



The Evolution of Transdermal Drug Delivery: From Patches to Smart Systems— A Review

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ABSTRACT

Transdermal drug delivery (TDD) has evolved significantly from its inception into a viable, non-invasive, and patient-centered option for drug delivery. This review presents an overview of TDD, how it began, the mechanisms of TDD, and the issues surrounding TDD in a larger context; the growing shift from passive diffusion-ranged methods to smart transdermal delivery systems is also discussed. Historically, drugs delivered through TDD adhered to passive diffusion methods, and only small lipophilic molecules could be delivered transdermally. However, recent developments have led to transdermal drug delivery systems that employ methods that [permeation enhancers, microneedles, and other nanocarrier methods have broadened the number of drugs delivered transdermally]. Transdermal drug delivery systems include smart TDD systems that incorporate biosensors, microelectronics, and responsive materials for deliverable options for selective precision, control, and peri-care delivery of drugs. Smart systems are being developed for multiple disease areas, including diabetes care, pain management in advanced cancer, hormone therapy, and neurological disorders. Smart transdermal systems targeting the regulatory changes that accompany smart devices for the biopharmaceutical markets have implications for pharmaceutical and medical devices. Electronic smart TDD systems are a burgeoning market and are emerging due to increased demand for patient-centered technologies, while advances in technology have led to classic approaches integrating with emerging technology. Future directions in TDD could include AI, wireless approaches, and system co-injection with biologics and vaccines in the future (including multiple use!), etc. Developments and progress in smart TDD systems, growing interest, and advances in materials, nanotechnology, and bioelectronics mark the next generation of smart partnerships and TDD interventions to push drug delivery forward and better patient outcomes.

Keywords: Transdermal drug delivery, Smart transdermal systems, Drug permeation, Microneedles, Nanocarriers, Biosensors, Personalized drug delivery

INTRODUCTION

Transdermal drug delivery (TDD) has become an important alternative to the traditional oral or parenteral drug administration with advantages that include improved patient compliance, a controlled release of drug, and avoiding the hepatic first-pass metabolism. The use of the skin as a route for delivering therapeutic agents is not entirely new, as medicines and herbal formulations have been applied to the skin for localized therapy for centuries. However, the modern era of transdermal drug delivery initiated in the late 20th century with the introduction of scopolamine in the first transdermal patch approved for use in 1979, representing the first pathway for transdermal drug development [1]. The skin presents a significant barrier to drug permeation due to the stratum corneum as a barrier to the entry of transdermal systems, and they were limited to relatively small, lipophilic, and low molecular weight molecules. But over the years there have been many new enhancement techniques presented in the literature, including chemical enhancement techniques, iontophoresis, and microneedle-based based techniques [2]. Although conventional transdermal patches have shown significant benefit in the clinical delivery of certain therapeutic drugs like nicotine, fentanyl, and clonidine, they exhibit drawbacks in terms of unpredicted absorption of drug delivery, potential skin irritation, or limitations in drug dosing. This limitation has led to the shift from conventional patches to more modern smart transdermal systems. Technological advances such as wearables with integrated sensors and stimuli-responsive drug release methods have changed transdermal therapy and allowed a higher level of control when it comes to drug delivery and monitoring patient response [3]. The desire for new smart transdermal systems is increasingly driven by advances in nanomedicine, artificial intelligence (AI), and the Internet of Things (IoT). Modern smart transdermal systems integrate microelectromechanical systems, biosensors, and programmable delivery platforms to improve patient compliance and the efficacy of therapeutic agents. As the pharmaceutical industry pivots toward individualized, patient-focused care, smart transdermal systems are expected to continue to play a significant role in drug delivery solutions in the future [4]. It will study the evolution as well as developments in modern, smart drug delivery systems through the historical perspective. The article will include highlights on all the milestones, mechanisms of drug permeation, older delivery via patches, emerging technologies, and regulatory considerations and challenges. Not least, it points out current challenges and future directions that could lead to another revolution in the next generation of transdermal drug delivery systems [5].

HISTORICAL OVERVIEW OF TRANSDERMAL DRUG DELIVERY

The historical background of transdermal drug delivery (TDD) is evident in ancient cultures, which included topical application of medicines as extensive efforts for their therapeutic properties. Early medical practices of Egyptian, Greek, and Chinese civilizations employed extracts of herbs, ointments, and poultices to treat a number of illnesses through dermal absorption. Nevertheless, these methods lacked scientific confirmation but formed the primary basis for percutaneous drug delivery [6].

