GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(REVIEW ARTICLE)

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A review on transdermal drug delivery system

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GSC Advanced Research and Reviews, 2024, 18(02), 347–361

Publication history: Received on 01 January 2024; revised on 15 February 2024; accepted on 17 February 2024

Article DOI: https://doi.org/10.30574/gscarr.2024.18.2.0052

Abstract

Drugs that are applied topically are delivered using transdermal drug delivery devices. These are pharmaceutical preparations of varying sizes, containing one or more active ingredients, intended to be applied to the unbroken skin in order to deliver the active ingredient after passing through the skin barriers, and these avoid first pass metabolism. Today about 74% of drugs are taken orally and are not found effective as desired. To improve efficacy transdermal drug delivery system was emerged. A notable advantage of transdermal drug delivery compared to other methods like oral, topical, intravenous (IV), and intramuscular (IM) administration is its controlled release of medication into the patient's system. This controlled release is achieved either by using a porous membrane enclosing a medication reservoir or by utilizing the patient's body heat to melt thin layers of medication embedded in the adhesive. Despite its benefits, transdermal drug delivery has certain limitations due to the skin's effective barrier function. Only molecules with small sizes can efficiently permeate the skin and consequently be delivered through this method.

Keywords: TDDS; Topical drug delivery; Transdermal patches; Microneedle.

1. Introduction

"Transdermal drug delivery (TDD) involves transporting medicinal substances across the skin, commonly for systemic administration, and has gained widespread acceptance in medical practice. Presently, the FDA has approved over twenty transdermal drugs, offering advantages such as sustained and controlled drug delivery, ease of termination, suitability for self-administration, and bypassing hepatic metabolism and gastrointestinal issues [1,2,3]. Transdermal drug delivery offers several advantages, including prolonged drug release at a consistent rate, easy cessation of drug administration by merely removing the device, suitability for self-application, and notably, the ability for the drug to bypass hepatic first-pass metabolism and gastrointestinal incompatibility.[4,5,6] TDD methods aim to achieve controlled molecule permeation through various skin layers, holding immense potential in treating chronic diseases by ensuring prolonged therapeutic durations while maintaining controlled drug levels. [7,8]

The prevailing transdermal systems in the market, notably patches based on semi-permeable membranes, are widely used as Transdermal Drug Delivery Systems (TDDS) or 'Skin patches.' These systems are designed to effectively deliver drugs through the skin and into the bloodstream.[9,10,11]TDDS possess advantages in managing skin diseases by avoiding first-pass metabolism and regulating drug input over extended periods.[12] Leveraging the skin's unique physiological structure, rich in blood and lymphatic vessels connected to the body, allows effective delivery of therapeutic agents for disease treatment. [13,14]

Furthermore, TDDS not only facilitate continuous drug transport through the skin but also assist in overcoming barriers and enhancing the transport of poorly soluble and bioavailable agents. [15,16] These systems can be tailored using various permeation enhancer materials to predictably control drug absorption profiles.[17] Especially promising for chronic

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diseases like obesity, TDDS could potentially become a primary mode for anti-obesity drug delivery.[18]However, challenges persist in delivering hydrophilic drugs, peptides, macromolecules, and genetic treatments like DNA or small-interfering RNA (siRNA) through the transdermal route due to hurdles posed by the intact stratum corneum. [19,20,21,22,23,24]

TDDS have emerged as a viable substitute for oral medications and hypodermic injections.[25,26]Numerous approaches, ranging from chemical enhancers to technologies like electroporation, iontophoresis, and ultrasound waves or their synergistic combinations, have been employed to enhance drug delivery, albeit with difficulty in predicting the exact degree of enhancement. [27]Compared to injection delivery, TDDS offer benefits such as reduced pain, bruising, bleeding, improved patient acceptance, compliance, and elimination of needle-associated risks and medical waste. [28,29]The transdermal route stands out as a practical and secure option for drug delivery. " [30]

Advantages of Transdermal Drug Delivery System :[31,32,9,33,34,35,36,37,38,39]

- Reduces dosing frequency.
- Lowers drug concentration, improving bioavailability.
- Bypasses first-pass metabolism by the liver.
- Decreases plasma drug levels, reducing side effects.
- Non-invasive, eliminating the need for parenteral therapy.
- Enhances compliance due to extended therapy with a single application.
- Allows rapid termination of drug therapy by removing the skin application.
- Facilitates self-administration.
- Reduces systemic drug interactions.
- Provides longer-lasting action.
- Maintains consistent blood levels over an extended period.
- Minimizes gastrointestinal side effects.
- Easily discontinued in case of toxicity.
- Exhibits similarities to intravenous infusions.[40]
- Empowers self-governance.[41]
- Enables the permeation of both lipophilic and hydrophilic drugs.[42]

