

TRANSDERMAL DRUG DELIVERY SYSTEMS: UNVEILING THE SCIENCE OF SKIN PERMEATION, INFLUENCING FACTORS, AND FORMULATION STRATEGIES

Abstract

One of the most innovative pharmaceutical products now on the market is the transdermal drug delivery system (TDDS), which offers a non-invasive way to distribute medication. In-depth investigation of the mechanics behind drug dispersion through the epidermis and dermis is provided, together with an understanding of the complex science controlling skin penetration. The complex interplay between the physicochemical qualities of medications, skin traits, and formulation complexities is shown by examining the impacting elements. The several parameters that impact the effectiveness of TDDS include molecular size, lipophilicity, skin thickness, and blood flow. This paper explores formulation techniques by breaking down matrix and reservoir systems and shedding light on the subtle differences between drug-in-membrane and drug-in-adhesive formulations. Carefully considered consideration is given to the design and development of transdermal patches, revealing the importance of the release liner, backing layer, adhesive layer, and drug reservoir in obtaining the best possible drug administration. Case studies highlight effective uses, such as how fentanyl and estradiol patches revolutionized pain treatment and hormone replacement therapy, or how nicotine patches helped smokers quit. To sum up, this investigation covers the science, difficulties, and potential applications of transdermal medication administration and provides a road map for physicians, researchers, and pharmaceutical industry experts. Transdermal medication administration has the potential to transform

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patient care with accuracy, efficiency, and improved treatment results as nanotechnology and smart systems redefine possibilities.

Keywords: Transdermal drug delivery system (TDDS), physicochemical, nanotechnology.

I. INTRODUCTION

Transdermal drug delivery system (TDDS) has become a viable substitute for conventional drug delivery methods. This chapter explores the complex science of skin penetration, identifying the variables that affect it and clarifying the formulation techniques used to maximize transdermal medication delivery.

The History and Development of Transdermal Medication Delivery

The use of plant extracts and other materials for medical reasons predates the idea of delivering medications via the skin by many years. On the other hand, transdermal medication administration started to become standardized and evolve methodically in the middle of the 20th century. The first transdermal patch was on sale in the 1960s thanks to the groundbreaking work of researchers like Dr. Alejandro Zaffaroni, who revolutionized the history of medication administration.

The development of novel delivery methods, improved drug permeation technologies, and ongoing formulation technique improvement have all contributed to the evolution of transdermal drug delivery. Simple adhesive patches have given way to intricate systems that can administer a wide variety of therapeutic agents, such as hormones, peptides, and small molecules, in TDDS's evolution throughout time(1).

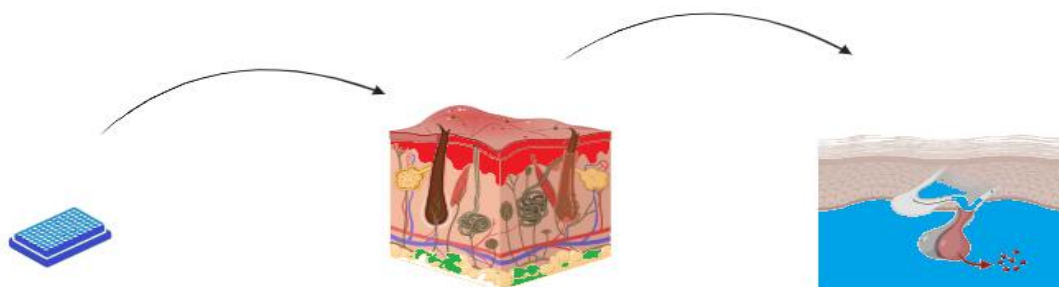


Figure 1: Transdermal Drug Delivery System

Advantages and Significance of Transdermal Drug Delivery

Transdermal medication delivery is significant because it can get around a number of issues with conventional methods of administration. There are several benefits of using TDDS:

- **Non-Invasiveness:** Transdermal medication distribution offers a non-invasive method that does not require invasive procedures or needles. In addition to improving patient compliance, this lowers the pain and infection risk connected with alternative administration modalities.
- **Steady and Prolonged Release:** Using TDDS, medications may be released gradually and under control for a longer amount of time. By limiting variations and

lowering the frequency of administration, this constant release pattern aids in the maintenance of therapeutic levels.

