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Transdermal drug delivery system recent advancements: A comprehensive review

Samiksha B. Rotake, Pooja R. Hatwar *, Ravindra L. Bakal and Nitin B. Kohale

Department of Pharmaceutics, Shri Swami Samarth Institute of Pharmacy, At Parsodi, Dhamangoan Rly, Dist -Amravati (444709) Maharashtra, India.

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Abstract

"The transdermal route offers numerous benefits when compared to traditional drug delivery methods. These advantages encompass high bioavailability, the absence of first-pass hepatic metabolism, maintaining consistent drug plasma levels, and the non-invasive nature of therapy. Additionally, transdermal drug delivery systems [TDDS] provide prolonged therapeutic effects, reduced side effects, enhanced bioavailability, improved patient compliance, and easy termination of drug therapy. TDDS finds applications not only in pharmaceuticals but also in the skincare and cosmetics industries. Studies have shown that the transdermal route causes minimal skin irritation and demonstrates superior performance in various in vivo parameters compared to oral administration. This review article provides a comprehensive overview of TDDS, highlighting its advantages over conventional dosage forms, addressing limitations, discussing the components of transdermal patches, exploring different types of transdermal patches, describing methods of preparation, and outlining the ideal requirements for TDDS. Furthermore, it delves into regulatory considerations, physicochemical methods of evaluation, therapeutic applications, and recent advancements in the field of transdermal drug delivery systems."

Keywords: Tdds; Transdermal Patch; Permeation Enhancer; Partition Coefficients; Iontophoresis.

1. Introduction

"Transdermal drug delivery systems [TDDS], commonly referred to as patches, provide an alternative method for the administration of medications via the skin."These systems are designed to efficiently deliver therapeutic doses of medication into the bloodstream, achieving effective concentrations for disease treatment and prevention [1]. A transdermal patch is a medicated adhesive that adheres to the skin [2] and delivers a precise amount of medication, often aiding in the healing of injured areas [3].This method of drug administration offers several advantages over oral, intravascular, subcutaneous, and transmucosal routes [4]. It provides more effective treatment with reduced risks of adverse events, maintaining steady drug levels while overcoming the challenges of conventional oral or injectable forms. Transdermal drug delivery is particularly suitable for diseases requiring long-term, frequent dosing [5].

TDDS is less invasive and painless, allowing self-administration by patients, making it convenient and cost-effective [6]. These systems can be tailored to deliver drugs through the epidermal or dermal layers of the skin [7]. They excel in managing skin diseases by avoiding first-pass metabolism and controlling drug release over an extended period [8].The primary goal of transdermal drug delivery is to ensure a consistent and predictable rate of drug delivery into the systemic circulation, minimizing variations between patients [9]. Historically, drug-loaded patches were the earliest forms of transdermal drug delivery systems, utilizing natural adhesive materials to facilitate drug absorption through the skin [10].

* Corresponding author: Pooja R. Hatwar

This review provides an overview of advancements in the development of chemical permeation enhancers and vehicles like gels, emulsions, and vesicular delivery systems, which enhance the effectiveness of transdermal drug delivery [11].

1.1. Advantages of TDDs

- It provides a continuous and steady infusion of medication over an extended period, reducing the risk of adverse effects and therapeutic failures associated with intermittent dosing [12].
- Patients can self-administer medication using these systems [12].
- Transdermal delivery avoids the fluctuating drug levels seen with peak and trough patterns, allowing for longer and less frequent dosing intervals [13].
- It offers a faster and more convenient administration method [14].
- The absorption rate can be controlled through a multilayered structure [14].
- It eliminates gastrointestinal compatibility issues [15].
- Patients are more likely to adhere to their treatment plans as they no longer need to take multiple doses [15].
- This approach empowers patients to manage their medication independently [15].