Disadvantages of Transdermal Drug Delivery System: [31,32,9,33,34,35,36]

- Limited to potent drugs for transdermal delivery.
- Possible skin irritation at the application site in some patients.
- Potential uneconomical nature of the system.
- Risk of drug binding to the skin leading to dose dumping.
- Primarily applicable for chronic conditions rather than acute ones.
- Cutaneous metabolism can affect the medication's efficacy.
- Unsuitability of ionic drugs for transdermal therapy.
- Suitable only for drugs with a molecular weight below 500 Daltons.

2. Anatomy and Physiology of Skin

2.1. Skin: The Largest Organ[33]

The skin, constituting the largest organ of the human body, spans approximately 2 square meters and receives nearly one-third of the body's blood circulation.[26] It acts as a protective barrier against the transdermal absorption of diverse chemical and biological agents, with a thickness ranging from a few millimeters (2.97-0.28mm).

This organ:

- Separates the internal blood circulation network from the external environment.
- Acts as a defense against physical, chemical, and microbial threats.
- Regulates body temperature like a thermostat.
- Plays a role in blood pressure regulation.
- Shields against the penetration of harmful UV rays. [43]

The skin significantly influences various aspects of drug delivery, including drug permeation and absorption across the dermis. The skin's diffusional resistance relies heavily on its anatomy and ultrastructure.[33] Functioning as a dynamic organ, the skin facilitates the migration of substances through and across its layers.[44]The primary function of the skin is to provide protection against physical assaults and pathogens. This attribute contributes to the skin's toughness and rigidity, which can pose challenges for drugs administered via the transdermal route.[45]

Anatomy of Skin: The human skin's structure comprises three main layers:

- Epidermis.
- Dermis.
- Hypodermis.

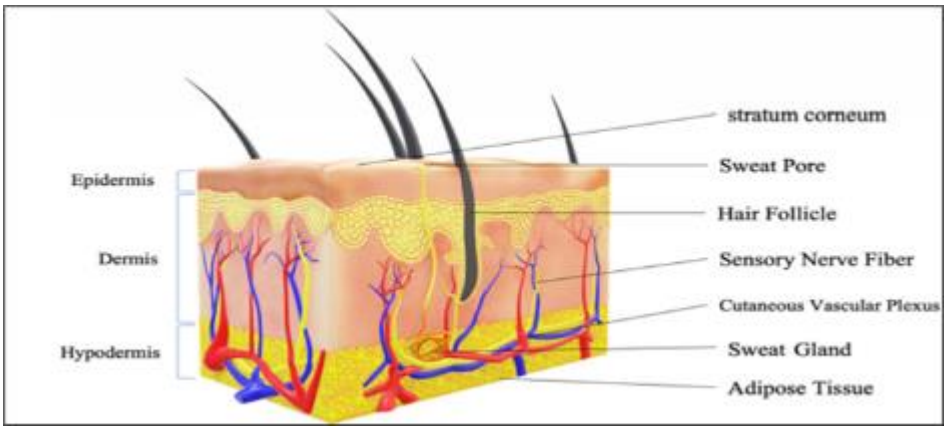

Figure 1 The Structure of human skin [80]

2.2. Epidermis

The epidermis, the outermost layer of skin measuring 10–20 mm, comprises dead cells forming the stratum corneum, functioning as a robust barrier.[46] This layer, approximately 150–200 mm thick, consists of viable cells organized into five layers based on varying degrees of cell keratinization: the stratum corneum (SC or horny layer), stratum lucidum (clear layer), stratum granulosum (granular layer), stratum spinosum (spinous or prickle layer), and stratum germinativum (basal layer). [47]The thickness of this multilayered epidermis varies across body regions, ranging from 0.8 mm on palms and soles to 0.06 mm on the eyelids. [9]