- **Avoidance of First-Pass Metabolism:** Transdermal administration prevents first-pass metabolism by avoiding the gastrointestinal tract, which enables a larger percentage of the delivered medicine to enter the systemic circulation unaltered. This is especially helpful for medications that the liver must extensively metabolize.
- **Increased Bioavailability:** By getting beyond obstacles like low solubility or gastrointestinal environment degradation, transdermal administration can increase the bioavailability of some medications.
- **Patient Convenience:** improved patient acceptability and convenience are fostered by the lack of frequent dosage and the simplicity of administration, which promotes improved adherence to treatment plans (2).

II. ANATOMY OF THE SKIN

Our skin, the biggest organ in our body, is a dynamic and intricate barrier that keeps out harmful substances and allows vital physiological functions to occur. Gaining an understanding of the complex structure of the skin is essential to comprehending the mechanisms involved in transdermal medication administration. The layers of the skin—the epidermis, dermis, and hypodermis—are examined in this section along with the function of skin appendages, such as sweat glands and hair follicles, in the drug-permeation process.

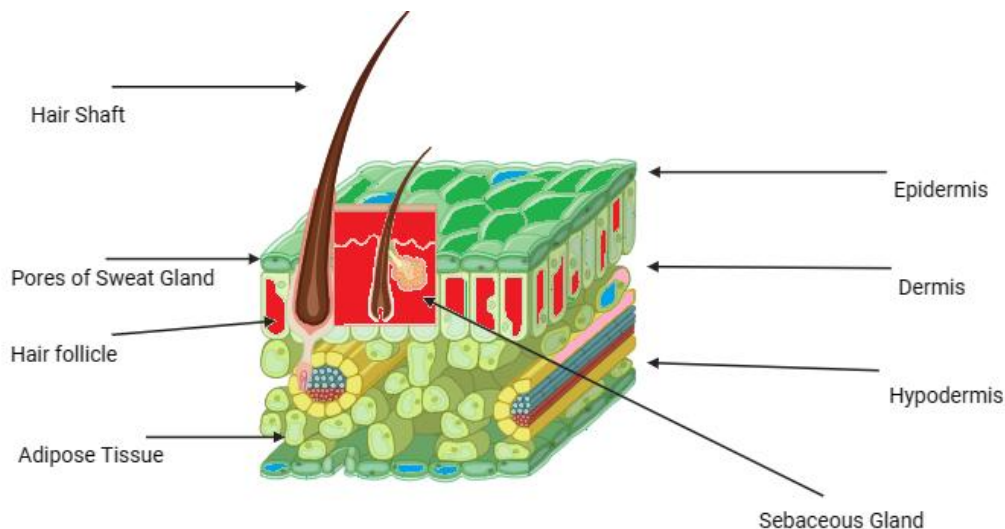


Figure 2: Structure of skin

1. Epidermis

Stratified squamous epithelial cells make up the majority of the epidermis, the skin's outermost layer. It acts as a barrier of defense, controlling water loss and blocking the entry

of germs. The stratum corneum, stratum granulosum, stratum spinosum, and stratum basale are some of the sublayers that make up the epidermis. Being the main barrier to transdermal medication absorption, the stratum corneum, with its thick arrangement of keratinized cells, is particularly significant in drug penetration.

2. Dermis

The dermis is a connective tissue layer that is rich in blood vessels, nerves, and appendages. It is located underneath the epidermis. The dermis contains vital elements like collagen and elastin fibers and gives the skin structural stability. Dermal blood vessels are essential for controlling body temperature and enabling the body to distribute medication systemically after transdermal absorption.

