REVIEW ARTICLE Am. J. PharmTech Res. 2025; 15(06) ISSN: 2249-3387

AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Recent Advances in Transdermal Drug Delivery Systems: Emerging Technologies and Future Perspectives

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ABSTRACT

Transdermal drug delivery systems (TDDS), particularly in the form of patches, have emerged as a major breakthrough in pharmaceutical science, enabling drugs to be administered directly through the skin in a non-invasive manner. These systems allow controlled and sustained drug release, leading to improved therapeutic efficiency. Unlike conventional oral route Skin, TDDS bypass first-pass metabolism and help maintain consistent plasma drug concentrations. Progress in this field has been driven by the development of innovative materials, novel polymers, advanced permeation enhancers, and smart delivery platforms. The incorporation of nanotechnology has broadened the applicability of TDDS, making it possible to deliver molecules that were previously unsuitable for transdermal administration. Deeper understanding of skin physiology and its barrier functions has facilitated the design of next-generation patches utilizing nanocarriers, microemulsions, and stimuli-responsive polymers. Additionally, approaches such as microneedle arrays, iontophoresis, and sonophoresis have significantly boosted drug permeation across the skin. Several marketed products highlight the practical success of these technologies, while ongoing research continues to refine delivery strategies and evaluation techniques. Overall, the evolution of TDDS has led to more effective, convenient, and patient-friendly therapeutic options, positioning them as a promising platform for addressing complex treatment challenges and catering to diverse healthcare needs in the future.

Keywords: Transdermal drug delivery system, skin barrier, Skin permeation, Controlled drug release, Transdermal patch.

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Received 28 September 2025, Accepted 25 October 2025

Please cite this article as: Chowdary S *et al*., Recent Advances in Transdermal Drug Delivery Systems: Emerging Technologies and Future Perspectives. American Journal of PharmTech Research 2025.

INTRODUCTION

Drug delivery system (DDS) is a generic term for a series. physicochemical technologies that can control delivery. The production and release of pharmacologically active substances into cells, tissues, and organs, allowing these active substances may have optimal effects. In other words: DDS addresses the routes of administration and drugs formulations that efficiently deliver the drug and maximize therapeutic efficacy while minimizing any side effects [1,2]. Based on the delivery route, there are many Various modes of administration, including oral administration transdermal administration, lung inhalation, mucosal administration and intravenous injection. Among they, the transdermal drug delivery system (TDDS) represents a desirable approach.

Transdermal drug delivery systems (TDDS) have emerged as one of the most extensively explored non-invasive routes for systemic drug administration through the skin. Unlike traditional delivery methods that often rely on needle-based injections, TDDS offers a painless and patient-friendly alternative. This approach has shown remarkable success in the delivery of therapeutic agents, particularly in areas such as pain management, hormone replacement therapy, and the treatment of cardiovascular and central nervous system disorders [3].

A major advantage of TDDS lies in its ability to bypass the gastrointestinal tract, thereby avoiding degradation by gastric pH, enzymatic activity, and intestinal microflora. This eliminates drug loss associated with first-pass hepatic metabolism and enhances systemic bioavailability. Furthermore, transdermal systems allow for controlled and sustained drug release, enabling precise regulation of therapeutic levels and reducing the frequency of administration.

Importantly, the non-invasive nature of TDDS minimizes discomfort and improves patient compliance, making it especially suitable for populations such as pediatric and geriatric patients who may experience difficulties with conventional dosage forms.

Barrier and Challenges in Transdermal Drug Delivery

Despite significant advances in transdermal drug delivery systems (TDDS), their full therapeutic potential remains limited by the skin's natural barrier properties. The skin, the body's outermost organ, plays an important protective role by shielding internal tissues from environmental threats such as chemical agents, heat, toxins, and pathogens [4]. The skin is made up of several layers, the epidermis, which is responsible for protective functions, and the dermis, which contains blood vessels and promotes cellular regeneration. Each of these layers has unique properties that can limit drug transport through the skin.

The stratum corneum, or outermost layer of the epidermis, is the primary barrier to transdermal delivery. Its tightly packed corneocytes embedded in a lipid matrix form an extremely effective barrier to foreign substances. This barrier property is especially problematic for high molecular weight compounds, which have limited permeation. Small drug molecules typically diffuse via intracellular routes; however, for larger molecules, additional mechanisms- such as intercellular transport or assisted delivery techniques—are required to improve permeability [5]. The stratum corneum's heterogeneous but organized arrangement of lipids results in both hydrophilic and hydrophobic domains, complicating drug transport. These physicochemical constraints necessitate the development of novel strategies for drug passage across the skin.