1.2. Disadvantages of TDDs

- To be suitable for transdermal delivery, a drug must have specific physicochemical properties that facilitate penetration through the stratum corneum. If the therapeutic dose exceeds 10 mg per day, achieving effective transdermal delivery becomes challenging [12].
- Currently, only small, lipophilic drugs can be effectively delivered through the skin [13].
- Transdermal administration allows for prolonged drug delivery, but it can be costly due to complex formulations [14].
- Challenges arise with drugs that have low solubility, limited stability, a short half-life, and susceptibility to oxidation and hydrolysis. This contributes to the high cost of manufacturing [16].
- Transdermal systems have limitations regarding the quantity of medication they can handle [17].
- Transdermal delivery may result in relatively low drug levels in the bloodstream [18] due to variations in skin barrier function, influenced by factors such as skin sites and age [19].

2. Anatomy And Physiology of Skin

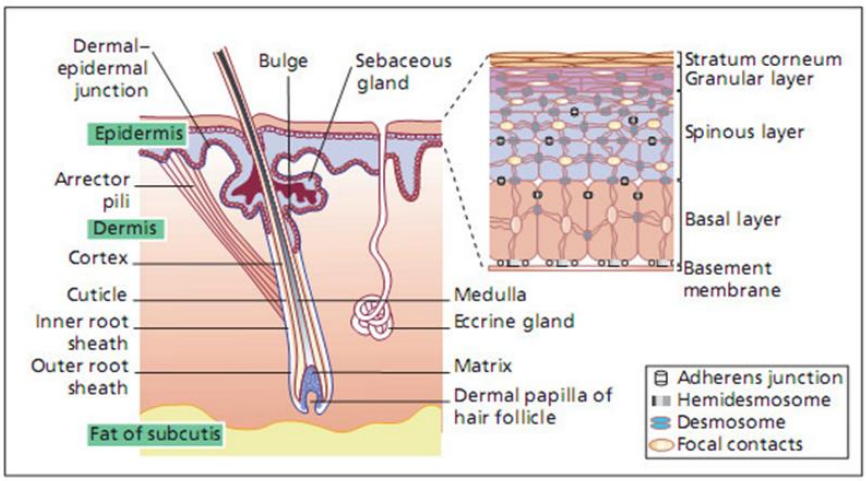

Figure 1 Anatomy and physiology of skin [20]

The skin serves as the body's primary defense against the external environment [21]. It is the largest organ, constituting approximately 16% of total body length, with a typical surface area ranging from 1.5 to 2.0 square meters and accounting for about 6-10% of total body weight. The skin consists of various layers of cells, and there are two primary types of human skin: non-hairy skin and hair-bearing skin. Hair-bearing skin encompasses both hair follicles and sebaceous glands [20].

2.1. Layers of skin

2.1.1. Epidermis

The epidermis, the outermost layer of skin, serves as a crucial tissue barrier. It comprises stratified epithelium and keratinocytes that proliferate in the suprabasal region with basal differentiation. The epidermal thickness differs, and the palms of the hands and the soles of the feet typically have a thickness of around 0.8 mm. It is organized into multiple layers of epithelial cells, and the lower layers of the epidermis are often referred to as the viable epidermis. Keratinocytes are the predominant cellular component within the epidermis [22].

2.1.2. Dermis

The dermis, positioned as the middle layer of the skin [23]. Dermis is an intricate fibro-elastic structure that imparts mechanical strength to the skin. Within this layer, there exists an extensive network of nerves and blood vessels. Pain experienced during parenteral drug delivery may arise from potential damage to the nerve endings within the dermis [24].

2.1.3. Hypodermis

The hypodermis, also known as subcutaneous fat tissue, plays a crucial role in supporting both the dermis and epidermis. It serves as a storage area for fat, contributing to temperature regulation, offering nutritional support, and providing mechanical protection. Within this layer, you can find major blood vessels and nerves that extend to the skin, and it may also contain sensory pressure organs. In the context of transdermal drug delivery, the drug needs to penetrate through all three layers [epidermis, dermis, and hypodermis] to reach the systemic circulation. On the other hand, in topical drug delivery, the primary requirement is the penetration through the stratum corneum, with drug retention in the skin layers being the desired outcome [25].