3. Hypodermis

Adipose (fat) tissue and connective fibers make up the hypodermis, also known as subcutaneous tissue, which is the deepest layer. It serves as a shock absorber, insulator, and energy storage device. The hypodermis modulates the kinetics of some medications' absorption and maintains the integrity of the skin overall, even though it is not directly engaged in drug penetration.

4. Hair Follicles

Dispersed across the skin, hair follicles penetrate the dermis and hypodermis from the epidermis. These follicles present possible routes for medication penetration, especially for molecules able to pass through the infundibulum of the hair follicle. Transdermal formulations' ability to distribute drugs is influenced by the size and density of hair follicles in different body areas.

5. Sweat Glands

Excretion and thermoregulation depend on sweat glands, which include eccrine and apocrine glands. Apocrine glands usually open into hair follicles, but eccrine glands are widely dispersed and open directly onto the skin's surface. These glands create sweat, which changes skin permeability and the stratum corneum's moisture status, both of which can impact how drugs are distributed(3)

III. MECHANISMS OF SKIN PERMEATION

The complex interactions between several processes that control the penetration of medicines through the layers of the skin are essential to transdermal drug delivery. The basic processes of skin permeation are explained in this section. These mechanisms include active transport mechanisms, iontophoresis and electroporation, and passive diffusion regulated by Fick's Law(4).

1. Passive Diffusion

The concept of Passive Diffusion is explained via Fick's Law. For most medications, the main way they pass through the stratum corneum and the layers of skin is by passive diffusion. It is dependent upon the drug's gradient of concentration between the target tissue and its preparation. The diffusion coefficient, the concentration gradient, and the barrier thickness are all inversely related to the rate of passive diffusion, as determined by Fick's Law, a foundational equation in the subject of diffusion.

Factors Affecting Passive Diffusion

- **Drug Properties:** Drug solubility, lipophilicity, and molecular size all have a big impact on how well pharmaceuticals diffuse passively.
- **Skin Characteristics:** The rate of passive diffusion is affected by the thickness, level of moisture, and presence of appendages.
- **Formulation Factors:** The rate of drug diffusion can be changed by using certain formulations and penetration enhancers (5).
- **Active Transportation:** Energy is used by active transport systems to move molecules against concentration gradients. While active transport is less prevalent in skin penetration than passive diffusion, it nonetheless contributes to the movement of some medications, particularly those that are big or polar (6).

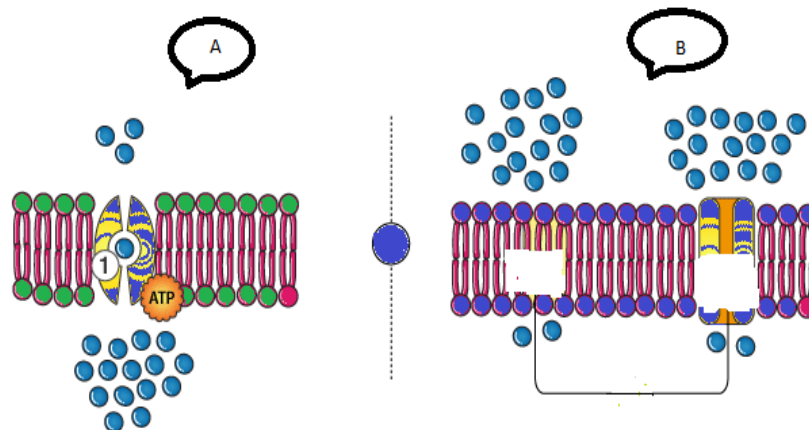


Figure 3: Diagram Presenting (A) Active and Passive Transport (B) Diffusion and Facilitated Diffusion

2. Electroporation and Iontophoresis

- **Iontophoresis:** Iontophoresis is a technique where an electric current is applied to the skin to increase the penetration of charged molecules. Iontophoresis produces an

electric field that has the ability to resist or attract charged medication molecules, therefore facilitating their passage through the skin.

