WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 24, 648-658. Review Article ISSN 2277–7105

TRANSDERMAL DRUG DELIVERY: REVOLUTIONIZING THE WAY WE DELIVER MEDICATION AND ENHANCE THERAPEUTIC OUTCOMES

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Article Received on
31 October 2024,
Revised on 20 Nov. 2024,
Accepted on 10 Dec. 2024
DOI: 10.20959/wjpr202424-34982

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I. ABSTRACT

A Transdermal Drug Delivery System (TDDS) is a controlled method of administering drugs through the skin at a predetermined rate, offering benefits such as extended therapeutic effects, reduced side effects, and improved bioavailability. The stratum corneum, the skin's outermost layer, regulates drug penetration via appendageal, transcellular, and intercellular pathways. TDDS comprises essential components like a polymer matrix, drug reservoir, penetration enhancers, adhesives, and a protective backing layer. Transdermal patches are categorized into reservoir, matrix, and micro-reservoir systems, each designed to facilitate drug absorption into the systemic circulation through the skin. Standardized evaluation of TDDS focuses on factors such as adhesion properties, in vitro drug release, permeation studies, and stability profiles. Recent advancements have enhanced the efficiency and scope of TDDS, addressing challenges like low drug permeability and skin irritation. This review aims to comprehensively explore the progress, challenges, and expanding ‘ applications of TDDS, particularly through transdermal patches, highlighting their potential for innovative therapeutic solutions.

KEYWORDS: Transdermal Drug Delivery System, Penetration Enhancer, Matrix System, Reservoir System.

II. INTRODUCTION

Transdermal Drug Delivery Systems (TDDS) represent a cutting-edge formulation strategy designed to administer precise doses of medications through the skin, enabling effective systemic drug delivery. The development of TDDS requires a comprehensive understanding of the skin's biophysical, morphological, and physicochemical properties to ensure optimal performance. This innovative approach overcomes many limitations associated with conventional drug delivery methods. TDDS offers numerous advantages over traditional routes such as oral and injectable administration. These systems enhance patient compliance, bypass hepatic first-pass metabolism, and provide controlled, sustained drug release. Such benefits are particularly valuable for drugs with short biological half-lives, as TDDS mitigates rapid systemic entry, reducing the likelihood of adverse effects while maintaining stable plasma drug concentrations. The first FDA-approved transdermal system, introduced in 1979 for nausea and vomiting prevention, marked a significant milestone in TDDS development. Transdermal patches, a prominent example of this technology, provide a convenient, painless, and continuous method of drug administration. These patches, available in various sizes and capable of delivering multiple active ingredients, utilize diffusion processes to ensure efficient drug absorption into systemic circulation. Percutaneous drug absorption is confirmed through measurable drug levels in the bloodstream, detection of drug metabolites in urine, and observation of clinical responses to therapy. The ability to discontinue patch application at any time further enhances safety and adaptability. TDDS has revolutionized drug delivery by providing a versatile, patient-centric approach, making it a promising solution for the treatment of a wide range of diseases.

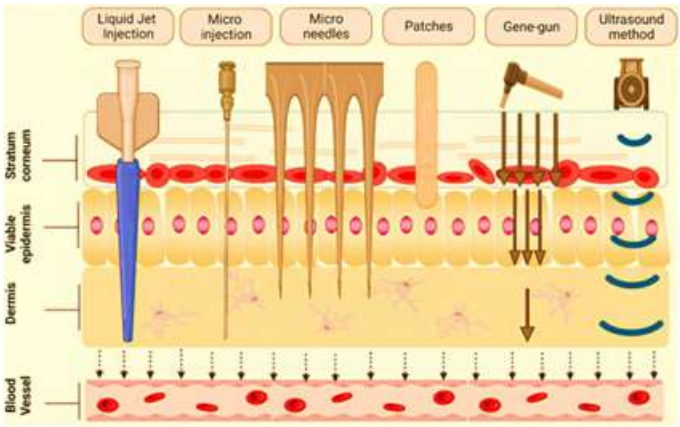

Figure 1: These Tools Include Liquid Jet Injection, Micro Injection, Micro Needles, Patches, Gene-Guns, And Ultrasonic Techniques.