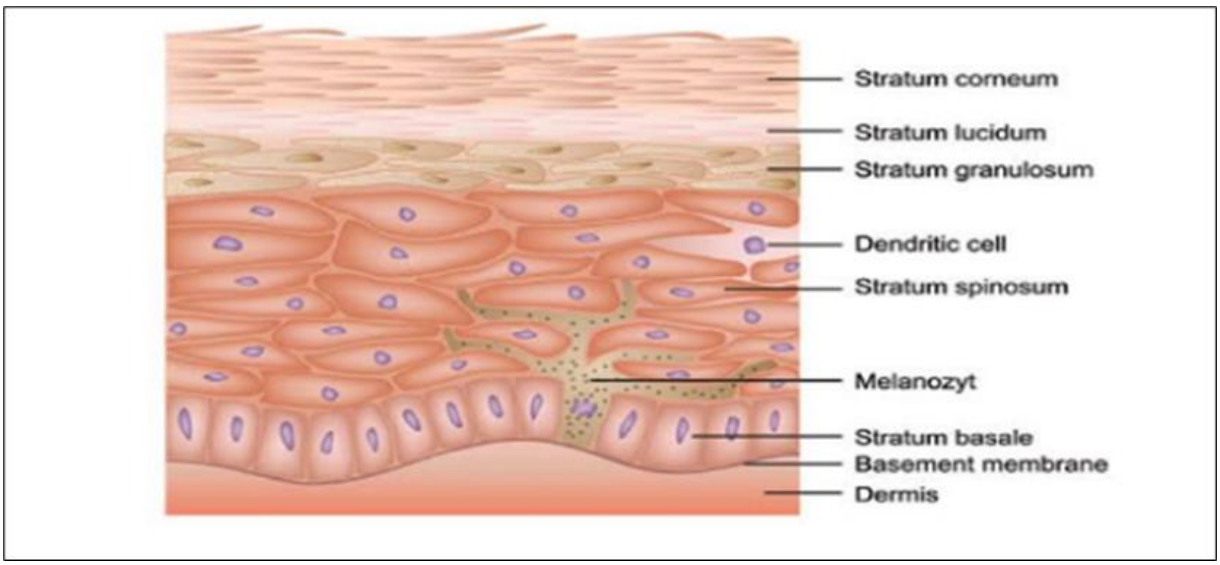

Figure 2 The Structure of Epidermis [81]

The layers of the epidermis comprise distinct characteristics:

- Stratum lucidum (Clear cell layer): These cells become flatter and densely packed during turnover, predominantly found in the soles and palms.[48, 49]
- Stratum granulosum (Granular cell layer): Consisting of 2-4 layers and approximately 3mm thick, cells in this layer flatten out. Keratinization of keratinocytes commences in a sublayer, leading to the resolution of organelles like mitochondria and nuclei. As cells fill with keratin fibers, they retain less moisture compared to cells in the prickle cell and basal layers.[48]
- Stratum spinosum (Prickle cell layer): Comprising 10-20 layers, cells in this layer become somewhat flatter, earning the name prickle cells. The sublayer's thickness ranges from 50-150µm.[48]
- Stratum basale (Basal cell layer): Serving as the deepest sublayer, the stratum basale consists of a single layer of basal cells responsible for producing keratinocytes. It acts as a boundary within the epidermis, containing about 8% of the water content. Over time, this layer becomes thinner and loses its ability to retain water. Additionally, melanocytes are present in this layer. [48]

2.3. Dermis

The dermis, ranging from 3–100 mm thick, constitutes the second layer after the viable epidermis. It consists of a diverse array of cells serving various functions, including connective tissue, vascular tissue, a network of lymphatic vessels, sweat and sebum glands, hair follicles, and macrophages.[47] The cutaneous blood supply plays a vital role in regulating body temperature, providing nutrients and oxygen to the skin, and eliminating toxins and waste products. Capillaries extend within 0.2 mm of the skin's surface, creating conditions that facilitate most molecules penetrating the skin barrier. Consequently, the dermal concentration of a permeant remains very low due to the blood supply, generating a concentration gradient across the epidermis necessary for transdermal permeation.[9]