The dermal layer, in addition to the epidermis, presents drug delivery challenges. This region has a dense vascular network, which includes a one-cell-thick endothelial layer that ends in the papillary loops of the superficial arteriovenous plexus near the dermal-epidermal junction. The endothelium serves as a dynamic interface between skin tissues and systemic circulation. The cutaneous endothelium, like other tissues in the body, responds to external stimuli by modulating vascular permeability and regulating vasodilation or constriction [6]. These responses can have an impact on drug transport, limiting the amount of active substance that reaches systemic circulation.

Therefore, overcoming the stratum corneum's barrier effect and guaranteeing adequate drug penetration through the epidermal and dermal tissues, followed by absorption into the vascular system, constitute the main challenge for TDDS. In reality, only a small quantity of medication can successfully pass through these barriers [7].

To address these limitations, researchers have developed a variety of innovative TDDS techniques. These include both passive approaches (such as chemical permeation enhancers, novel polymeric systems, and nanocarriers) and active enhancement methods (such as microneedles, iontophoresis, sonophoresis, and electroporation). Collectively, these technologies aim to improve drug penetration, enhance bioavailability, and enable the delivery of a wider range of therapeutic molecules. Importantly, advances in TDDS not only improve therapeutic efficacy but also offer economic advantages by reducing dosing frequency and improving patient adherence [8].

In this review, we present an overview of recent advances in TDDS, with emphasis on active and passive delivery strategies, characterization methods, and future directions that highlight the potential of transdermal systems as a competitive alternative to traditional routes of administration.

Transdermal drug delivery systems

There are several non-invasive medication administration tools, each with Unique attributes and benefits include liquid jet injection, microinjection, Microneedles, patches, gene guns, and ultrasonic techniques. These tools allow drugs to enter the skin in a controlled way, Before entering the bloodstream, it must pass through several layers of skin [9]. TDDS outperform oral delivery by avoiding liver first-pass effects and improving bioavailability and reduced adverse reactions. Furthermore, their Non-invasiveness makes them more convenient for patients, reducing the risk of infections associated with other types of drug administration. As a result, patients taking TDDSs are more likely to self-administer their medications. TDDSs maintain consistent and controlled absorption rates, Maintaining consistent drug concentrations in the bloodstream. This concludes increases their safety and effectiveness in treating a variety of diseases [14]. Moreover, TDDS's extended-release capability reduces dosing frequency, providing a constant and steady supply of medication in the body to maintain therapeutic levels. This benefit is especially helpful for Individuals with chronic conditions require continuous medication, ensuring consistent drug administration over time in order to effectively manage Control chronic illnesses[15].Furthermore, the non-invasive character of TDDSs simplifies medication administration by eliminating discomfort. Associated with injections and other invasive procedures. This makes it Patients are more likely to adhere to their treatment plans, resulting in better Overall treatment outcomes.

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.
- Patients are more likely to adhere to their treatment plans as they no longer need to take multiple doses.
- This approach empowers patients to manage their medication independently.

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 [15].

- 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 [15].
- Transdermal systems have limitations regarding the quantity of medication they can handle [16].
- Transdermal delivery may result in relatively low drug levels in the bloodstream due to variations in skin barrier function, influenced by factors such as skin sites and age [17].

Anatomy And Physiology of Skin

The skin is the body's primary defense against the external environment. It is the largest organ, containing approximately 16% of total body length, with a typical surface area ranging from 1.5 to 2.0 square meters, making up roughly 6–10% of the body weight. There are two main layers of cells that make up the skin.

Human skin comes in two varieties: hair-bearing and non-hairy. Skin that bears hair includes both hair follicles and sebaceous glands.

Layers of skin

Epidermis

The epidermis, or outermost layer of skin, functions as an important tissue barrier. It includes stratified epithelium and Keratinocytes that proliferate in the suprabasal region and undergo basal differentiation. The epidermal thickness varies the palms of the hands and soles of the feet have a thickness of approximately 0.8 mm. It is organized into several the viable epidermis is made up of epithelial cell layers, and the lower layers are commonly referred to as viable epidermis. keratinocytes are the most common cellular component in the epidermis [18].

Dermis

The dermis, located beneath the epidermis, is a complex fibro-elastic layer responsible for providing the skin with mechanical strength. It contains a dense network of blood vessels and nerve fibers. During parenteral drug administration, pain may result from injury to the nerve endings present in this layer [19].