III. Needs and Objectives

1. To Explore Transdermal Drug Delivery Systems (TDDS)
2. To Analyze the Components of TDDS
3. To Examine Patch Designs
4. To Identify Factors Influencing Transdermal Delivery
5. To Review Evaluation Parameters
6. To Discuss Advancements and Challenges
7. To Explore Applications of TDDS

IV. Advantage of TDDS

1. Transdermal delivery circumvents first-pass metabolism by facilitating a sustained and controlled release of the therapeutic agent, thereby ensuring a continuous and prolonged permeation of the substance through the skin and into the systemic circulation.
2. Increase Patient compliance.
3. It does not interact with or alter the gastrointestinal environment, including the stomach and intestinal fluids.
4. Maintains consistent and stable blood levels, ensuring effective control over an extended duration.
5. Reduced plasma concentration levels of drugs.
6. Reduce fluctuations of drug in plasma levels, Utilize drug candidates with short half-life and Low therapeutic index.
7. In the event of toxicity, transdermal drug delivery systems can be readily removed, allowing for swift discontinuation of therapy and mitigation of adverse effects.
8. Reduce of dosing frequency an enhance Patients compliance.
9. Transdermal delivery optimizes the therapeutic efficacy of various medications by overcoming challenges associated with oral administration, including poor bioavailability, gastrointestinal irritation, and first-pass metabolism, thereby providing a more reliable and patient-friendly treatment option.
10. The streamlined medication schedule results in decreased differences in drug response both within and among patients.

V. Disadvantage of TDDS

1. Optimal transdermal absorption necessitates that a drug exhibit suitable physicochemical characteristics, enabling it to effectively permeate the stratum corneum.

2. For effective transdermal drug delivery, the daily dosage should ideally not exceed 5 mg/day. Dosages exceeding 10-25 mg/day pose significant challenges due to limitations in skin permeability and the difficulty of maintaining therapeutic drug levels within the systemic circulation.
3. The components of a transdermal patch, comprising the active pharmaceutical ingredient, adhesive, and excipients, may potentially induce local skin irritation or adverse reactions in some individuals.
4. The use of a transdermal drug delivery system should be justified by a clear clinical requirement, ensuring its application addresses specific therapeutic needs that cannot be effectively met by conventional delivery methods.
5. Achieving high drug concentrations in the blood or plasma is not feasible with transdermal delivery systems.
6. Large molecular size of drugs cannot be formulated.
7. Possibility of inflammation on the site of application.
8. Not comfortable to wear.
9. May not be economical.
10. The skin barrier varies among individuals and can even change within the same person over time.

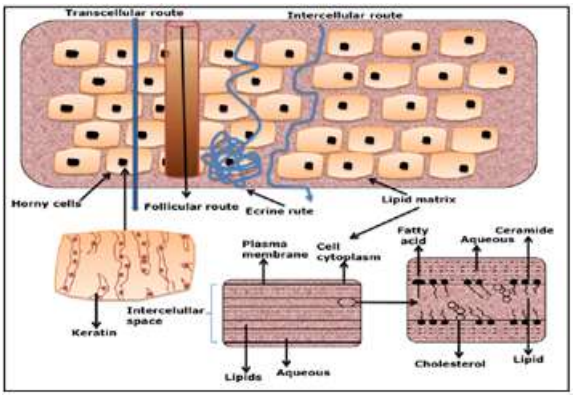

Figure 2: Schematic Representation of Penetration Routes of Drugs Throughout The Skin.

VI. Skin Structure

The skin, the largest organ of the human body, serves as a critical protective barrier against a multitude of external factors and potential threats. With an average surface area of approximately 1.7 square meters, it effectively shields the body from microorganisms,

ultraviolet (UV) radiation, chemicals, allergens, and excessive water loss. This essential barrier function is pivotal for maintaining overall health and homeostasis.