- **Electroporation:** Using brief, high-voltage pulses, electroporation creates transient holes in the cell membrane. By improving skin permeability, this method facilitates more effective medication administration. When distributing macromolecules that would normally find it difficult to get through the epidermal barrier, electroporation is very helpful (7).

Factors Influencing Skin Permeation

In order to successfully develop transdermal drug delivery systems (TDDS), a thorough grasp of the many elements affecting skin permeability is required. This section explores three main types of parameters: skin features, formulation factors, and physicochemical aspects of medications (8).

- **Molecular Size:** A drug's capacity to cross the epidermal barrier is greatly influenced by its size. Larger molecules may have trouble passing through the stratum corneum, whereas smaller ones often permeate more easily.
- **Lipophilicity:** Medications that are lipophilic (fat-soluble) penetrate the skin more readily than those that are hydrophilic (water-soluble). Lipophilic compounds are more likely to diffuse in the lipid-rich stratum corneum.
- **Stratum Corneum Solubility:** The drug's penetration is influenced by its solubility in the lipid-rich stratum corneum. Drugs that are extremely lipophilic may build up in the stratum corneum, which would impact the kinetics of absorption as a whole.
- **Epidermal Thickness:** A thicker skin layer acts as a stronger barrier to the penetration of drugs. The application site selection of transdermal patches is influenced by variations in thickness in various body areas.
- **Skin Morphology:** Differences in the morphology of the skin, such as the existence of sweat glands and hair follicles, can produce barriers or favored routes for the diffusion of drugs.
- **Blood Flow:** Faster medication absorption occurs in areas with increased blood flow. Drugs absorbed via the skin are distributed throughout the body in part by means of blood vessels located in the dermis.
- **Temperature:** By raising skin blood flow and the fluidity of the stratum corneum lipids, a higher skin temperature can improve medication penetration.
- **Chemical Enhancers:** Substances that break the structure of the stratum corneum, such as alcohols, fatty acids, and surfactants, can improve medication penetration. Maintaining the safety and effectiveness of a compound requires careful penetration enhancer selection and tuning.

- **Physical Enhancers:** Drug penetration is facilitated by physical disruption of the skin barrier using techniques such as sonophoresis and microneedle arrays.
- **Polymer Selection:** Drug release and penetration are impacted by the polymer used in transdermal patches. Polymers have the capacity to regulate medication solubility, regulate release rates, and enhance the formulation's overall stability.
- **Matrix Systems:** The rate of drug release and subsequent skin penetration in matrix systems is determined by the interaction between medications and polymers (9).

Formulation Techniques

It takes a sophisticated approach to formulation to create transdermal drug delivery systems (TDDS) that work well. This section goes into the design and development of transdermal patches, including essential elements such the backing layer, drug reservoir, adhesive layer, and release liner. It also examines different formulation methodologies, such as matrix systems and reservoir systems (10).

- **Matrix Systems**
 - ❖ **Drug-in-Adhesive Systems:** In this type of system, the drug is directly incorporated into the transdermal patch's adhesive layer, which not only helps to stick the patch to the skin but also allows for controlled drug release. Benefits include ease of manufacturing, simplicity in design, and extended drug release.
 - ❖ **Drug-in-Membrane Systems:** In this type of system, the drug is dispersed within a membrane that regulates the rate of drug release. The membrane acts as a barrier, controlling the drug's diffusion through the skin. Benefits include precise control over drug release kinetics and a lower risk of skin irritation when compared to drug-in-adhesive systems (11).
- **Reservoir System**
 - ❖ **Single Reservoir Systems:** A drug reservoir is encased in an adhesive layer and an impermeable backing layer in single reservoir systems. A rate-controlling membrane allows the medication to be released from the reservoir. It enables exact control over medication release rates and the distribution of a variety of drug kinds.
 - ❖ **Multi-Layered Reservoir Systems:** Stacking different drug reservoirs with different drug concentrations is the process of creating multi-layered reservoir systems. Every layer adds something to the overall profile of drug release. Its benefits include the ability to customize medication release profiles to meet particular therapeutic needs and formulation design flexibility (12).