Medical exploration of TDD achieved relevance during the 20th century, when two principal concepts emerged: a better understanding of the physiology of the skin and the permeability of drugs to it. During the 1940s and 1950s, scientists researched how certain drugs appeared to penetrate the stratum corneum, the outer layer of the skin. This was the beginning of an entire field of studies that led to the first experimental transdermal formulations. These early studies began the process of further characterizing both controlled and systemic drug delivery through the skin and began the differentiation of transdermal from topical drug delivery [7].

In 1979, TDD saw a substantial milestone with the approval of the first transdermal patch for scopolamine that was intended for the alleviation of motion sickness. This innovation demonstrated that drug delivery using the skin was possible and marked the beginning of transdermal therapeutics for commercial use. Following the breakthrough of scopolamine patches, nicotine patches became available in the early 1990s to help people cease smoking, lessons that were significant in expanding the clinical use of TDD [8].

After scopolamine and nicotine patches, the application of TDD during the late 1990s and early 2000s diversified, in part, due to the improvement of formulation science and polymer sciences, as well as drug permeation enhancers. Examples included fentanyl patches for pain control, contraceptive hormone patches and testosterone delivery with patches, and clonidine patches for hypertension. While passive drug diffusion was successfully established in TDD, resulting in these examples, the inherent limitations of passive diffusion drug delivery, such as low drug permeability and drug selection, incited further research development of innovative drug penetration technologies [9].

Recently, the evolution of TDD, occurring in the last few decades, has surpassed the use of conventional patches to include new methods such as microneedles, iontophoresis, and sonophoresis, and advanced systems for smart drug delivery. Such systems promote drug absorption, provide real-time monitoring, and enable personalized dosing, hence circumventing the concerns surrounding the field of transdermal therapeutics. Therefore, the field has transitioned from simple patch-based delivery to advanced platforms integrated with sensors that use nanotechnology and digital health innovations for patient benefit [10].

MECHANISMS OF TRANSDERMAL DRUG DELIVERY

Transdermal drug administration (TDD) refers to drug delivery that enters the body as transdermal systems and bypasses the skin barrier to reach systemic circulation. The skin plays an important role in protecting the body against alien substances. The penetration process of drugs is complicated due to all this. Factors affecting TDD include physicochemical properties of the drugs, formulation composition, and penetration-enhancing techniques used [1].

Skin structure and barrier function

The skin comprises the three layers of epidermis, dermis, and hypodermis. Among these, the stratum corneum is the outermost layer and the major barrier to permeation of drugs. It consists of keratinized corneocytes embedded in a lipid matrix and, together with these structures, severely limits the diffusion of most hydrophilic and high-molecular-weight drugs yet permits the absorption of very small lipophilic molecules (less than 500 Da) by passive means through skin tissues [6]. Under the stratum corneum, some resistance is provided by the viable epidermis and dermis, which allow drug molecules that successfully break across the outer barrier to diffuse out into the capillary-rich dermal layer for systemic absorption [7].

Drug Penetration Pathways

Drugs can move through the skin via three main pathways:

1. **Transcellular Route**—This is where the drug molecules move directly through the corneocytes and into the lipophilic and aqueous domains. The transcellular route is most direct but extremely restrictive, mainly due to corneocytes being keratinized and therefore having a strong structure, which limits the penetration of most drugs [11].
2. **Intercellular Route**—The intercellular route is the primary pathway for transdermal uptake, as drug molecules diffuse into the local lipid content between or around the corneocytes. This route most favors lipophilic drug molecules due to the stratum corneum being lipid-rich as an outer barrier of the skin [3].
3. **Appendageal Route**—Known as the shunt pathway, this pathway occurs when drug compounds penetrate the skin surface into hair follicles and sweat glands. The appendageal route can provide an additional pathway, especially for hydrophilic and larger drug molecules; however, these appendageal structures only comprise a small portion of the total skin surface area, limiting the dynamic overall for drug uptake [12].

Factors Affecting Transdermal Absorption

Multiple variables impact drug diffusion through the skin, including the following:

1. Drug Physicochemical Properties - Suitable drugs for TDD are small (≤ 500 Da), lipophilic, and have moderate partition coefficients (log P between 1 and 3), allowing skin permeability and solubility in systemic circulation [2].
2. Skin Hydration - More hydrated skin enhances drug penetration due to the lipid matrix of the stratum corneum being disrupted, thereby decreasing the barrier function [13].
3. Temperature and Blood Flow - Increased temperature and blood flow in the dermis may drive greater diffusion of the drug through the skin and absorption into systemic circulation [14]. Use of Permeation Enhancers -

Some chemical enhancers (e.g., ethanol, terpenes, surfactants) are used to alter the lipid matrix and enhance drug permeation. One partnership concern is the potential for skin irritation and systemic toxicity with too much enhancer [15].