3. Skin and drug permeation

To understand the concept of Transdermal Drug Delivery Systems [TDDS], it's essential to examine the structural and biochemical characteristics of human skin that contribute to its barrier function and affect the rate at which drugs can access the body through the skin. The skin is one of the body's largest organs, covering approximately 2 square meters in an average adult. It receives about one-third of the body's total blood circulation. The epidermis, which is the outermost layer of the skin, is around 150 micrometers thick and is the result of the continuous activity of basal epithelial cells. These cells migrate from the basal layer

towards the skin's surface during the process of differentiation. Beneath the epidermis, there are additional layers, including the stratum lucidum, stratum granulosum, stratum spinosum, and stratum germinativum, collectively referred to as the viable epidermis.

The dermis, on the other hand, serves as the foundational connective tissue on which the epidermis rests and originates from the mesoderm. It consists of a dense network of connective tissue, primarily composed of collagenous fibers, along with some elastic tissue in the superficial layers. The dermis contains networks of blood vessels, lymphatics, nerves, as well as structures like hair follicles, sweat glands, and sebaceous glands.[26]

3.1. Functions of skin

- Provides a protective barrier against mechanical, thermal, and physical injury, as well as hazardous substances.
- Prevents the loss of moisture, helping to maintain skin hydration.
- Reduces the harmful effects of UV radiation from the sun.
- Acts as a sensory organ, allowing us to sense touch and detect changes in temperature.
- Assists in regulating body temperature by sweating and cooling the body when necessary.
- Functions as an immune organ, capable of detecting and responding to infections.
- Plays a role in the production of vitamin D when exposed to sunlight.

[The skin's multifaceted functions make it a vital and versatile organ in the human body.]

3.2. Barrier functions of the skin

The top layer of the skin, known as the stratum corneum, plays a pivotal role in maintaining the skin's barrier function. In this layer, individual cells are densely packed and overlap, creating a formidable defense against the entry of bacteria

while preserving the skin's moisture-retaining properties. The stratum corneum primarily consists of keratinized dead cells, and its water content is relatively low compared to other skin components. To fortify this barrier, lipids are secreted by cells from the base layer of the skin to the surface. These lipid molecules come together to form a robust, interconnected network, akin to the mortar that binds the bricks of a wall [27].

4. Basic components of TDDs

- Drug
- Polymer matrix
- Permeation enhancers
- Adhesives
- Backing membrane
- Release Linear [28]

4.1. Drug

To enable drug absorption through the skin, drugs must exhibit specific physicochemical traits. These include effectiveness, non-irritating properties, low molecular weights [up to 1000 Daltons], low melting points, short half-lives, and affinities for both lipophilic and hydrophilic compounds [29]. The selection of drugs for a Transdermal Drug Delivery System requires careful consideration to ensure successful development [30].

4.2. Polymer matrix

Polymers play a central role in Transdermal Drug Delivery Systems [TDDS] as they govern the controlled release of drugs from the system. The polymer matrix can be prepared by incorporating the drug in either a liquid or solid state. When it comes to Intramuscular Drug Delivery devices, the use of a biodegradable polymer, whether natural or synthetic, is crucial. This polymer matrix is formed by dispersing the drug within it.

For targeted drug delivery via injectable methods, the chosen polymer must demonstrate good stability and compatibility with the drug and other components of the system. It should efficiently release the drug in a secure and controlled manner.

In the realm of transdermal drug delivery systems, several types of polymers are utilized:

- Synthetic elastomers, such as polybutadiene, polyisobutylene, silicone rubber, butyl rubber, hydrin rubber, and more.
- Synthetic polymers, including polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, and others.
- Natural polymers like cellulose derivatives, waxes, gums, glycol, polyethylene, and eudragits, among others [30].

4.3. Permeation enhancers

These substances have the ability to reversibly alter the structure of the stratum corneum, thereby increasing the permeation of drugs from the skin into the bloodstream [31]. They achieve this by disrupting the highly organized intercellular lipid layers of the stratum corneum, either by inserting amphiphilic molecules or by extracting lipids. This reversible process reduces the barrier resistance, facilitating improved permeation of co-administered drugs.

An ideal enhancer should meet specific criteria: it should be inert, non-toxic, non-allergenic, non-irritating, function unidirectional, and be compatible with both the excipients and drugs used in the formulation. The effectiveness of these enhancers can vary depending on the specific drug, the characteristics of the skin, and the concentration used [26].A diffusion cell is an instrument utilized for quantifying the amount of drug that penetrates the skin [32]. These chemical compounds enhance the permeability of the stratum corneum, ultimately achieving therapeutic levels of the drug candidate. They enhance permeability by interacting with the stratum corneum [33].