- **Transdermal Patches: Concept and Creation**

- ❖ **Supporting Layer:** The backing layer protects the drug reservoir and ensures appropriate skin adherence while giving the transdermal patch structural support. The choice of material influences the patch's comfort and flexibility. Impermeable materials are frequently employed to stop medication loss.
- ❖ **Medication Storage:** The formulation to be administered is stored in the drug reservoir. Its matrix might be liquid, solid, or gel depending on how it was made. For medication release to be successful, there must be ideal drug loading, homogeneous distribution, and compatibility with the chosen membrane.
- ❖ **Layer of Adhesion:** The adhesive layer facilitates medication release and guarantees that the patch adheres to the skin properly. Polyisobutylene, silicone, and acrylic adhesives are popular options. Drug release kinetics, adhesion strength, and skin compatibility are a few examples of the criteria that influence the selection.
- ❖ **Liner for Release:** Function: Before application, the release liner shields the adhesive layer; it is removed before usage. Materials that are easier to remove without sacrificing the integrity of the patch are those with poor adherence to the adhesive layer(13, 14).
- **Case Study:** In this section, case studies of three commonly used medications—nicotine, fentanyl, and estradiol—that demonstrate effective transdermal drug delivery methods are presented. The efficacy and adaptability of transdermal patches in administering a range of medicinal substances are demonstrated by these case studies.
- ❖ **Nicotine Patches:** Nicotine patches are intended to help people stop smoking by delivering a steady and regulated nicotine delivery via the skin. Reducing cravings and withdrawal symptoms related to quitting smoking is the main objective. Nicotine is mixed with an adhesive layer that sticks to the skin in a drug-in-adhesive system. Over the course of a day, the patch releases nicotine gradually and under strict supervision a better level of patient compliance as a result of daily application.

Withdrawal symptoms are lessened by gradual nicotine administration, which replicates the actual smoking experience (15,16).

- ❖ **Problems**

Skin Irritation: At the application site, some consumers may suffer moderate skin irritation.

- **Transdermal Fentanyl Patches:** Transdermal fentanyl patches are used to treat chronic pain, especially in those who need long-term opioid medication. The powerful analgesic fentanyl is delivered conveniently and under control via the patches. A rate-controlling membrane allows fentanyl to be released from a drug reservoir inside the patch. Different strengths of the patches provide customized pain treatment. Extended analgesic impact, which lessens the need for dosage adjustments (16, 17).

❖ **Problems**

Delayed Onset: It might take the patches a few hours to start working as an analgesic.

- **Estradiol Transdermal Delivery:** Hormone replacement treatment is administered to postmenopausal women using transdermal estradiol patches. In addition to providing a regulated release of estradiol, the patches are intended to relieve menopausal symptoms. The release of estradiol is regulated by its distribution inside a polymer matrix. The purpose of the patches is to introduce estradiol into the bloodstream. regulated hormone replacement with a lower chance of adverse gastrointestinal consequences(18, 19).

❖ **Problems**

Skin Reactions: A few people may have problems with adhesives or itchiness on their skin.

- **Challenges in Transdermal Drug Delivery**

- ❖ **Permeability Barriers:** Getting beyond the stratum corneum's innate barrier to medication absorption.

Problem: striking a balance between improved permeability and skin integrity.

- ❖ **Dose Loading:** Enhancing drug loading capabilities for medications with limited permeability or large molecular weight is a challenge.

Problem: Reaching therapeutic medication concentrations without sacrificing comfort or patch size.

- ❖ **TDDS and Nanotechnology:** Using nanoparticles to increase the penetration, stability, and solubility of drugs. Improving transdermal administration while resolving formulation constraints.

- ❖ **Transdermal Smart Systems:** Adaptive medicine administration and real-time monitoring through sensor integration is an example of innovation. Possibilities include better patient adherence, tailored care, and enhanced therapeutic results(20, 16).

- **Regulating Factors**

- ❖ **FDA and EMA Guidelines for Transdermal Drug Products**

Issue: Guaranteeing adherence to safety, effectiveness, and quality requirements.