Recognizing these mechanisms and influential factors is important for developing effective TDD systems. New advances in penetration enhancement, such as microneedles and electroporation, continue to broaden the types of drugs available for TDD, creating significant advancements in transdermal engineering [10].

TRADITIONAL TRANSDERMAL PATCHES: ADVANCEMENTS AND LIMITATIONS

"Transdermal patches have long been a pillar of transdermal drug delivery (TDD) since their initial commercial approval at the end of the century. These patches have many advantages over traditional routes of drug administration, including continuous drug delivery, enhanced patient compliance, and avoidance of hepatic first-pass metabolism. Over the years, there have been vast improvements in patch technology, culminating in more efficacious and patient-friendly systems; nevertheless, there are also drawbacks to traditional transdermal patches due to their restrictions for suitable off-label use to a limited number of drugs [1].

Types of Transdermal Patches and Their Mechanisms

Transdermal patches can be classified into three types depending on the design and drug release mechanism—reservoir patches, matrix patches, and drug-in-adhesive patches. Reservoir patches contain a liquid or gel drug formulation inside a membrane, which controls the release rate. Matrix patches are drugs incorporated into a polymeric matrix and released based on diffusion. Drug-in-adhesive patches, the newest category, incorporate drugs directly into the adhesive that allows for uniform drug distribution and perfect skin adherence [16]. Years of improvements have achieved the clinical success of patches targeting nicotine, fentanyl, clonidine, and hormonal therapies [17].

Benefits of Traditional Transdermal Patches

Probably the most significant advantage of transdermal patches is their ability to facilitate controlled and sustained drug release and improve fluctuations in plasma drug levels and side effects. Moreover, transdermal administration improves patient adherence by eliminating the need for frequent dosing, which is especially beneficial for chronic conditions such as pain management and hormone replacement therapy [13]. Another advantage is the avoidance of gastrointestinal degradation and first-pass hepatic metabolism, as with many drugs it improves bioavailability and reduces systemic toxicity, such as nitroglycerin and estradiol [18].

Limits and Obstacles of Traditional Patches

Even though these modes of delivery have a variety of advantages, their widespread application has met a number of challenges. The most critical is that transdermal delivery is restricted to a limited number of drugs; only small, lipophilic molecules with a molecular weight ≤ 500 Da and an appropriate partition coefficient (log P of 1 to 3) permeate the stratum corneum satisfactorily [2]. In addition, skin irritation and allergic reactions can occur simply from prolonged adhesive and excipient contact, creating discomfort and noncompliance with the patch in patients [19].

Another notable limitation is the variability in drug absorption from different skin and anatomical sites, which yields variability in outcomes from therapy. In addition to that, the patch has a low drug-loading capacity that restricts the use of high-dose medications; patches are also not appropriate routes of administration for medications that need high systemic concentration doses, such as antibiotics and biologics [15].

Recent Advancements to Overcome Limitations

As a result of the increased willingness following these hurdles to expand the number of transdermal drugs, there is now more innovation testing for permeation enhancers, microneedles, and nanocarriers. Chemical enhancers, including terpenes, fatty acids, surfactants, etc., are focused on enhancing skin permeability, and physical enhancers such as iontophoresis and ultrasound enhance the diffusion of these drugs [10]. In addition to these more conventional physical enhancers, new strategies are in development, including water-soluble polymers or bioadhesives, which create adhesion, help reduce irritation, and increase wear time [20].

Viewing normal transdermal patches, which changed the landscape of drug delivery, on the one hand has its limitations and has led to more intelligent transdermal systems being developed for remote digital monitoring, sensor-controlled drug delivery, and personalized medicine. These technological improvements represent the next generation of transdermal therapy in the continuum of knowledge by which drug efficacy, safety, and patient compliance improve. [4]

EMERGING TECHNOLOGIES IN TRANSDERMAL DRUG DELIVERY

The shortcomings of conventional transdermal patches have led to the introduction of novel technologies like microneedles, iontophoresis, sonophoresis, nanocarriers, and smart transdermal systems. These technologies can enhance drug permeability, increase patient compliance, and expand drug types for transdermal delivery [1].