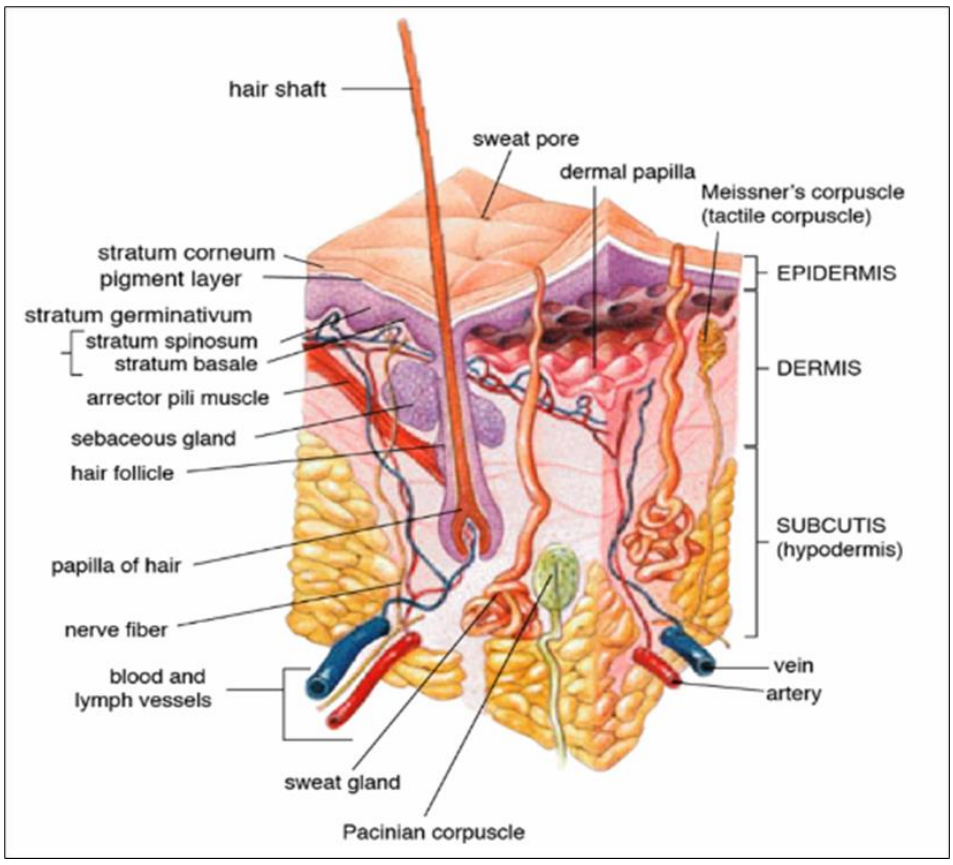

Figure 3 The Structure of Dermis [82]

2.4. Hypodermis (subcutaneous fat layer)

The hypodermis or sub cutis, positioned beneath the dermis, consists of loose connective tissue. Predominantly housing adipocytes, this layer functions in storing fat, aiding in body temperature regulation during cold conditions, and providing cushioning against external impacts.[47] It serves as a pathway for primary blood vessels and nerves to reach the skin and might contain sensory pressure organs.[9] Additionally, the hypodermis or subcutaneous fat tissue provides support to the dermis and epidermis.[50]

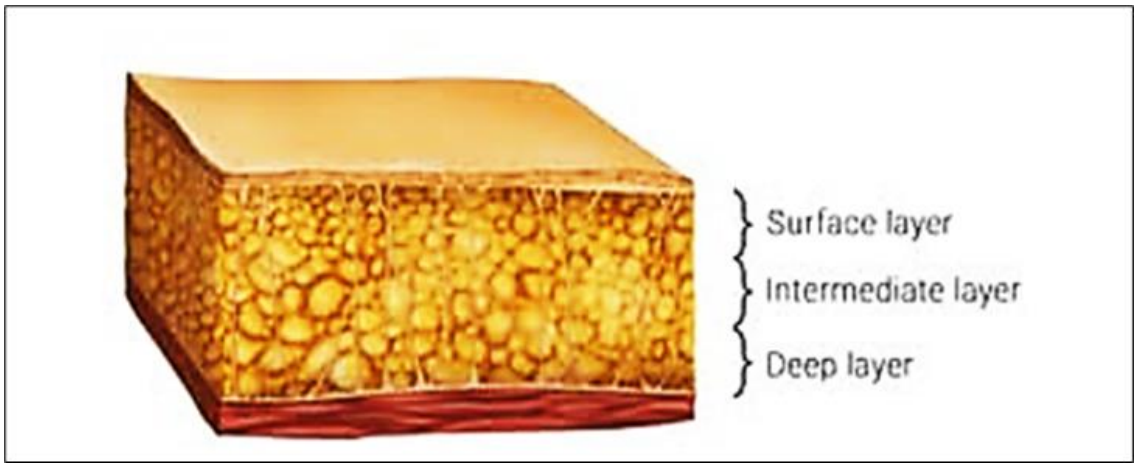

Figure 4 The Structure of Hypodermis [83]

3. The Generation of Transdermal Drug Delivery System :[19,51,52,53]

The first generation of transdermal delivery systems has been pivotal in introducing a majority of the transdermal patches available in clinical practice. Advances in patch technology and increased public acceptance have led to a recent surge in these patches reaching the market. However, this growth is expected to slow down as suitable drugs for such systems become scarce. Candidates for first-generation delivery must possess specific characteristics: they should be low-molecular weight, lipophilic, and effective at low doses. Typically, these candidates are preferred when transdermal delivery offers advantages over oral administration, such as low oral bioavailability, the need for less frequent dosing, consistent delivery profiles, or other relevant factors. [19, 51, 52]Over the past few years, clinical usage of small, lipophilic, low-dose medications has continued to rise steadily. [54]