Hypodermis

The hypodermis, or subcutaneous fat layer, provides structural support to the dermis and epidermis. It functions as a fat reservoir that aids in thermal regulation, supplies nutrients, and cushions the body against mechanical stress. This layer also houses larger blood vessels and nerves, along with sensory receptors for pressure. For transdermal drug delivery, medications must pass through the epidermis, dermis, and hypodermis to enter systemic circulation, whereas topical delivery mainly requires passage across the stratum corneum, with the goal of retaining the drug within the skin layers.[20].

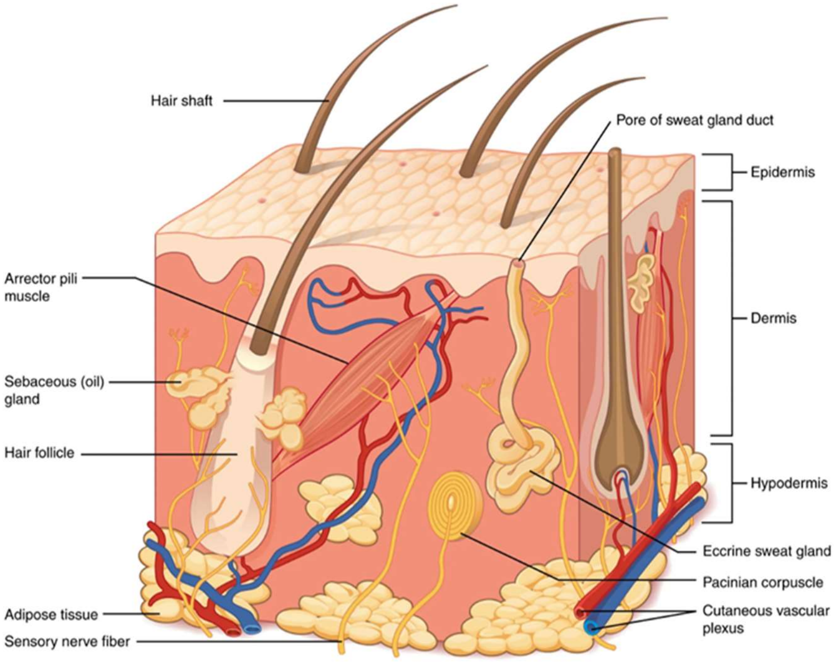

Figure 1: Figure of skin

Skin and drug permeation

To comprehend Transdermal Drug Delivery Systems (TDDS), it is important to consider the structural and biochemical features of the skin that form its protective barrier and influence drug permeation into the body. The skin, being the largest organ, spans nearly 2 m^2 in an average adult and receives roughly one-third of the total blood supply. The epidermis, the outermost skin layer, measures about 150 µm in thickness and is maintained by the constant proliferation of basal epithelial cells, which gradually move upward 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, functions as the foundational connective tissue on which the epidermis rests and originates from the mesoderm. It is made up of a dense network of connective tissue, mostly collagenous fibers, along with some elastic tissue in the upper layers. The dermis includes networks of blood vessels, lymphatics, and nerves, as hair follicles, sweat glands, and sebaceous glands are also present [21].

Functions of skin

1. Protection – Acts as a barrier against mechanical injury, harmful chemicals, UV radiation, and microorganisms.

2. Sensation – Contains receptors for touch, pressure, temperature, and pain.
3. Thermoregulation – Maintains body temperature through sweating and control of blood flow.
4. Excretion – Eliminates small amounts of waste products like salts, water, and urea through sweat.
5. Metabolic function – Synthesizes Vitamin D when exposed to sunlight.
6. Immunological defense – Provides first-line defense through immune cells (Langerhans cells) in the epidermis.
7. Storage – Stores fat, water, and electrolytes in deeper layers.
8. Absorption – Allows limited absorption of substances, including drugs in transdermal delivery.
9. Aesthetic & communication – Contributes to appearance, facial expressions, and social interactions

Basic components of TDDs

- Drug
- Polymer matrix
- Permeation enhancers
- Adhesives
- Backing membrane
- Release Linear

Drug

Drugs must have specific physicochemical properties that allow them to be absorbed through the skin. They include effectiveness, non-irritating properties, low molecular weights (up to 1000 Daltons), low melting points, short half-lives, and affinities for hydrophilic and lipophilic compounds. Selecting drugs for a transdermal drug delivery Systems must be carefully considered to ensure successful development.