Microneedles

Microneedles (MNs) create microchannels in the skin, enabling effective delivery of peptides, proteins, and vaccines. Microneedles can be solid, coated, dissolving, or hollow, although dissolving and hollow microneedles can achieve precise release. Microneedles have been shown to effectively deliver insulin and vaccines and manage pain, thus lessening the burden of injections [10, 2].

Iontophoresis and Electroporation

Iontophoresis involves delivering small amounts of drug using a low-intensity current through the skin. Electroporation, on the other hand, uses high-voltage pulses to create temporary pores in skin, which can enhance drug permeation. Both iontophoresis and electroporation show promise for drug delivery of peptides, proteins, and therapies based on genes, although it is especially important to achieve precision in the application to reduce skin irritation concerns [19, 21].

Sonophoresis and Ultrasound-Enhanced Delivery

Only ultrasound waves are used in sonophoresis to disrupt the skin barrier and aid in drug penetration. Sonophoresis works really well with corticosteroids and insulin, as well as chemotherapy drugs, especially with nanocarrier systems to improve solubility and stability [22].

Nanocarriers in Transdermal Systems

The nanocarrier, which is liposomes, ethosomes, and polymeric nanoparticles, can enhance solubility, stability, and target delivery of the drug. Ethosomes can penetrate hydrophilic molecules faster, while polymeric nanoparticles allow controlled release of these molecules, facilitating their chronic use [23,24].

Smart Transdermal Systems

Recent technological evolution in biosensors, wearable devices, and artificial intelligence (AI) machinery enabled intelligent transdermal patches determined by/ governed via physiological signal reading and drug release responsive to these physiological signals. Examples include sugar-responsive human insulin patches and programmable drug patches capable of delivering real-time, patient-specific doses for patient compliance and patient treatment effectiveness [4, 25].

Future Considerations

The allocation of nanotechnology, bioelectronics, and AI is currently affecting the direction of the intelligent transdermal drug delivery drug patch market. All the technologies have immeasurable future potential, but costs, scale, and regulatory approval will need to be addressed for clinical implementation [26].

SMART TRANSDERMAL DRUG DELIVERY SYSTEMS

Transdermal drug delivery has evolved into smart transdermal drug delivery systems (TDDS) that utilize advanced technologies including biosensors, microelectronics, and responsive polymers of both hydrophilic and hydrophobic origins for improved drug absorption, controlled release, and real-time health parameter monitoring to enhance adherence and treatment outcomes [1].

Biosensor-Integrated Transdermal Patches

Biosensor-based transdermal patches are designed for continuous monitoring of physiological parameters, including glucose, temperature, pH, and sweat biomarkers, to deliver specific medication to the patient at the correct dose. For example, glucose-responsive insulin patches use microneedles containing loaded insulin and glucose-responsive polymers to release insulin on demand from glucose levels in blood. This bioregulatory approach largely improves diabetes management as it reduces multiple daily glucose monitoring and injections of insulin [4, 25].

Electric and Thermally Controlled Systems

Smart TDDS also use external stimuli, such as electric fields (iontophoresis), ultrasound (sonophoresis), and thermal energy for drug penetration. These can include wearable iontophoretic patches where mild electrical currents transport charged drug molecules through the skin and thermoresponsive hydrogels that swell and contract in response to body temperature to regulate drug release. There is a high degree of control overdose delivery, and these technologies have been investigated for pain management, hormone therapy applications, and cardiovascular drugs [19, 21].

pH- and Enzyme-Responsive Drug Delivery

Some smart transdermal patches utilize pH-sensitive and enzyme-responsive polymers to release drugs in a controlled manner in response to biological changes. For instance, the patches used for cancer therapy release chemotherapeutic agents only in the presence of tumor-specific enzymes, thus reducing systemic toxicity. Likewise, pH-sensitive hydrogels can be manufactured to release antibiotics or anti-inflammatory drugs based on the pH of the epidermis, following the presence of infected or inflamed skin [24].

Wireless and Wearable Drug Delivery Systems

In recent years, wireless, transdermal systems designed with Bluetooth technology have emerged, enabling healthcare professionals to remotely monitor both drug administration and patient responses. Wearable patches can be programmed to deliver drugs on a specified schedule or on-demand, which can help to improve adherence for patients taking long-term medications, including those for hypertension or psychiatric disorders [26].