The second generation of transdermal delivery systems acknowledges the necessity of enhancing skin permeability to broaden the range of transdermal drugs. Ideal enhancers should increase skin permeability by temporarily disrupting the stratum corneum structure, offer an additional driving force for transport into the skin, and avoid causing damage to deeper living tissues. However, methods developed in this generation, like conventional chemical enhancers, iontophoresis, and noncavitational ultrasound, have faced challenges in balancing increased delivery across the stratum corneum while protecting deeper tissues. Consequently, this second generation has primarily advanced clinical practice by improving small-molecule delivery for localized, dermatological, cosmetic, and some systemic applications but has had limited impact on delivering macromolecules.

The third generation of transderma" delivery system is positioned to significantly impact drug delivery by targeting effects to the stratum corneum. This targeted approach allows for more robust disruption of the stratum corneum barrier, leading to more effective transdermal delivery while still safeguarding deeper tissues. Technologies like novel chemical enhancers, electroporation, cavitational ultrasound, microneedles, thermal ablation, and microdermabrasion have demonstrated the ability to deliver macromolecules, including therapeutic proteins and vaccines, across the skin in human clinical trials. These advancements were facilitated by technologies localizing effects to the stratum corneum and acknowledging that safety through localization should make these more aggressive approaches acceptable in medical contexts.

3.1. Basic Components of Transdermal Drug Delivery System

- Polymer matrix /drug reservoir
- Drug
- Permeation enhancers

- Pressure sensitive adhesive (PSA)
- Backing laminats
- Release linear
- Other excipeints like plasticizers and solvent

3.2. Polymer Matrix/Drug Reservoir

Polymers form the foundation of TDDS, controlling drug release from the device. The polymer matrix can be created by dispersing the drug in a liquid or solid state synthetic polymer base. These polymers must exhibit biocompatibility and chemical compatibility with other components like penetration enhancers and PSAs (Pressure Sensitive Adhesives). [55]

- Natural Polymers: e.g., cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber, chitosan, etc.
- Synthetic Elastomers: e.g., polybutadiene, hydrin rubber, polyisobutylene, silicone rubber, nitrile, acrylonitrile, neoprene, butyl rubber, etc.
- Synthetic Polymers: e.g., polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate, etc. [56]

3.3. Drug

The transdermal route is highly advantageous for drugs with suitable pharmacology and physical chemistry. Transdermal patches are particularly beneficial for drugs susceptible to extensive first-pass metabolism, those with narrow therapeutic windows, or drugs with short half-lives causing non-compliance due to frequent dosing. Recent approvals for transdermal delivery include drugs like rivastigmine for Alzheimer's and Parkinson's dementia, rotigotine for Parkinson's, methylphenidate for attention deficit hyperactivity disorder, and selegiline for depression.[55]

3.4. Permeation Enhancers

Permeation enhancers play a crucial role in augmenting stratum corneum permeability by interacting with its functional elements. They facilitate improved drug permeation through the stratum corneum to achieve optimal drug levels. These compounds elevate the conductivity of the stratum corneum's skin surface, enabling therapeutic substance levels to be reached. They alter the protein and lipid packing within the stratum corneum, inducing chemical changes that enhance permeability. Examples include dimethyl sulfoxide, propylene, among others. [44]

3.5. Pressure Sensitive Adhesive (PSA)

The mechanism of the transdermal drug delivery system relies on firmly adhering to the skin through a pressure-sensitive adhesive (PSA). An ideal PSA should adhere firmly without causing excessive skin irritation, endure prolonged wear without losing its grip, and be removable from a surface without leaving any residue. It needs to be skin-friendly, allowing painless removal without causing trauma or residue, and capable of dissolving in small amounts. [44]

3.6. Backing Laminate

In designing the backing layer, considerations of material chemical resistance are crucial. Compatibility with excipients is also important to prevent leaching or diffusion of additives, drugs, or penetration enhancers. However, focusing excessively on chemical resistance may result in stiffness and high occlusivity to moisture vapor and air, potentially causing patch lifting and skin irritation during extended wear. The most comfortable backing exhibits low modulus or high flexibility, good oxygen transmission, and a high moisture vapor transmission rate. [56]

3.7. Release Liner

A protective layer covers patches during storage, removed before application. As the liner intimately contacts the delivery system, it must meet specific requirements concerning chemical inertness and permeation to dry, permeation enhancers, and water. [57, 58]