4.4. Adhesives

In contrast to multi-layer drug-in-adhesive systems and single-layer systems, the reservoir transdermal system features a unique drug layer. This drug reservoir is fully enclosed within a shallow compartment made of a drug-impermeable metallic plastic laminate. Additionally, it includes a rate-controlling membrane composed of a polymer similar to vinyl

acetate on one surface. To ensure separation, a special adhesive layer, such as polyacrylates, polyisobutylenes, and silicone derivatives, is employed [31].

4.5. Backing membrane

The backing layer in a transdermal patch serves a protective role against the external environment. It needs to be impermeable to both drugs and penetration enhancers. Additionally, it functions as structural support for the entire system and shields the drug reservoir from exposure to the atmosphere. Commonly used backing materials include polyesters, aluminized polyethylene terephthalate, and siliconized polyethylene terephthalate [34].Backing laminates play a crucial role as support systems for transdermal patches [35]. These backing membranes are flexible and provide a strong bond to the drug reservoir. They prevent the drug from escaping the dosage form through the top surface and allow for printing on the patch [36].

4.6. Release Linear

During storage, the transdermal patch is typically protected by a liner that is removed and discarded just before applying the patch to the skin. This liner is considered a component of the primary packaging material rather than an integral part of the drug delivery system itself [37]. Other materials commonly used for release liners in Transdermal Drug Delivery Systems [TDDS] include polyester foil and metalized laminate [38].

5. Transdermal systems can be divided into two layer systems:

- The single-layer drug in adhesive
- The multi-layer drug in adhesive

5.1. Single Layer Drug in Adhesive

In the Single Layer Drug-In-Adhesive approach, drugs are applied as a single layer directly onto the skin, and this layer adheres to the skin's surface [Al Hanbali et al. 2019]. A typical transdermal patch comprises three main layers: a backing membrane, a drug-containing adhesive layer, and a liner layer [39]. The adhesive layer is situated between a temporary liner and a backing layer [40].

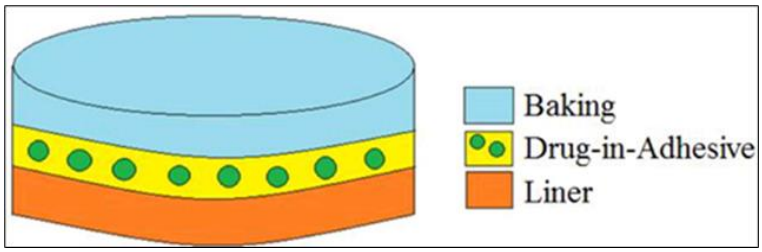

Figure 1 Single layer drug in adhesive [39]

5.2. Multi-layer drug in adhesive

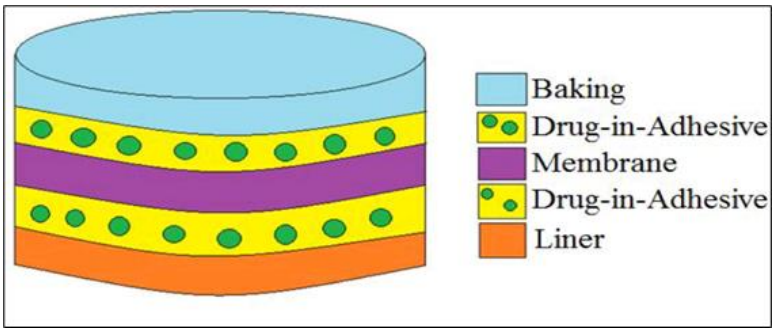

Figure 2 Multi-layer drug in adhesive [39]

Much like the single-layer approach, the multi-layer drug-in-adhesive patch releases the drug through both adhesive layers. It consists of one layer for quick drug release and an additional layer for controlled drug release from a reservoir.

However, the multi-layer approach differs in that it includes an extra layer of drug-in-adhesive, typically separated by a membrane. This is referred to as the Drug-in-Adhesive Multilayer, although it's not used in all cases. Additionally, this patch features a permanent backing and a removable liner layer [41].