Polymer matrix

Polymers play an important role in Transdermal Drug Delivery Systems [TDDS] because they regulate the controlled release drugs were removed from the system. The polymer matrix can be created by incorporating the drug in either liquid or solid form. For intramuscular drug delivery devices, the use of a biodegradable polymer, whether natural or Synthetic is critical. This polymer matrix is created by dispersing the drug throughout 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.

A variety of polymers are used in transdermal drug delivery systems:

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

Permeation enhancers

These agents can temporarily modify the structure of the stratum corneum, enhancing the passage of drugs from the skin into systemic circulation. Their action involves disturbing the well-organized lipid matrix of the stratum corneum, either through the insertion of amphiphilic compounds or by lipid extraction. This reversible alteration lowers the barrier properties of the skin, thereby promoting better penetration of drugs administered alongside them.

An ideal penetration enhancer should possess certain qualities: it must be chemically inert, non-toxic, non-irritant, non-allergenic, act in a unidirectional manner, and remain compatible with both the drug and formulation excipients. Their efficiency is influenced by factors such as the type of drug, skin properties, and the concentration applied. To measure drug permeation across the skin, a diffusion cell is commonly employed. These enhancers work by modifying the stratum corneum, thereby increasing its permeability and enabling the drug to reach therapeutic concentrations.

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 vinylacetate on one surface. To ensure separation, a special adhesive layer, such as polyacrylates, polyisobutylenes, and silicone derivatives, is employed [23].

Backing membrane

The backing layer of a transdermal patch acts as a protective barrier against external factors and must remain impermeable to both the drug and penetration enhancers. It also provides mechanical strength to the system while safeguarding the drug reservoir from atmospheric exposure. Materials such as polyesters, aluminized polyethylene terephthalate, and siliconized polyethylene terephthalate are commonly used for this purpose. Backing laminates are vital structural components, offering flexibility and strong adhesion to the drug reservoir. They stop the drug from diffusing through the upper surface and also permit printing on the patch [24].

Release Linear

During storage, transdermal patches are covered with a protective liner, which is peeled off and discarded before application. This liner is regarded as part of the primary packaging rather than a functional element of the drug delivery system. Commonly employed materials for release liners in TDDS include polyester foils and metallized laminates [22].

Enhancement of transdermal delivery by equipment (active delivery)

External stimuli (electrical, mechanical, or physical) can improve skin permeability and drug absorption over simple topical application. When combined with devices, this is known as active transdermal delivery, which results in faster, more consistent drug transport and improved therapeutic efficacy.

Iontophoresis

Iontophoresis uses a low electrical current (<0.5 mA/cm^2) to drive ions across the skin, improving penetration and release of drugs with poor absorption. Drug transport depends on factors like polarity, charge, mobility, electrical cycle, and formulation. Since absorption is current-controlled, it is less influenced by biological variations. This method can also be paired with electronic reminders to improve patient compliance [25].

Sonophoresis

Sonophoresis uses ultrasound waves to enhance transdermal drug delivery, with low-frequency ultrasound being more effective as it promotes drug transport by disrupting the skin barrier. In sonophoresis, ultrasound waves (20 kHz–16 MHz) are transmitted to the skin using a coupling medium like gel or cream. This disrupts the skin layers through cavitation, forming aqueous channels for drug passage. The process also generates heat, further enhancing penetration. It can deliver a wide range of drugs, including hydrophilic compounds and large molecules like insulin. However, limitations include incomplete understanding of the mechanism, difficulty in optimizing exposure conditions, limited device availability, and risks such as skin burns [30].

Electroporation

Electroporation is the process of applying short, high-voltage pulses (5-500 V for milliseconds) to the skin, resulting in temporary pores in the stratum corneum that increase permeability and drug diffusion. The technique employs closely spaced electrodes to ensure safe and painless delivery and has been proven effective for transporting a variety of drugs. Only low molecular weight drugs, such as doxorubicin, mannitol or calcein, but also high molecular weight ones like antiangiogenic Peptides, Oligonucleotides, and the negatively charged Heparin is an anticoagulant. However, this approach has disadvantages of small delivery loads, massive cellular perturbation, which can include cell death and heating Induced drug damage and protein denaturation Other biomacromolecular therapeutics [27].

Photomechanical waves

Photomechanical waves use controlled laser pulses to create temporary channels in the stratum corneum, enabling drug penetration. With low radiation exposure (5–7 J/cm²), they achieve limited ablation at depths of 50–400 µm, providing longer-lasting permeability than direct ablation methods. A single nanosecond laser pulse can rapidly enhance skin permeability, allowing diffusion of large molecules such as 40 kDa dextran and 20 nm particles. Careful adjustment of wave properties is required to target the desired skin depth effectively [34].