3.8. Other Excipients like Plasticizers and Solvents

Various solvents like chloroform, methanol, acetone, isopropanol, and dichloromethane are used to prepare drug reservoirs. Additionally, plasticizers such as polyethylene glycol and propylene glycol are added to impart plasticity to transdermal patches. [55]

4. Transdermal patches

A transdermal patch refers to an adhesive medicated patch applied onto the skin's surface to deliver a precise drug dosage through the skin into the bloodstream at a predetermined release rate within the body.[9] The transportation of a drug across the skin is influenced by several factors, including skin permeability, application area, duration of application, and the metabolic activity of the skin (such as first-pass metabolism). Each drug possesses unique properties that impact its transdermal delivery. To ensure adequate skin absorption and penetration, the drug should typically be non-ionic and relatively lipophilic to effectively traverse the skin barrier.[59]

Figure 5 Transdermal patches [31]

4.1. Components of Transdermal Patch: [60, 61, 62]

- Liner: This layer serves to protect the patch during storage and should be removed before the patch is applied for use.
- Drug: The drug solution comes into direct contact with the release liner within the patch.
- Adhesive: It functions to bind the various components of the patch together and to attach the patch onto the skin. Examples of adhesives include Acrylic, Polyisobutylene (PIB), and Silicone.
- Membrane: This component regulates the release of the drug from the reservoir, particularly in multi-layer patches.
- Backing: This film acts as a barrier, shielding the patch from the external environment.

4.2. Types of Transdermal patches

- Single layer drug in adhesive.
- The Multi- layer drug in adhesive.
- Drug reservoir -in-Adhesive.
- Drug Matrix -in-Adhesive.
- Vapour patch.

4.2.1. Single layer drug in adhesive

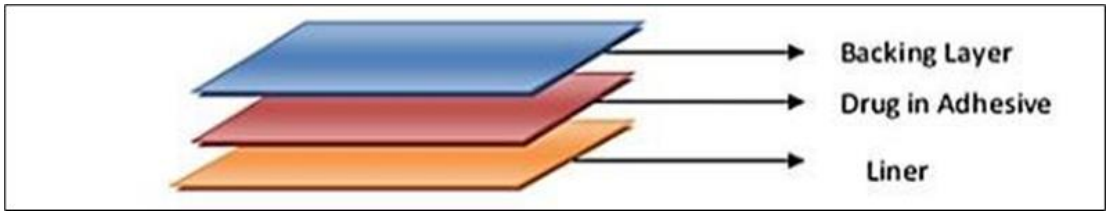

Figure 5a) Single layer drug in adhesive

In a single-layer drug-in-adhesive system, the adhesive layer not only functions as the sticky element but also houses the medication. This adhesive layer facilitates drug release while affixing the multiple layers of the system onto the skin. The adhesive layer is surrounded by a temporary liner and backing for the patch. [36] An instance of this type of transdermal product is Daytrana®, a patch containing methylphenidate. [17]

4.2.2. The Multilayer drug in adhesive

Multilayer drug-containing adhesive patches bear resemblance to monolayer systems in that both layers contribute to drug release. However, their distinction lies in the inclusion of an extra layer of drug adhesive, often separated by a membrane (although not universally present). [36] These multilayer patches find application in delivering pain medication, aiding smoking cessation, and hormone therapy, providing a useful method for prolonged drug release.[17, 63]

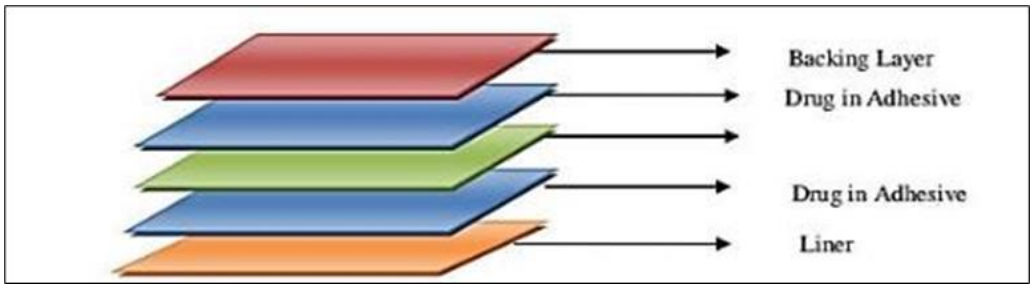

Figure 5b) Multilayer drug in adhesive

4.2.3. Drug reservoir in adhesive

A transdermal patch comprises a drug reservoir, an impermeable metallic plastic laminate backing layer, and a porous polymeric membrane regulating drug release. The membrane, made of polymeric materials like hypoallergenic adhesive polymer or ethylene vinyl acetate copolymer, controls drug release over time. [17] Within this system, the drug layer forms a liquid compartment housing a drug solution or suspension, separated by the backing layer. Notably, in this setup, the release rate follows a zero-order pattern.[9, 64]