5.2.1. Reservoir

Reservoir systems in transdermal drug delivery are distinguished by the presence of a liquid compartment containing a drug solution or suspension. This compartment is separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component responsible for attaching the patch to the skin can either be a continuous layer between the membrane and the release liner or have a concentric design surrounding the membrane [42].

One essential requirement for a reservoir system is that it should allow for zero-order release of the drug throughout the delivery period. Zero-order release ensures a constant and predictable drug delivery rate over time.[43]

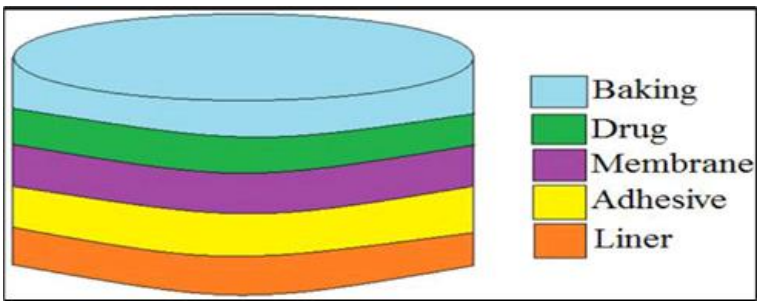

Figure 3 Reservoir [39]

5.2.2. Matrix

A simple design for transdermal patches consists of three key components: the drug, adhesive, and a mechanical backbone for the patch. In this design, the drug is embedded within a polymer network matrix, making it relatively easier to manufacture. Unlike reservoir systems, there is no rate-controlling membrane present in this design. However, it should be noted that these patches may have limited flexibility when compared to reservoir systems. The rate of drug release in such patches is primarily determined by the skin's permeability [44].

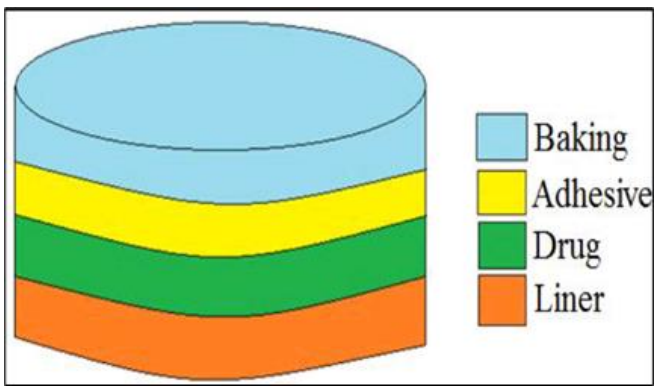

Figure 4 Matrix **[39]**

5.3. Route of drug penetration across skin

When a molecule comes into contact with intact skin, it encounters cellular debris, microorganisms, sebum, and various other materials. Subsequently, the diffusant has three potential pathways to enter viable tissue: it can pass through the hair follicles along with their associated sebaceous glands, travel through the sweat ducts, or permeate across the uninterrupted stratum corneum that lies between these skin appendages [45].

5.3.1. Transcellular route

Drugs that enter the skin through the transcellular route traverse the corneocytes. These corneocytes, which are rich in hydrated keratin, create an aqueous environment through which hydrophilic drugs can pass. The transcellular pathway

involves not only partitioning into and diffusion through the keratin "bricks" but also penetration into and movement across the intercellular lipids [46].

5.3.2. Intercellular route

The intercellular route involves the diffusion of drugs through the continuous lipid matrix. Solutes move through the intercellular lipid domains by diffusing through the horny cells in the stratum corneum, viable cells in the epidermis, and the dermis [47].

This route poses a significant obstacle for two main reasons:

- [i] In line with the "bricks and mortar" model of the stratum corneum, the interdigitating nature of the corneocytes creates a tortuous pathway for intercellular drug permeation. This contrasts with the relatively direct path of the transcellular route.
- [ii] The intercellular domain consists of alternating structured bilayers. As a result, a drug must sequentially partition into and diffuse through repeated aqueous and lipid domains.