APPLICATIONS OF SMART TRANSDERMAL DRUG DELIVERY

Smart transdermal drug delivery systems (TDDS) changed the drug delivery landscape, as they allow targeted, controlled, and patient-specific drug delivery. These systems administrations have made their way into multiple therapeutic areas, including diabetes treatment, pain relief, hormones, cardiovascular drugs, and neurological drugs, to name a few. Smart TDDS could potentially provide improved drug absorption, fewer systemic side effects, and enhanced patient compliance through the application of biosensors, microelectronics, and nanotechnology [1].

1. Diabetes Management

One area where smart TDDS appear especially promising is in the delivery of insulin for the treatment of diabetes. Glucose-responsive insulin patches utilize glucose-sensitive polymers that incorporate microneedles to release insulin in accord with changes in blood glucose levels. Patches of this design can ameliorate the number of subcutaneous injections required and simultaneously improve adherence and reduce the risk of hypoglycemia [4, 25].

2. Pain Management and Analgesic Delivery

Smart transdermal patches (TDPs) are commonly used in pain management, particularly for opioid and non-opioid analgesics (e.g., fentanyl, lidocaine, diclofenac). These TDPs provide a sustained release of the drug, which can reduce the need for p.m. analgesics and the gastrointestinal side effects due to oral administration of opioids and non-opioid analgesics. Some of the more advanced systems created to prevent overdose and provide optimal analgesia in the user involve iontophoresis and microelectronics, which modulate drug release based on the needs of the patient [19, 21].

3. Hormone Replacement Therapy (HRT)

Route of hormone therapy delivery, including in patients with menopause, hypogonadism, and disorders of endocrine hormone composition, has rapidly advanced with smart TDDS. Patches, for example, to deliver estrogen and testosterone can deliver stable pharmacologic levels, rather than fluctuate highs and lows that can create mood swings and metabolic derangements in patients. The smart patches have controlled-release hydrogels, allowing the drug in each patch to be regulated by the body (i.e., by temperature and time of day) [24].

4. Management of Cardiovascular Drug Delivery

Smart transdermal drug delivery systems (TDDS) have been designed and employed in clinical practice for treating hypertension and cardiovascular diseases that allow advanced distributions of medications (like nitroglycerin and a beta-blocker) through biosensor systems that monitor physiological parameters like heart rate and blood pressure, distributing medication when values are abnormal. Thus, they are limited as drugs that enhance therapeutic outcomes but minimize abnormal side effects like hypotension or tachycardia [26].

5. Management of Neurological and Psychiatric Disorders

Transdermal patches have become more readily used in the treatment of neurological and psychiatric conditions such as Parkinson's disease, depression, and schizophrenia. Rotigotine patches can provide continuous dopamine receptor stimulation to treat the motor symptoms of Parkinson's patients that have been traditionally treated with systemic administration of medication. Antidepressant and antipsychotic medications that are administered transdermally can provide drug levels over a longer duration and less variability from peak levels and therefore a lower risk of relapse and improved adherence versus medication that is taken orally [22, 27].

6. Healing Wounds and Skin Disorders

Smart TDDS has made reasonable advancements in healing— including dermatologic conditions such as psoriasis, eczema and chronic ulcers— through its targeted and controlled release of growth factors, anti-inflammatory agents, and antimicrobial drugs. Some systems utilize electrostimulation or light-activated delivery systems to promote more rapid tissue repair and increase the absorption of drugs at the site of action [28].

REGULATORY CONSIDERATIONS AND MARKET TRENDS

The progress and marketing of transdermal delivery systems (TDDS), especially "smart" TDDS, necessitate adherence to strict regulations to guarantee their safety, efficacy, and quality. At the same time, transdermal technology markets are greatly expanding, driven by the aversion to injections, patient-friendly dosage forms, and increased technological advancements [1].

1. Regulatory Frameworks for Transdermal Drug Delivery

Regulatory entities, such as the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and other global regulatory bodies, impose strict guidelines to gain approval of TDDS. The FDA considers transdermal patches to be combination products, which products, which also means they meet the requirements of both drugs and medical devices. The development of TDDS will require wide-ranging preclinical and clinical studies to assess their pharmacokinetics, bioavailability, and overt safety [29]. Smart TDDS, especially those that involve biosensors, microneedles, and/or nanotechnology, are in the realm of measuring digital health technologies and medical device regulations. When developed smart TDDS, the constructed systems will require manufacturers to also meet Good Manufacturing Practices (GMP), International Council for Harmonization (ICH) guidelines, and ISO standards for wearable medical devices. Furthermore, such high-risk innovations may also exceed regulatory requirements involving the FDA 510(k) clearance or premarket approval (PMA) pathways [30].