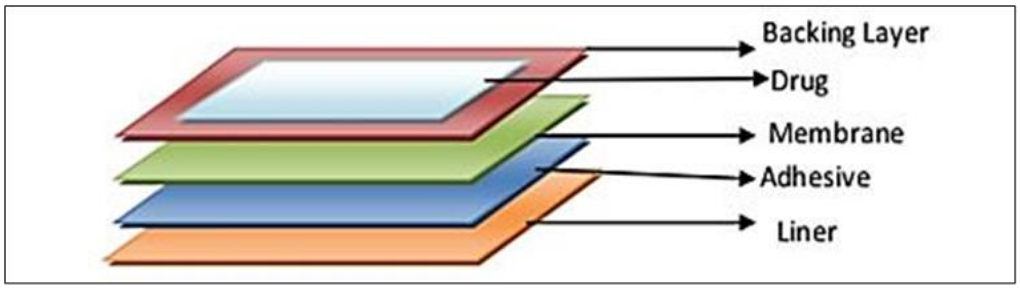

Figure 5c) Drug reservoir in adhesive

4.2.4. Drug Matrix in adhesive

In this matrix system, the transdermal patch includes a drug layer comprising a semisolid matrix containing a drug solution or suspension. The adhesive layer of this patch partially surrounds the drug layer. Notably, this particular transdermal type lacks a membrane. [65]Situated between the release liner and backing layers is a specific layer that houses the drug. [63]

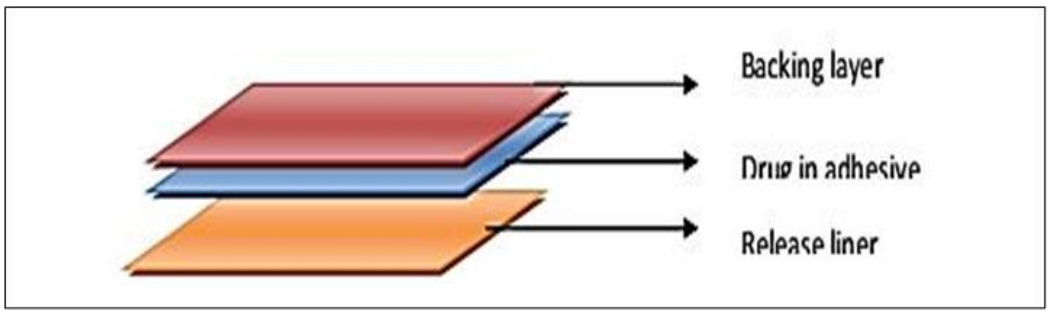

Figure 5d) Drug matrix in adhesive

4.2.5. Steam plaster

In this specific type of patch, the adhesive layer not only functions to bind the different layers together but also facilitates the release of vapor. These vapor patches, a relatively new offering in the market, release essential oils for a duration of up to 6 hours.[31]An illustration of such patches is seen in products like nicoderm CQ®, nicotine vapor transdermal patches containing essential oils aimed at aiding smoking cessation. [17] Additionally, several other types of vapor patches are available in the market, serving purposes such as enhancing sleep quality and alleviating cigarette smoking conditions. [66]

5. Factors affecting transdermal drug delivery system :[67,68]

5.1. Physicochemical properties affecting the penetration of molecules:

5.1.1. Partition Coefficient

A lipid/water partition coefficient of 1 or higher is generally necessary, and it can be modified chemically without altering the drug's pharmacological activity. An optimal partition coefficient (K) is crucial for effective action. [9, 34]

5.1.2. pH Conditions

pH primarily influences the absorption rate of acidic and basic drugs, with the unchanged form of the drug exhibiting better penetration.[69] Skin pH typically ranges from 4 to 6.[34] The transport of ionizable species from aqueous solutions displays significant pH dependence.[70]

5.1.3. C. Penetrant Concentration

Assuming membrane-related transport, an increase in the concentration of dissolved drug leads to a proportional rise in flux. Concentrations surpassing solubility levels allow excess solid drug to act as a reservoir, maintaining a constant drug constitution for an extended period.[9, 71]