Beyond protection, the skin plays significant roles in thermoregulation, sensory perception, and the synthesis of vitamin D through sunlight exposure. Proper care is crucial to preserving its integrity and supporting these vital functions.

Anatomically, the skin is composed of three distinct layers.

(a) Epidermis: The outermost layer, primarily responsible for the skin's barrier properties.

(b) Dermis: The middle layer, which contains connective tissues, blood vessels, and sensory nerves.

(c) Hypodermis: The innermost layer, comprising subcutaneous fat that provides insulation and cushioning.

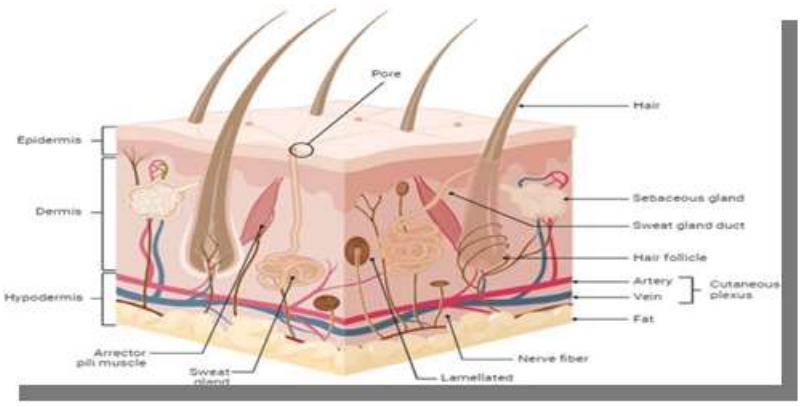

Figure 3: Structure of The Skin.

VII. Transdermal Patches

A transdermal patch, also referred to as a skin adhesive patch, is an innovative drug delivery device designed to administer precise medication dosages through the skin into the bloodstream. This system incorporates a specialized membrane that controls the release of liquid medication from the patch reservoir, ensuring a consistent and regulated delivery. Transdermal patches are particularly advantageous for patients who experience difficulties swallowing tablets or aversion to injections. Additionally, they offer prolonged therapeutic effects, reducing the need for frequent dosing compared to oral medications. These patches are widely utilized across various therapeutic areas, including pain management, cardiovascular disease treatment, smoking cessation, motion sickness prevention, and hormone replacement therapy. Their ability to provide a non-invasive, convenient, and

effective alternative to traditional drug delivery methods has made transdermal patches a valuable tool in modern medicine.

A) Components of Transdermal Patches

a. Liner: The liner serves as a protective layer during the storage of the transdermal patch, preventing drug loss from the polymer matrix. It is a component of the primary packaging and must be removed before use to ensure proper application of the patch.

b. Adhesive: The adhesive component binds the various elements of the patch together and facilitates secure attachment to the skin. Common examples of adhesives used in transdermal patches include polyacrylate, polyisobutadiene, and silicone-based polymers.

c. Membrane: The membrane controls the release of the drug from the reservoir or multi-layer patch. It is typically composed of materials such as chitosan or poly-2-hydroxyethylmethacrylate. Other materials used include silicones, polyester elastomers, polyacrylonitrile, ethylene-vinyl acetate copolymer, and high-density polyethylene,

d. Drug: The drug is the active ingredient of the patch, which is in direct contact with the release liner, allowing for its controlled release into the skin and bloodstream.

e. Polymer: The polymer in a transdermal patch must be biologically and chemically compatible with the drug, as well as with other additives, including permeation enhancers, plasticizers, and adhesives, to ensure the patch's stability and effective drug delivery.

