transdermal systems effectively deliver local anesthetics, providing targeted pain relief for minor surgical procedures and enhancing patient comfort during treatment.[71]

- **Anti-inflammatory Drugs**

Transdermal delivery of arthritis medications targets inflamed areas directly, improving effectiveness, reducing systemic side effects, and enhancing patient comfort and compliance with treatment. [72]

10. ADVERSE DRUG REACTIONS (ADRS) OF TDDS

Transdermal medication administration, while effective for delivering active ingredients can lead to various skin responses as primary side effects. Transdermal patches are among the mostcommonly utilized delivery systems providing a convenient and non-invasive method for medication administration. These patches allow for a steady release of the drug into the bloodstream enhancing patient compliance and providing sustained therapeutic effects.

However, despite their advantages, transdermal patches can cause skin irritation which may manifest in several forms, including burns, pruritus (itching) and erythema (redness) in the areasurrounding the patch. This irritation can result from several factors. First, the active ingredientswithin the patch may trigger allergic reactions or sensitivities in some individuals, leading to discomfort. Additionally, the materials used in the construction of the patches, such as adhesivesand excipients, can also contribute to skin irritation. Adhesives in particular may cause reactions ranging from mild irritation to severe dermatitis, depending on the individual's skin type and sensitivity.[73]

In summary, while transdermal patches offer significant benefits in medication delivery awareness of potential skin reactions is essential. By maintaining open communication with healthcare providers and monitoring skin responses patients can enhance their treatment experience and minimize adverse effects.[73]

Allergic reactions are also a concern with various types of skin patches primarily due to the active ingredient or components of the patch itself including adhesives and excipients. The two most common skin reactions associated with transdermal patches are irritant contact dermatitis and allergic contact dermatitis. These conditions occur when the skin reacts negatively to either the medication or the materials used in the patch, highlighting the importance of monitoring skin health during treatment.[74]

Additionally, there is a risk of medication overdose which can occur if patients apply more patches than necessary or remain on a treatment regimen longer than recommended. This risk underscores the need for

careful adherence to dosage guidelines and monitoring by healthcare providers. Ensuring that patients are educated about proper patch application and the importance of following prescribed guidelines can help mitigate these side effects and enhance the overall efficacy of transdermal medication delivery. Addressing skin reactions and potential overdosing is essential for optimizing treatment outcomes and maintaining patient safety.[75]

11. REGULATORY AND MARKET PERSPECTIVE

Drug (Tradename, year of FDA approval	Type	Indication	Patch Design	Site of Application	Duration of application
Asenapine (Secuado, 2009)	Therapeutic	Antipsychotic		Hip, abdomen, upper arm, or upper back area	24 hr
Buprenorphine (Butrans®, 2010)	Therapeutic	Chronic pain	DIA	Upper outer arm, upper chest, upper back or the side of the chest	7 days
Clonidine (Catapres-TTS®, 1984)	Therapeutic	Hypertension	Reservoir/ Membrane	Upper outer arm or upper chest	7 days
Oestradiol (Estraderm®, 1986)	Therapeutic	Female HRT	Reservoir/ Membrane	Trunk of the body including the buttocks and abdomen	3–4 days
Oestradiol (Climara®, 1994)	Therapeutic	Female HRT	DIA	Lower abdomen or upper quadrant of the buttock	7 days
Oestradiol (Vivelle®, 1994)	Therapeutic	Female HRT	DIA	Trunk of the body including abdomen and buttocks	3–4 days
Oestradiol (Alora®, 1996)	Therapeutic	Female HRT	DIA	Lower abdomen, upper quadrant of the buttock or outer aspect of the hip	3–4 days
Oestradiol (Vivelle-Dot®, 1999)	Therapeutic	Female HRT	DIA	Lower abdomen	3–4 days
Oestradiol (Menostar®, 2004)	Therapeutic	Female HRT	DIA	Lower abdomen	7 days
Oestradiol (Minivelle®, 2012)	Therapeutic	Female HRT	DIA	Lower abdomen or buttocks	3–4 days
Oestradiol (E)/Norethindrone (NT) (Combipatch®, 1998)	Therapeutic	Female HRT	DIA	Lower abdomen	3–4 days
Ethinyl oestradiol (EE)/ Norelgestromin (NL) (Ortho Evra®, 2001)	Therapeutic	Female contraception	DIA	Buttock, abdomen, upper outer arm or upper torso	7 days
Oestradiol E/Levonorgestrel (L) (Climara Pro®, 2003)	Therapeutic	Female HRT	DIA	Lower abdomen	7 days
Fentanyl (Duragesic®, 1990)	Therapeutic	Chronic pain	DIA	Chest, back, flank, or upper arm	72 hr
Granisetron (Sancuso®, 2008)	Therapeutic	Chemotherapy-induced nausea and vomiting	DIA	Upper outer arm	Up to 7 days
Methylphenidate (Daytrana®, 2006)	Therapeutic	ADHD	DIA	Hip area, avoiding the waistline	Up to 9 hr in a day

Table No. 1: Some Transdermal drugs for systemic delivery launched in the USA and EU[80]

11.1. FDA Approval

The FDA's 505(b)(2) new drug application (NDA) process offers applicants the ability to leverage existing data from previously approved drugs known as the 'reference' or 'listed' drug. This provision helps minimize the need for redundant studies by allowing the FDA to rely on data that was not directly generated by the NDA applicant. This is particularly advantageous for pharmaceutical and generic companies as it can significantly reduce the burden of conducting non-clinical studies and extensive safety or efficacy trials.