Importance: Patient safety and market approval depend on regulatory scrutiny.

❖ **Safety and Efficacy Assessments**

Issue: Extended safety evaluations for transdermal systems intended for long-term usage. Continuous observation and post-marketing surveillance are essential for maintaining safety assurance (21, 19).

• **The Following were Prospective Areas of Interest for Progress in Transdermal Medication Delivery**

- ❖ **Microneedle Technology:** Microneedles have become more popular because of their capacity to make skin channels that are just a few microns in size. By getting over the stratum corneum, these needles can increase drug permeability and make a variety of medications, including macromolecules, easier to administer.
- ❖ **Nanotechnology:** As this field continues to advance, new avenues for transdermal medication administration are becoming possible. Medications can be made more stable and soluble by using nano-sized drug carriers like liposomes and nanoparticles, which also increase the medications' capacity to penetrate the skin(22, 23).
- ❖ **Smart Transdermal Systems:** Real-time physiological parameter monitoring is made possible by the incorporation of smart technologies, such as feedback systems and sensors, onto transdermal patches. This makes it possible to provide medications in a tailored and flexible way, improving each patient's treatment success.
- ❖ **3D Printing:** Transdermal medication delivery devices are now part of the pharmaceutical industry's use of 3D printing technology. This makes it possible to precisely fabricate patches with personalized medication release patterns that correspond to the treatment requirements of individual patients (20,24).
- ❖ **Hydrogel-Based Systems:** Because of their special qualities, such as their high water content and flexibility, hydrogels are being investigated for transdermal medication administration. These systems may be customized for certain uses and can deliver medications with a sustained release.
- ❖ **Microfabrication Methods:** More complex transdermal devices may be made because of developments in microfabrication methods. These gadgets may have microfluidic channels for dynamic drug delivery in addition to exact control over medication release rates(12, 25).

An emerging and Joint Strategy using Transdermal Drug Delivery System and Nanotechnology

- **Transdermal Drug Delivery System (TDDS):** Using the skin to provide therapeutic chemicals for systemic effects, TDDS is a non-invasive drug delivery technique. One of the main challenges in TDDS is removing the skin's natural barrier, specifically the stratum corneum.

- **Nanotechnology:** Materials manipulated at the nanoscale (usually 1-100 nanometers) have the potential to revolutionize medical practice. Nanotechnology provides special techniques to improve the solubility, stability, and bioavailability of drugs (20, 25).

Traditional Transdermal Delivery's Challenges

- **Permeability Barriers:** The kinds of medications that can be efficiently administered are restricted by the stratum corneum, which presents a strong obstacle to drug penetration.
- **Dose Loading:** It might be difficult for some medications to reach therapeutic levels, particularly if they have large molecular weights or low skin permeability (16, 26).

Nanotechnology's Function in Transdermal Medication Delivery

- **Nanoparticles**
 - ❖ Drugs can be encapsulated in nanoparticles, such as liposomes and polymeric nanoparticles, to increase their stability and solubility.
 - ❖ Utilizing the nanoscale passageways in the stratum corneum, nanosized carriers improve medication penetration.
- **Dendrimers**
 - ❖ Drug-carrying dendrimers are highly branched macromolecules that may be engineered with specific architectures. Their dimensions and form may improve skin penetration.
- **Nanoemulsions**
 - ❖ Made up of tiny droplets, nanoemulsions can increase transdermal penetration and provide better medication solubilization (22,23).

TDDS Benefits from Nanotechnology

- **Enhancement of Drug Adsorption:** Drug penetration and permeability obstacles can be overcome by interacting with the stratum corneum using nano-sized carriers.
- **Release under Control:** By limiting fast removal and preserving therapeutic levels, nanocarriers enable regulated and prolonged drug delivery.
- **Targeted Distribution:** By maximizing tailored distribution to certain skin layers or cells, functionalization of nanoparticles reduces systemic exposure (17,27).