This route is widely accepted as the most common pathway for small, uncharged molecules to penetrate the skin [48].

5.3.3. Transappendegeal route

This route is also referred to as the "shunt pathway." In this pathway, drug molecules may traverse through the hair follicles, follow the sebaceous pathway within the pilosebaceous apparatus, or use the aqueous pathway of the eccrine sweat glands. However, the transappendegeal pathway is considered of minor importance due to its relatively small surface area, accounting for less than 0.1% of the total skin surface [49].

Kinetics of Transdermal Permeation

Understanding transdermal dynamics is crucial for the successful development of transdermal devices. These dynamics involve several key aspects:

- "Horny layer absorption": Refers to the absorption of drugs through the stratum corneum, the outermost layer of the skin [50].
- "Drug absorption across skin layers": Involves the process of drug molecules permeating through various skin layers, including the epidermis and dermis, to reach the bloodstream [50].
- "The drug's absorption in the epidermal-dermal papillae": Focuses on the absorption of drugs within the structures known as epidermal-dermal papillae, which are located within the epidermis and interface with the dermis [50].

Each of these aspects plays a critical role in the overall process of transdermal drug delivery.

5.3.4. Factor affecting transdermal permeability

Physicochemical Factors

- Partition coefficient [51]

A lipid/water partition coefficient of 1 or greater is typically needed for optimal transdermal permeability. This coefficient reflects how a drug distributes between lipid [fat] and water, with values greater than 1 indicating a preference for lipid environments, which is important for transdermal absorption.

It's worth noting that chemical modifications can sometimes alter this partition coefficient without significantly affecting the pharmacological activity of the drug. This can be a valuable strategy in drug development to enhance transdermal delivery while maintaining the drug's therapeutic effectiveness.

- Skin Hydration

Skin's permeability significantly increases when it comes into contact with water. Hydration is a critical factor in promoting skin permeability. Therefore, the use of humectants is common during transdermal administration [52].

Humectants are substances that help retain moisture and maintain hydration in the skin, which can enhance the absorption of drugs or other substances through the skin.

- Temperature and pH

Temperature plays a significant role in drug permeability through the skin. As temperatures rise, drug permeability can increase dramatically, often by a factor of ten or more. Conversely, when temperatures drop, the diffusion coefficient of drugs in the skin decreases, which can affect the rate at which drugs are absorbed through the skin.[52]

- Penetrant concentration

In membrane-related transport, it's generally observed that increasing the concentration of dissolved drug leads to a proportional increase in flux, which is the rate of drug transport across the membrane. Additionally, when the drug concentration is higher than its solubility limit, any excess solid drug can act as a reservoir. This reservoir effect helps maintain a constant drug concentration at the membrane interface for an extended period, contributing to sustained drug release. [53]

- Molecular Weight

Percutaneous absorption, the process by which substances pass through the skin, is generally inversely proportional to the molecular weight of the drug. Smaller molecules tend to be absorbed more readily. For passive diffusion in a transdermal drug delivery system, the preferred molecular weight of the drug is typically less than 500 Daltons. However, the rate of permeation can be increased through the use of various penetration enhancers, which help larger molecules or substances with less favorable properties pass through the skin. [54]

5.4. Biological factors [55]

5.4.1. Skin condition

Skin serves as a natural barrier to many agents, but some substances like acids and alkalis can penetrate through the skin, especially if they are corrosive or capable of breaking down skin tissues. Methanol and chloroform are solvents known to remove the lipid fraction of the skin. They can create small openings or shunts in the skin, potentially allowing other substances to penetrate more easily. These effects highlight the importance of understanding how various agents interact with the skin's barrier properties, particularly in contexts such as chemical exposure or transdermal drug delivery.

5.4.2. Skin age

The susceptibility of skin to various substances can indeed vary among individuals and age groups. It's often observed that the skin of young children and adults can be more sensitive or susceptible to certain substances compared to older individuals. This is due to differences in skin thickness, composition, and the presence of natural protective barriers.

Some substances, like certain acids, steroids, boric acid, and hexachlorophene, may have specific side effects or adverse reactions when applied to the skin of children. Children's skin is generally more delicate and can absorb and react to substances differently than the skin of adults or the elderly. Therefore, it's important to exercise caution and follow appropriate guidelines when using such substances on children, especially in medical or healthcare contexts.