2. Challenges in Regulatory Approval

In spite of technologically advanced progress, regulatory approval will remain a central roadblock to smart TDDS manufacturing. These roadblocks include:

- Skin absorption will be variable by patient as a result of variability in skin physiology.
- Clinical trials will be longer trials, given the requirement for lengthier evaluation of safety and efficacy.
- Device-drug interaction studies will be required at the point of proving efficacy, given the biosensors and electronic components contained in TDDS.
- Ongoing monitoring of adverse effects and system malfunction will be required post-marketing and will require pharmacovigilance [24].

To work through such barriers, researchers and manufacturers would need to have relevant, early discussions with regulators concerning their TDDS. Strong pharmacovigilance programs will be necessary, as will design, development, manufacturing, research, and testing based on interdisciplinary regulatory discussions with pharma and medical device regulations [21].

3. Market Trends in Smart Transdermal Drug Delivery

The global market for transdermal drug delivery systems is opening and growing, with projections of a compound annual growth rate (CAGR) of more than 8% from 2023 to 2030. Key factors driving this increased demand are

- Increased prevalence of chronic conditions (i.e., diabetes, cardiovascular disease, neurological disease)
- Higher demand for non-invasive drug delivery approaches to support patient adherence
- Tech advances in wearable medical technology, including real-time monitoring and regulated drug delivery [31].

The higher-profile companies in the industry— Novartis, Johnson & Johnson, Medtronic, and 3M— are making heavy investments in the development of next-generation transdermal patches, including microneedle-based delivery, nanocarrier-based delivery, and personalized drug-dosing abilities. New startups are also looking at AI-driven TDDS, which will help aid in delivery through automated changes in dosing based on real-time physiological data. [26]

FUTURE DIRECTIONS AND INNOVATIONS

The area of transdermal drug delivery systems (TDDS) is rapidly changing by the intersection of advanced biomaterials, nanotechnology, and artificial intelligence (AI). Future advances will provide solutions to current limitations of drug permeability, precision dosing, and real-time monitoring. The new generation of TDDS will transform drug delivery by facilitating personalized medicine, boosting bioavailability, and increasing patients' adherence [1].

1. Smart and responsive transdermal systems

- Emerging TDDS are being manufactured using stimuli-responsive materials that enable on-demand drug release in response to an environmental or physiological signal. Examples of this development include:
- pH-sensitive hydrogels that release drugs when the calm pH is reached.
- Thermoresponsive polymers that alter drug delivery in response to naturally occurring body temperature changes.
- Enzyme-triggered release mechanisms designed for target area delivery and disease response strategies [4].

These innovations serve to improve drug delivery while minimizing systemic side effects. Wearable, biosensor-integrated patches will further enhance precision by assessing biomarkers and modifying drug release rates, viscosity, and rate of absorption [25].

2. Microneedle Arrays and Nanotechnology-Enhanced TDDS

Microneedle technology is expanding within the category of minimally invasive assessments to enhance transdermal drug delivery. Future advances will include:

- Biodegradable microneedles to minimize the potential for residual waste after drug administration.
- 3D-printed microneedle patches to support personalized drug formulations and, potentially, rapid prototyping.
- Microneedles that incorporate nanoparticles to enhance delivery of biologics/macromolecules, such as insulin, vaccines, and monoclonal antibodies [19, 21].

Nanotechnology-based TDDS systems could improve transport across the skin barrier and be used to increase bioavailability and, therefore, transdermal delivery of large-molecule drugs that have previously been delivered via either oral or injectable methods [24].

3. AI and Machine Learning for Personalized Drug Delivery

Artificial intelligence (AI) and machine learning are expected to lead to TDDS systems that can operate as highly personalized therapeutic systems. AI-based TDDS systems will be able to:

- Analyze real-time patient data that is collected through biosensory technology to administer personalized drug dosing.
- Predict skin permeability changes based on genetic and physiologic characteristics of the patient.
- Optimize drug formulation through deep learning algorithms [26].

Such systems could help to create a transformative change in the management of chronic disease through automatic, patient-specific drug delivery with a low burden [32].