New and Emerging Technologies

- **Nanogels:** In reaction to external stimuli, responsive nanogels can alter their porosity or structure, allowing for the regulated release of medications.
- **Quantum Dots:** The use of semiconductor nanocrystals known as quantum dots in imaging and diagnostics may improve the tracking of medication administration procedures.

Overcoming Conventional Obstacles

- **Optimized Dose Filling:** Despite even poorly permeable medicines, nanoparticles can effectively load and deliver larger drug concentrations.
- **Overcoming Obstacles to Permeability:** Drug transport is made easier by nanotechnology's capacity to interact with the stratum corneum, which gets over restrictions in conventional TDDS.

Smart Nanosystems

- **Responding Nanocarriers:** When the right circumstances arise for medication release, nanosystems may be programmed to react to environmental stimuli like pH or temperature.
- **Sensor Integration:** By incorporating nanosensors, intelligent transdermal systems provide adaptive drug delivery by providing real-time drug level and physiological parameter monitoring (11, 20).

IV. CONCLUSION

Transdermal medication delivery is still a potential drug administration method in spite of its difficulties. There are promising developments ahead thanks to ongoing research initiatives to overcome permeability limitations, enhance dosage loading, and use cutting-edge technology. With the ongoing advancements in nanotechnology and smart transdermal systems, tailored and effective medication administration might soon be a reality, transforming the industry and enhancing patient treatment options. Ensuring that these innovations fulfill rigorous safety and effectiveness requirements will be a key responsibility of regulatory agencies, which will enable their successful adoption into clinical practice. From its conception to its current status as a revolutionary force in the field of pharmaceutical sciences, the Transdermal Drug Delivery System (TDDS) has been an incredible journey. As we draw to a close our investigation of TDDS, it is clear that this novel approach to medication administration has not only surmounted previous obstacles but also created new opportunities for individualized, patient-focused treatment.

The advancement of TDDS over the years, highlighted by trailblazing events like the launch of the first transdermal patch for scopolamine, highlights the technology's accomplishments. This established a new standard for medication administration by highlighting the skin as a

feasible route for systemic distribution. The fact that TDDS has been expanded to include a wide range of treatment domains, such as hormone replacement therapy, pain management, and smoking cessation, is evidence of its adaptability and clinical significance.

The many processes controlling TDDS, ranging from active transport mechanisms and developing technologies like nanotechnology to passive dispersion via the stratum corneum, constitute a scientific tapestry. The way to successful transdermal medication administration has been made clearer by our growing understanding of the physicochemical properties of medicines, skin traits, and formulation techniques. As these mechanisms are uncovered, new avenues for improving current systems and creating innovative ones keep opening up.

Future Horizons: TDDS has a bright and promising future ahead of it. A new age of precise control over drug release, better dose loading, and greater penetration across the skin barrier are made possible by the incorporation of nanotechnology. The emergence of smart transdermal systems, which possess sensors and adaptive capabilities, portends a personalized medicine future in which therapeutic treatments are customized to meet the specific requirements of each patient.

Ongoing Innovation and Exploration: Rather than coming to an end, the TDDS adventure continues as researchers go deeper into uncharted territory and improve upon preexisting ideas. The investigation of responsive nanocarriers, quantum dots, and other cutting-edge technology demonstrates the continuous search for innovation. Regulatory factors guarantee that safety and effectiveness are prioritized, creating an environment that is favorable for the creation and application of innovative TDDS.

In summary, the Transdermal Drug Delivery System is a perfect example of how tradition and innovation may coexist, fusing past successes with forward-thinking goals. Its effects on treatment efficacy, convenience, and patient care are seen throughout the medical community. The future looks bright as we negotiate the challenges of formulation techniques, skin penetration, and developing technology. Drug delivery is still being shaped by TDDS, which encourages scientists, doctors, and other pharmaceutical workers to push the envelope and rethink what patient wellbeing looks like. As the journey continues, the prospect of consistently improving transdermal medicine delivery in the future beckons.

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