5.5. Different generations of TDDS

There are Four generations of TDDS according to the advancement of the TDDS, which are as follows.

❖ First Generation
❖ Second Generation
❖ Third Generation
❖ Fourth Generation

5.5.1. First Generation

The first generation of simple transdermal patches began to emerge in the early 1970s. After receiving the first approval from the U.S. Food and Drug Administration [FDA] for the scopolamine patch used for motion sickness, approximately 19 different patches have been commercially available to date, including nicotine, menthol, and estradiol patches.

However, the number of drugs suitable for patch formulation remains limited due to the physiological barrier presented by the epidermis. The majority of first-generation transdermal drugs are highly lipophilic, with partition coefficients greater than 10^4, small particle sizes, and molecular weights not exceeding 400 Daltons. Research during this era focused on customizing the physicochemical properties of these chemical drugs. In essence, drugs for transdermal delivery were either carefully chosen or modified to possess a high partition coefficient and a low molecular weight to facilitate their diffusion through the skin barrier [56].

5.5.2. Second Generation

The second generation of Transdermal Drug Delivery Systems [TDDSs] was developed to expand the capacity to deliver small molecule drugs through the skin. These systems are designed based on two main principles:

- Modification of Drug Properties: On one hand, drugs are modified to have suitable characteristics, such as a suitable logarithm of the partition coefficient [log P], to facilitate their transfer through the skin.
- Structural Changes in the Stratum Corneum [SC]: On the other hand, the SC structure is disrupted or pore channels are formed within the SC using various physicochemical methods. These modifications provide an additional driving force for drug entry into the skin, enhancing transdermal drug delivery efficiency.

While second-generation TDDSs laid the foundation for maximizing drug delivery efficiency, they had limitations. One significant challenge was finding the right balance between maximizing drug passage through the SC while protecting deeper tissues from potential damage. This challenge led to the emergence of third-generation TDDSs, which likely aimed to address these issues and further improve transdermal drug delivery systems. [57]

5.5.3. Third Generation

The third generation of Transdermal Drug Delivery Systems [TDDS] is characterized by a minimally invasive approach that involves disrupting the stratum corneum [SC] to allow for the penetration of large-molecule medications and even vaccines through the skin. Two key methods employed in third-generation TDDS are electroporation and microneedling [58, 59].

Electroporation involves the application of electric pulses to the skin, which temporarily disrupts the SC structure, creating temporary pores. This method allows for more effective transdermal medication distribution while safeguarding deeper tissues. Micro needling, on the other hand, uses tiny needles to create microchannel in the SC, facilitating drug delivery into the skin. These methods offer the potential for delivering a wider range of medications and vaccines through the skin while minimizing invasiveness and maintaining the safety of deeper tissues. [60]

5.5.4. Fourth Generation

Personalized therapy represents a significant departure from conventional medical treatments because it tailors the treatment to each individual's unique pathophysiological conditions. Achieving personalized therapy involves precise control of the administered dose, guided by real-time monitoring of the patient's physiological parameters. This approach helps determine the progression of the disease and the effectiveness of the drug in a highly individualized manner.

In response to the growing demand for personalized treatment, advanced transdermal delivery systems, enhanced by soft bioelectronics, have gained attention as a promising strategy for the next generation of drug delivery methods. These systems have the potential to provide more accurate and adaptable drug delivery, better meeting the specific needs of individual patients. [61]

6. Recent innovations in transdermal drug delivery system

6.1. Iontophoresis

Iontophoresis is a method that utilizes physiologically acceptable electrical currents, typically in the range of 0.1 to 1.0 mA/cm2. This electrical current is applied to facilitate the transport of charged permeants into the skin through electrostatic effects. It works by creating an electrical potential gradient that helps drive ionic drugs across the skin and into the body. What sets iontophoresis apart from other transdermal enhancement methods is its reliance on the combination of the concentration gradient [related to the drug concentration] and the electrical potential gradient as driving forces. This makes it effective not only for charged species but also for uncharged molecules, which can be delivered through a process known as electro-osmosis [62,63,64].