4. Merging Wireless and IoT-Enabled TDDS

The development of smart TDDS will focus heavily on wireless functionality and the integration of Internet of Things (IoT) devices. Specifically, the following will be seen:

- Bluetooth-enabled patches for remote monitoring and
- Intervention: Cloud-based patient drug adherence systems to improve patient compliance. Patches that utilize electrostimulation for the purpose of enhancing drug delivery via rate of absorption [27].

All of these efforts will result in the ability to remotely modulate drug delivery for real-time improvement of TDDS efficiency in telemedicine and home care for patients [28].

5. Transdermal Delivery of Vaccines and Biologics

A new emerging direction in TDDS development is the transdermal delivery of vaccines and biologics. A group of investigators is developing microneedle vaccine patches designed to be self-administered that could:

- Replace the need for any trained healthcare professionals being needed to administer the vaccination.
- Improve global distribution of vaccines, as there is no need to worry about storage or transport because of refrigeration or cold chain considerations.
- Improve immune response due to localized antigen presentation in the skin [33].

This area of research is most timely considering the current pandemic preparedness and mass immunization [34].

CONCLUSION

The advancement of transdermal drug delivery systems (TDDS) has redefined drug administration with a non-invasive option to traditional routes of therapy, including oral and injection. Currently, we are experiencing a transdermal system that has reached new levels of sophistication through smart drug delivery with advanced biomaterials, nanotechnology, and wearables that improve drug bioavailability, physician and patient compliance, and therapeutic levels of efficacy. Accordingly, innovations are underway to further remove significant barriers to skin permeability and accuracy of dosage to make TDDS more suitable for a wider range of pharmaceutical drugs, including biologics, macromolecules, and further routes of administration. Smart transdermal systems represent the new frontier of personalized medicine through biosensors, AI, and live updates in drug delivery specific to the patient. Smart TDDS systems are certain to change the realm of chronic disease management in diabetes, cardiovascular disease, and neurological disorder in the inhospitable medical setting while requiring the least dosage. The advances made to microneedle patches, nanoparticle carriers, and transdermal delivery with electrostimulation are only a few examples of the exposure to more practical uses of TDDS systems to develop self-administered vaccines, hormone therapy, and even pain management solutions. As aspirational as this all sounds, there remain similar barriers on the way a TDDS product connects with regulatory bodies, industrial-scale synthesis, and cost to the potential user. Smart TDDS will achieve widespread acceptance into clinical care only when safety, efficacy, and standardization can be established. Future studies should address effective formulation strategies, provision to patients, and a better understanding of issues related to scale in order to leverage the potential benefits. Moving forward, TDDS will play an important role in the future of drug delivery, disease management, and precision medicine.