Micro needle

The microneedle drug delivery system is an advanced approach that enables drug transport into the bloodstream through micron-sized needles [31]. It is one of the most promising and widely studied methods in transdermal delivery research. These tiny needles puncture only the outer skin layers, creating pathways for drug diffusion across the epidermis and into capillaries, while minimizing pain due to their small size and shallow penetration.

Extensive research has focused on optimizing microneedle geometry, dimensions, and insertion efficiency for effective delivery. Fabrication methods include laser-based techniques (for metal or polymer microneedles, where the 3D shape is formed by laser cutting/ablation) and photolithography (which allows precise design and production of dissolving, hydrogel, or silicon microneedles using inverse molds). Newer techniques such as 3D printing, micro stereolithography, and two-photon polymerization are also being explored to expand design flexibility [32].

Microneedles can be classified into several types:

- Solid microneedles: create microchannels to enhance drug absorption.
- Coated microneedles: deliver drugs coated on the needle surface during insertion.
- Dissolving microneedles: made from drug-loaded biodegradable materials that dissolve after application.
- Hollow microneedles: allow storage and direct injection of drug solutions.

- Microneedle patches: integrate microneedles with transdermal patches for convenient application.

This system offers a versatile platform for painless, controlled, and efficient transdermal drug administration, making it a rapidly growing field of investigation.

Thermal ablation, or thermophoresis, is a promising method for selectively disrupting the localized heat promotes stratum corneum structure. Provides enhanced drug delivery via microchannels developed in the skin [55]. To ablate the stratum corneum thermal ablation produces a high temperature above 100°C required, resulting in heating and vaporization of thermal ablation enhances transdermal drug delivery by creating micron-sized pores (50–100 µm) in the stratum corneum using brief, localized heat without damaging deeper tissues. This controlled method improves permeability for both small molecules and large biomacromolecules while minimizing pain and irritation [33].

Two main techniques are used:

Laser thermal ablation: Laser energy heats and vaporizes skin water content, forming microchannels. Parameters such as wavelength, pulse length, and energy can be tuned to control depth. Er: YAG lasers can boost drug penetration over 100-fold for both hydrophilic and lipophilic drugs, including peptides, proteins, vaccines, and DNA.

Radiofrequency ablation: Uses microelectrode arrays delivering high-frequency currents (100–500 kHz) to generate localize Jud heat and form pores up to 50 µm deep. These microchannels allow hydrophilic molecules to diffuse, supporting sustained drug release with low-cost disposable devices. This approach offers precise, reproducible, and efficient drug delivery compared to mechanical or chemical methods [34].

TDDS using chemical enhancers (passive delivery)

For effective transdermal delivery and therapeutic action, drugs should ideally have a molecular weight below 1 kDa, be compatible with both lipophilic and hydrophilic environments, possess a short half-life, and cause no skin irritation. Several factors influence skin penetration, including species variation, age, application site, skin condition, temperature, exposure time, and the drug's physicochemical properties. Recent advancements highlight the use of chemical enhancers, microemulsions, vesicles, and novel formulations to improve drug solubility and permeability. Combination approaches, such as eutectic mixtures and nanoparticle-based self-assembled vesicles, show superior results compared to individual enhancers. Current research also emphasizes molecular simulations to better understand the skin lipid barrier, mechanisms of drug transport, and the role of enhancers in modulating skin permeability [39].

Vesicles

Vesicles are water-filled colloidal carriers made of amphiphilic molecules arranged in bilayers. In excess water, they can form multilayered structures capable of encapsulating both hydrophilic and lipophilic drugs, enabling transdermal delivery with controlled or sustained release. Based on composition, vesicles are categorized into types such as liposomes, transfersomes, and ethosomes. Liposomes, the most common form, are soft, spherical vesicles composed mainly of phospholipid bilayers, sometimes stabilized with cholesterol. Phospholipids consist of polar head groups and two hydrophobic chains that vary in length and saturation. When dispersed in water, they self-assemble into liposomes, which can encapsulate both hydrophilic and lipophilic drugs. Although liposomes mostly stay on the skin surface and do not penetrate deeply, they enhance local drug retention, prolong action, and provide sustained release making them ideal for topical therapy. Transfersomes, also known as elastic or deformable liposomes, differ by containing single-chain surfactants that increase bilayer fluidity and flexibility. This unique property enables efficient penetration through the skin, with newer generations further optimized by modified bilayer components. Second-generation transfersomes are composed of phosphatidylcholine lipids and other polar lipophilic substances, whereas third-generation transfersomes include amphiphilic surfactants, with or without phospholipids. Their high deformability enables them to pass through skin pores that are much smaller than their size, allowing for the delivery of large molecules such as peptides and proteins weighing up to 1000 kDa. Ethosomes, on the other hand, are made up of phospholipids, alcohol, and water, with a higher alcohol concentration than liposomes. In comparison to conventional vesicles, this composition improves flexibility, penetration, and stability, allowing for deep skin delivery, improved systemic absorption, extended drug retention, and more efficient controlled release [40].