6.2. Electroporation

The technique you're describing is likely electroporation, a method that involves the application of an electrical pulse with a DC voltage of more than 100 volts [milliseconds]. This electrical pulse can create temporary pores or openings in the lipid bilayer of the corneocytes, which are the outermost cells of the epidermis.

Electroporation is used to enhance transdermal drug delivery by facilitating the passage of molecules that might not otherwise penetrate the skin. It can be particularly effective for small charged molecules. The application of high voltage can induce the formation of aqueous pores into the epidermis, allowing for improved drug delivery [65].

6.3. Sonophoresis

The technique you're describing is known as sonophoresis, which involves the use of ultrasound waves with an energy range typically between 20 kHz and 16 kHz for transporting drug molecules in transdermal drug delivery. Sonophoresis works by increasing the temperature of the skin, which disrupts the skin's barrier layer and allows drug molecules to permeate into different layers of the skin. To facilitate this process, the drug is often coupled with a specific coupling agent, such as a gel or cream. The fundamental principle behind sonophoresis is the thermal effect created by the ultrasound waves, which aids in the penetration of drug molecules. These ultrasound waves can penetrate the skin to a depth of about 4-6 cm. Sonophoresis is used not only in transdermal drug delivery but also in treatments for conditions like muscle soreness, tendonitis, and bursitis [66]. Additionally, iontophoresis, as mentioned in your previous message, involves the application of an electrochemical potential gradient to transport ionic or nonionic drugs in vivo. Both techniques offer valuable options for enhancing drug delivery through the skin.[67]

6.4. Microneedle

The initial discovery of micro needles dates back to 1976. ALZA Corp has recently introduced a technology known as Macro-flux, which offers the distinct advantage of being compatible with both other drug reservoirs and drug coatings. This innovative transdermal drug delivery system is gaining popularity for distributing drugs through needles. It encompasses various needle types, including solid micro needles and micro needle patches, each with unique mechanisms of action. This method is predominantly employed in the manufacturing of dissolving/hydrogel microneedles [68].

6.5. TDDS using chemical enhancers [passive delivery]

To achieve improved transdermal delivery and therapeutic effectiveness, it is essential for drugs to possess certain characteristics, including a low molecular weight [less than 1 kDa], an affinity for both lipophilic and hydrophilic phases, a short half-life, and minimal potential for causing skin irritation. Various factors influence the penetration of drugs through the skin, including the species involved, the age and location of the skin, skin temperature, its condition, the application site, exposure duration, skin moisture levels, pretreatment methods, and the physical properties of the drug. Recent research has primarily concentrated on various aspects of transdermal drug delivery technology [69].

7. Conclusion

TDDS offer significant advantages over traditional drug delivery methods, such as high bioavailability, avoidance of first-pass metabolism, consistent drug plasma levels, non-invasiveness, prolonged therapeutic effects, reduced side effects, and improved patient compliance. These systems are particularly effective for drugs requiring long-term, frequent dosing, and they provide a convenient, cost-effective, and self-administrable option for patients.

The anatomy and physiology of the skin are crucial for understanding how TDDS work. The skin acts as a primary barrier to drug penetration, and effective TDDS must facilitate drug passage through the skin layers—epidermis, dermis, and hypodermis—to reach the systemic circulation. Various components, including the drug, polymer matrix, permeation enhancers, adhesives, backing membrane, and release liner, play critical roles in the design and functionality of TDDS.

TDDS can be categorized into single-layer and multi-layer drug-in-adhesive systems, as well as reservoir and matrix systems, each with specific advantages and limitations. The route of drug penetration across the skin includes transcellular, intercellular, and trans appendageal pathways, with the intercellular route being the most common for small, uncharged molecules.

While TDDS provide numerous benefits, they also face challenges such as the need for drugs to possess specific physicochemical properties, limited suitability for high-dose medications, and higher production costs due to complex formulations. Additionally, variations in skin barrier function can affect drug delivery efficiency.

Overall, TDDS represent a promising and innovative approach to drug delivery, with ongoing advancements aimed at overcoming existing limitations and expanding their therapeutic applications.

Compliance with Ethical Standards:

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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