REFERENCES

1. Prausnitz, M. R., & Langer, R. (2008). Transdermal drug delivery.
2. Nature Biotechnology, 26(11), 1261-1268. Ita, K. (2015). Transdermal drug delivery: progress and challenges.
3. Journal of Drug Delivery Science and Technology, 29, 162-170. Kalia, Y. N., Guy, R. H. (2001). Modeling transdermal drug release.
4. Advanced Drug Delivery Reviews, 46(1-3), 159-171. Yu, J., Zhang, Y., & Gu, Z. (2017). Advances in smart transdermal drug delivery systems.
5. Current Pharmaceutical Design, 23(18), 2664-2671. Dhawan, S., Kapil, R., Kapoor, D. N. (2009). Development and evaluation of novel smart transdermal drug delivery systems.
6. Pharmaceutical Research, 26(8), 1752-1761. Bos, J. D., & Meinardi, M. M. (2000). The 500 Dalton rule for the skin penetration of chemical compounds and drugs.
7. Experimental Dermatology, 9(3), 165-169. Hadgraft, J. (2004). Skin, the final frontier.
8. International Journal of Pharmaceutics, 274(1-2), 1-6. Guy, R. H., & Kalia, Y. N. (1998). Transdermal drug delivery by iontophoresis.
9. Advanced Drug Delivery Reviews, 35(1), 1-19. Prausnitz, M. R., Mitragotri, S., & Langer, R. (2004). Current status and future potential of transdermal drug delivery.
10. Nature Reviews Drug Discovery, 3(2), 115-124. Bariya, S. H., Gohel, M. C., Mehta, T. A., & Sharma, O. P. (2012). Microneedles: An emerging transdermal drug delivery system.
11. Journal of Pharmacy and Pharmacology, 64(1), 11-29. Barry, B. W. (2001). Novel mechanisms and devices to enable successful transdermal drug delivery.
12. European Journal of Pharmaceutical Sciences, 14(2), 101-114. Lademann, J., Richter, H., Meinke, M. C. (2008). Hair follicles: An efficient storage and penetration pathway for topically applied substances.
13. Journal of Investigative Dermatology, 128(5), 1156-1158. Benson, H. A. (2005). Transdermal drug delivery: penetration enhancement techniques.
14. Current Drug Delivery, 2(1), 23-33. Prow, T. W., Grice, J. E., Lin, L. L. (2011). Nanoparticles and microparticles for skin drug delivery.
15. Advanced Drug Delivery Reviews, 63(6), 470-491. Williams, A. C., & Barry, B. W. (2012). Penetration enhancers.
16. Advanced Drug Delivery Reviews, 64, 128-137. Guy, R. H. (2010). Current status and future prospects of transdermal drug delivery.
17. Pharmaceutical Research, 27(4), 563-570. Patel, D., Patel, M., & Naik, S. (2012). A review on transdermal drug delivery system.
18. International Journal of Pharmaceutical & Research Sciences, 3(5), 101-115. Hadgraft, J., & Lane, M. E. (2005). Skin permeation: the years of enlightenment.
19. International Journal of Pharmaceutics, 305(1-2), 2-12. Brown, M. B., Martin, G. P., Jones, S. A., & Akomeah, F. K. (2006). Dermal and transdermal drug delivery systems: current and future prospects.
20. Drug Delivery, 13(3), 175-187. Morrow, D. I., McCarron, P. A., Woolfson, A. D., & Donnelly, R. F. (2007). Innovative strategies for enhancing topical and transdermal drug delivery.
21. Open Drug Delivery Journal, 1(1), 36-59. Denet, A. R., Vanbever, R., & Pr eat, V. (2004). Skin electroporation for transdermal and topical delivery.
22. Advanced Drug Delivery Reviews, 56(5), 659-674. Polat, B. E., Blankschtein, D., & Langer, R. (2012). Low-frequency sonophoresis: Application to the transdermal delivery of macromolecules and hydrophilic drugs.
23. Expert Opinion on Drug Delivery, 9(6), 677-695. Toutou, E., Dayan, N., Bergelson, L., Godin, B., & Eliaz, M. (2000). Ethosomes—Novel vesicular carriers for enhanced delivery: Characterization and skin penetration properties.
24. Journal of Controlled Release, 65(3), 403-418. Jain, S., Patel, N., & Madan, P. (2017). Nanotechnology-based drug delivery systems for transdermal applications: Challenges and opportunities.
25. Drug Delivery and Translational Research, 7(2), 271-282. Wang, C., Ye, Y., Hochu, G. M., & Gu, Z. (2016). Enhanced transdermal drug delivery via synergistic action of hydrogel and microneedle array.
26. Advanced Healthcare Materials, 5(22), 2713-2718. Kearney, C. J., & Mooney, D. J. (2013). Macroscale delivery systems for molecular and cellular payloads.
27. Nature Materials, 12(11), 1004-1017. Schwartz, J. B., & Lek, Y. L. (2011). Advances in transdermal delivery of CNS drugs.
28. Expert Opinion on Drug Delivery, 8(8), 1011-1029. Rinaldi, F., Hanieh, P. N., & Passeri, D. (2017). Smart nanocarriers for transdermal drug delivery.

29. European Journal of Pharmaceutics and Biopharmaceutics, 115, 122-136.U.S. Food and Drug Administration (FDA). (2022). Guidance for industry: Transdermal and topical delivery systems. Retrieved from <https://www.fda.gov>
30. European Medicines Agency (EMA). (2021). Regulatory framework for transdermal drug delivery products. Retrieved from <https://www.ema.europa.eu>
31. Market Research Future. (2023). Transdermal drug delivery market growth analysis. Retrieved from <https://www.marketresearchfuture.com>
32. Choi, S., Son, D., Kim, J., et al. (2018). Recent advances in flexible bioelectronics for wearable health monitoring and drug delivery applications. *Advanced Healthcare Materials*, 7(8), 1701310.
33. Kim, Y. C., Park, J. H., & Prausnitz, M. R. (2012). Microneedles for drug and vaccine delivery. *Advanced Drug Delivery Reviews*, 64(14), 1547-1568.
34. GlobalData Healthcare. (2024). Market trends and regulatory landscape in transdermal drug delivery. Retrieved from <https://www.globaldata.com>