1. Example: Natural polymers: Shellac, gelatin, chitosan, waxes, cellulose derivatives, natural rubber. 2. Synthetic polymer: PVA, polyurea, polyamide, polyethylene, polyvinyl pyrrolidone, polypropylene. 3. Synthetic elastomer: Synthetic elastomers include polyurethane, polyisobutylene, polybutadiene, nitrile rubber, hydrin rubber, silicone rubber, and butyl rubber.

f. Backing: It protects the patch from environmental factors, provides structural support, and enhances the flexibility and appearance of the patch.

B) Types Of Transdermal Patches

a. Single-Layer Drug-in-Adhesive Patches: Single-layer drug-in-adhesive patches utilize a polymer layer with adhesive properties to deliver the drug. The medication is embedded within this layer and adheres to it, releasing from the backing laminate layer, which provides structural support. An example of a single-layer drug-in-adhesive patch is Daytrana, which delivers methylphenidate.

b. Multilayer Drug-in-Adhesive Patches: Multilayer drug-in-adhesive patches offer controlled drug release over an extended period. These patches feature a drug reservoir layer, an adhesive layer, a protective release liner, and a backing laminate. Multilayer patches can provide extended drug delivery for up to seven days and are commonly used for pain management, smoking cessation, and hormone therapy.

c. Vapor Transdermal Patches: Vapor transdermal patches consist of a single adhesive polymer layer designed to release therapeutic vapors through the skin. These patches serve various purposes, with examples such as *Nicoderm CQ*®, a nicotine vapor transdermal patch used for smoking cessation. Introduced to the European market in 2007, this patch releases essential oils to assist individuals in quitting smoking. Another example is *Altacura* vapor patches, which contain essential oils for decongestion. Other vapor patches are formulated with antidepressant medications or sedatives.

d. Membrane-Modulated Transdermal Reservoir Patches: Membrane-modulated transdermal reservoir patches include a drug reservoir, a backing layer composed of an impermeable metallic plastic laminate, and a porous polymeric membrane that regulates drug release. The membrane is commonly made from materials like ethylene-vinyl acetate copolymer and hypoallergenic adhesive polymers. The drug's release is controlled through molecular dispersion within a polymer matrix, which is carefully prepared to ensure consistent delivery.

e. Micro-Reservoir Transdermal Patches: Micro-reservoir transdermal patches integrate a drug reservoir with a matrix dispersion, enabling controlled drug release. The drug is suspended in an aqueous solution of a hydrophilic polymer, which is then uniformly dispersed in a lipophilic polymer. This process involves applying high shear mechanical force to create microscopic, non-leachable spheres. These patches release the drug at a zero-order kinetic rate, ensuring stable and consistent plasma drug levels over time. To maintain thermodynamic stability, crosslinking polymeric agents are typically incorporated into the drug dispersion.

VIII. Dermis

The **dermis** lies beneath the **epidermis** and typically measures 3 to 5 mm in thickness, making it thicker than the epidermis. It plays a vital role in supplying nutrients to the epidermis and contains the skin's appendages, such as hair follicles, sweat glands, and sebaceous glands. Additionally, the dermis houses sensory receptors that are responsible for

detecting touch, pain, temperature, and pressure, contributing to the skin's overall function in sensation and protection.

It comprises diverse structures, such as.

1. Blood vessels
2. Hair follicles
3. Sweat glands
4. Sebaceous glands
5. Nerve endings
6. Collagen and elastin fibers.

Approximately 2 mm beneath the surface, capillaries function as drains, removing most substances attempting to pass through the skin. This mechanism is crucial for maintaining a low concentration of substances entering the skin. The concentration gradient between the inside and outside of the skin facilitates the movement of these substances.

When delivering medications through the skin, the stratum corneum layer acts like a gel composed primarily of water. For water-soluble medications, this layer poses minimal resistance, allowing easier absorption. However, for oily substances, such as certain lotions or creams, this layer presents a greater challenge to the passage of the medication.