However, for a product to succeed in the market, companies must address several critical questions early in the development process. Key factors include identifying whether there is an unmet medical need for the product, what unique characteristics the product must possess to stand out in the market and whether healthcare providers and patients will be willing to adopt the product. Therefore, it is essential for companies to thoroughly understand the product's therapeutic role, the competitive landscape and broader market trends to increase the likelihood of success.[80]

11.2. Patient Landscape

A quick search for "transdermal drug delivery" and "patches" returns 216 and 358 results, respectively while searching "transdermal patches" on patents yields a significantly larger number. Some of these patents may not directly pertain to patches but focus on transdermal drug delivery in general. Other related methods for delivering drugs through the skin include ionic liquids, active delivery techniques like forced drug infusion via an external pump or device-assisted transdermal drug delivery (TDD) and microdermabrasion (Andrews, Lee, Choi, & Prausnitz, 2011).

The reviewed patents primarily focus on transdermal patches (TDP), microneedle (MN) arrays and related manufacturing methods. Innovations also include packaging, shipping and storage processes as well as formulations with adjuvants, solubility enhancers, nanoparticles and polymer matrices. These formulations contain both hydrophilic and hydrophobic active ingredients with unique physicochemical properties. The growing volume of intellectual property in transdermal drug delivery reflects the rapid advancement of the technology. As new molecules, once unsuitable for passive delivery become viable, the number of patents in this field is expected to increase significantly.[80]RECENT TECHNIQUES FOR ENHANCING TDDS

- **Microneedle Technologies:** Microneedles create micro-scale channels in the skin, enabling the delivery of larger molecules like peptides and vaccines. Recent advancements include dissolvable and coated microneedles which enhance drug release and absorption rates. This innovative technology is gaining traction for its potential in efficient and painless transdermal drug delivery.

➢ **Nanocarriers**: The use of nanoparticles and liposomes in transdermal drug delivery is growing, enhancing skin permeability, stabilizing drugs and enabling sustained release. These nanocarriers improve bioavailability, offering innovative solutions for more effective treatment across a wide range of medical applications.

➢ **Iontophoresis and Sonophoresis**: These techniques utilize electrical or ultrasound energy to enhance drug penetration through the skin. Recent studies demonstrate improved efficacy across various drugs when employing iontophoresis and sonophoresis. By leveraging these methods, transdermal drug delivery systems can achieve better therapeutic outcomes and patient compliance making them increasingly valuable in clinical applications.

➢ **Polymer-Based Systems**: Innovations in polymeric films and patches have led to better drug-loading capacities and controlled release profiles. Researchers are exploring biodegradable and bioadhesive polymers to improve wearability and drug stability.

➢ **3D Printing**: This technology is being applied to create customized transdermal patches that can deliver precise dosages and combinations of drugs tailored to individual patient needs.

➢ **Formulation Enhancements:** Recent advancements in transdermal drug delivery involve exploring new permeation enhancers and formulation techniques. The use of chemical enhancers and surfactants is being investigated to improve skin barrier permeability for variousdrugs. These innovations aim to facilitate better absorption and bioavailability, enabling a wider range of therapeutic agents to be effectively delivered through the skin, ultimately enhancing patient outcomes and treatment options.[76,77]

12. FUTURE PROSPECTS

The primary method for passive transdermal drug delivery is now adhesive technology, whichhas become a focal point in formulation science. Adhesives and excipients are critical components in developing effective transdermal systems as they directly influence drug stability, release profiles and overall patient compliance. Research in adhesive technology aimsto enhance medication stability and solubility while minimizing lag time thereby improving the rate of distribution across the skin barrier.

One of the main objectives is to optimize the adhesive properties to ensure strong skin adherence throughout the application period. Customizing adhesive chemistry allows formulators to fine-tune the interaction between the drug and the adhesive, maximizing the efficacy of the transdermal patch. Since there is no universal adhesive suitable for all medications and formulation chemistries, extensive research is necessary to find the right combinations. This is particularly important for drugs that may have varying solubilities or stability profiles.

Additionally, the incorporation of novel excipients can further enhance drug permeation, facilitating a more efficient transdermal delivery system. As a next-generation drug delivery technology, transdermal drug delivery systems (TDDS) represent a practical and innovative approach to therapeutic administration. They provide advantages such as improved patient compliance, reduced side effects and a more controlled release of medication. With ongoing advancements in adhesive technology and formulation science, TDDS continues to evolve offering promising solutions for a range of medical applications and improving therapeutic outcomes for patients.[78,79]

13. CONCLUSION

The transdermal drug delivery system represents a significant advancement in pharmacotherapy, offering a non-invasive alternative to traditional methods like oral or injectable administration. These systems come in various forms including matrix, reservoir and microemulsion types each designed to enhance drug absorption and provide controlled sustained release. This approach bypasses first-pass metabolism ensuring better bioavailability and more consistent plasma drug levels, which can improve patient compliance and comfort.

Despite these benefits challenges remain such as overcoming the skin's natural barrier to drug penetration and dealing with the complexities of formulating stable, effective products. However, recent innovations like nanotechnology and microneedle arrays show promise in addressing these issues, enhancing both the efficiency and versatility of transdermal systems. Additionally, the development of personalized medicine and smart delivery systems, which can adjust drug release based on real-time data, may further revolutionize treatment approaches in the future.

In conclusion, the transdermal drug delivery system holds great potential for improving therapeutic outcomes, offering a more convenient and patient-friendly alternative to traditional drug delivery methods, while ongoing research continues to tackle existing challenges and unlock new possibilities in healthcare.

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