5.1.4. Molecular Weight & Size

Higher molecular weight drugs exhibit lower permeation. Smaller particle sizes display higher permeability compared to larger particles. Drug molecules larger than 500 daltons can impede percutaneous transport, with increased molecular weight generally leading to decreased absorption.[34, 35]

5.1.5. Solubility

Drugs possess either lipophilic or hydrophilic natures. The partition coefficient dictates the drug's solubility or diffusion in lipid and aqueous systems. Drugs with both lipid and water solubility are suitable for percutaneous absorption since the skin comprises a lipid bilayer, necessitating some lipid solubility for absorption while also needing hydrophilicity for diffusion within the aqueous environment. [35]

5.2. Physicochemical property of drug delivery system

5.2.1. Release Characteristics

The drug's solubility in the dosage form dictates the release time. Additionally, the carrier's affinity for the drug, its solubility in the solvent, and the drug's interfacial partitioning from the formulation to the skin influence the drug's release rate. [34, 35]

5.2.2. Composition of Drug Delivery System

This not only impacts the rate of drug release but also affects the skin's permeability through hydration and interaction with skin lipids.[34]

5.2.3. Presence of Permeation Enhancers

Various categories of permeation enhancers modify skin integrity temporarily, opening skin pores for absorption. These enhancers can be chemical substances that act chemically or physical agents that interact physically with the skin. [35]

5.3. Physiological and Pathological Conditions of the Skin

5.3.1. Hydration of Skin

Hydration leads to stratum corneum swelling, providing fluidity to the skin. This increased hydration enhances permeant solubility and partitioning, facilitating drug molecule permeation. [35]

5.3.2. Skin Temperature

Elevated skin temperature increases percutaneous drug absorption by fluidizing lipids and dilating blood vessels, which elevates blood flow and enhances drug absorption.[35, 72]

5.3.3. Skin Age

Skin permeability is assumed to be higher in younger and elderly individuals compared to middle-aged individuals. Premature infants lack a stratum corneum, making children more susceptible to drug effects via the skin. [35]

5.3.4. Blood Flow

Changes in peripheral circulation influence transdermal absorption. Increased blood flow alters the concentration gradient across the skin, reducing the residence time of drug molecules in the dermis. [73]

5.3.5. Pathology of the Skin

Skin diseases or injuries alter skin penetration by disrupting lipid layers in the stratum corneum. Pathogens and injuries can rupture skin layers, changing skin integrity. [35]

5.3.6. Regional Site of Skin

Variations in anatomical features such as stratum corneum thickness, hair follicles, and sweat gland density per unit area result in differing percutaneous absorption rates. [35]

5.3.7. Skin Flora and Enzymes

The skin hosts metabolizing enzymes and microbes that metabolize drugs passing through the skin. Most drugs undergo varying degrees of metabolism in the skin before reaching the circulation. For example, about 95% of absorbed testosterone gets metabolized in the skin.

6. Evaluation parameters :[74,75,76,77]

- Thickness of the patch
- Weight uniformity
- Folding endurance
- Content uniformity test
- Moisture Uptake
- Drug content
- Shear Adhesion test
- Peel Adhesion test
- Water vapor transmission studies (WVT)
- Rolling ball tack test
- Quick Stick (peel-tack) test
- Probe Tack test
- In vitro drug release studies
- In vitro skin permeation studies
- Skin Irritation study
- Stability study

6.1. Pharmaceutical Transdermal Formulation Developments :[78,79]

Absolutely, developing effective transdermal products demands a multidisciplinary approach involving experts in pharmaceutics, biology, material science, and engineering. These professionals collaborate to ensure the successful development of an optimal transdermal system.The initial steps involve assessing the technical compatibility of the drug

with excipients and predicting skin permeability to determine the feasibility of transdermal delivery. Understanding the properties of the drug, the target patient group, and the desired delivery profile are crucial elements in this process.This comprehensive approach allows for the creation of transdermal products that offer favorable attributes, promoting better patient compliance with treatment regimens

7. Conclusion

Absolutely, review articles on Transdermal Drug Delivery Systems (TDDS) serve as invaluable resources for research scientists involved in this field. They provide detailed insights into the evaluation process, mechanisms, and optimization techniques crucial for TDDS development.The potential of TDDS is immense, catering to both hydrophobic and hydrophilic active substances, transforming them into promising deliverable drugs. However, to enhance and optimize this drug delivery system, a deeper understanding of various mechanisms of biological interactions and polymers is necessary. With ongoing advancements and a comprehensive understanding of these aspects, TDDS represents a realistic and practical application poised to become the next generation of drug delivery systems. This potential makes it an exciting area for further exploration and innovation in pharmaceutical research.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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