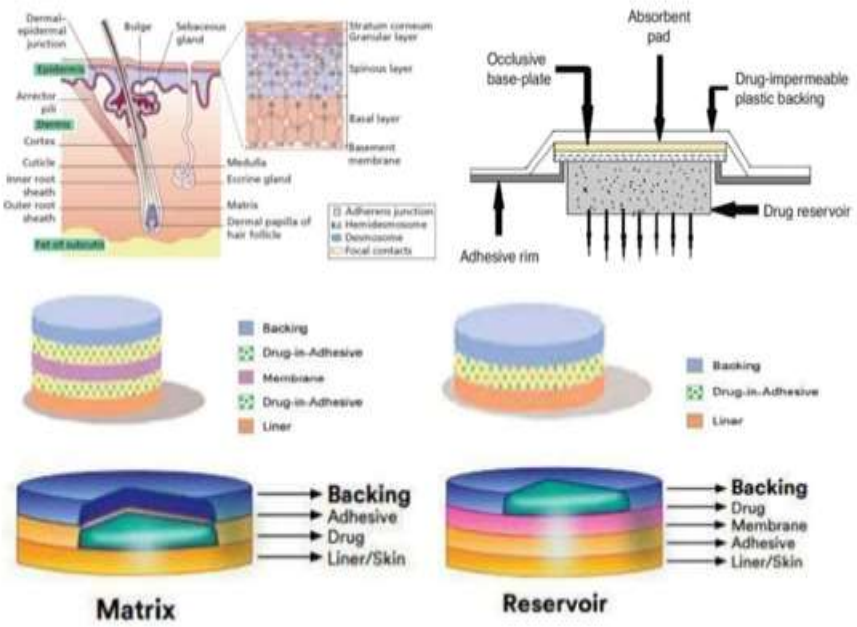

Figure 4: Enhancing Patient Experience and Treatment Efficacy: The Evolution of Transdermal Drug Delivery Systems.

IX. Penetration Enhancers

Penetration enhancers, also known as permeation enhancers or skin penetration enhancers, are substances used to improve the permeability of active compounds, such as drugs, through the skin. They work by temporarily modifying the structure and properties of the stratum corneum, the skin's outermost layer. This modification facilitates the deeper penetration of active ingredients into the bloodstream or underlying skin layers, thereby enhancing the efficacy of topical medications.

X. DISCUSSION

The transdermal drug delivery system (TDDs) has emerged as a promising approach in controlled drug delivery, offering numerous benefits such as extended therapeutic effects, reduced adverse reactions, and enhanced patient compliance. The outermost layer of the skin, the strourm corneum, plays a crucial role in regulating the transdermal penetration of substances. The development of TDDs involves careful consideration of various factors, including skin condition, physicochemical properties, and environmental influences. The design of TDDs typically comprises a polymer matrix, membrane, drug, penetration enhancers, and adhesives. Transdermal patches can be categorized into reservoir, matrix, and micro-reservoir systems, each engineered to deliver active ingredients into the circulatory system through the skin. Standardized evaluation methods are employed to assess aspects such as adhesion properties, in vitro drug release, and stability. Further research and development in TDDs are necessary to overcome existing challenges and explore potential applications of this innovative drug delivery method.

XI. CONCLUSION

The transdermal drug delivery route is recognized for its safety and effectiveness when compared to other administration methods. Various drugs, including hormonal therapies, a wide range of analgesics, and medications for heart diseases, are formulated in Transdermal Drug Delivery Systems (TDDS) to reduce gastrointestinal side effects and first-pass metabolism. With the growing popularity and numerous benefits of transdermal drug delivery, researchers are increasingly exploring the introduction of new drugs in this delivery format.

However, it is important to recognize that the skin serves primarily as a protective barrier for the internal organs. Therefore, when designing a transdermal drug delivery system, it is essential to minimize any disruption to the skin's natural functions. While transdermal drug

application can impact skin physiology, it is crucial to limit such effects as much as possible. A comprehensive understanding of skin physiology and anatomy is vital for advancing this field. Achieving optimal transdermal delivery requires in-depth knowledge of the interactions between various polymers and skin components, which is fundamental to the design and optimization of transdermal drug delivery systems.

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