Polymeric Nanoparticles

Nanoparticles (NPs) range in size from 1 to 1000 nm and act as drug carriers, allowing for targeted delivery, controlled release, longer circulation time, improved bioavailability, and fewer side effects. They are typically produced through polymerization or crosslinking of biodegradable polymers such as gelatin, PLA, or PLGA. Polymeric nanoparticles are preferred for transdermal delivery because they protect unstable drugs, prevent degradation, and provide long-term release. Nanospheres, nanocapsules, and polymer micelles can all be classified based on their preparation and structure. PLA, PLGA, polycaprolactone, polyacrylic acid, and natural polymers like chitosan, gelatin, and alginate are all widely used. Polymeric nanoparticles are formed by linking one or more polymer units under specific conditions, often using synthetic membranes that resemble the lipid bilayer. Due to their high molecular weight chains, these nanoparticles have a rigid and structured membrane, giving them strong mechanical stability but limiting their ability to pass through pores equal to or smaller than their size. Their resistance to breakdown allows them to retain drugs for extended periods, enabling a slow release and subsequent diffusion into deeper skin layers [40].

Nano emulsion

Nano emulsions are low-viscosity, transparent or translucent mixtures that maintain thermodynamic and kinetic stability. They are composed of tiny oil droplets dispersed in water and stabilized by surfactants or co-surfactants, with droplet sizes ranging from 100 to 1000 nm. Nanoemulsions differ in structure and long-term stability from microemulsions, despite their similar appearance. Their small droplet size, large surface area, and low surface tension improve skin contact, solubility, stability, and bioavailability, while also extending shelf life. They are also quick to prepare and require little energy. Nanoemulsions allow for faster and more efficient transdermal absorption than traditional topical formulations and can be oil-in-water, water-in-oil, or bicontinuous systems. Among these, oil-in-water types are most commonly used to deliver lipophilic drugs, making nanoemulsionsz extremely promising for advanced transdermal drug delivery.[39].

The advantages and disadvantages of various transdermal delivery system

Delivery type	Method	Advantages	Disadvantages
Active delivery	Iontophoresis	• Improving the delivery of polar molecules as well as • high molecular weight compounds • Faster and easier administration • Enabling continuous or pulsatile delivery of drug	• Risk of burns if electrodes are used improperly • Difficulty stabilizing the therapeutic agent in • the vehicle • Complexity of the drug release system
	Sonophoresis	• Makes transdermal diffusion rates strictly controllable. • More patient approval in many situations • Lower risk of systemic absorption. • Beneficial for dissolving blood clots • Not overly sensitizing.	• Prolonged administration • A slight burning, tingling, and irritation • For a drug to be effective, SC must remain intact. • penetration
	Electroporation	• Highly effective, reproducible • Enables quick stopping of medication delivery by Termination • Not overly triggering	• Unsuitable for use over a wide area • If high voltage is used, the cargo may be disturbed. • Potential harm to cells • Not particularly specific
	Photomechanical waves	• Facilitate the transport of molecules across the cellular plasma membrane in vitro without compromising cell viability. • Appear to be non-damaging to the viable layers of the skin. • Do not elicit pain or discomfort upon application.	• Lack of human clinical data
	Microneedle	• Painless administration of the active pharmaceutical. ingredient • Quicker healing at the injection site • No fear of needles. • A specific skin area can be targeted for the appropriate drug delivery	• Lower dosing accuracy compared to hypodermic needles • The penetration depth of various particles. • Depending on the skin layers • Risk of venous collapse from repeated injections
	Thermal ablation	• Prevents complications such as pain, bleeding, and infection. • Enables selective removal of the stratum corneum while preserving underlying tissues. • Provides improved precision and reproducibility. • Cost-effective and designed for single use.	• There must be structural changes in the skin. • evaluated • Existing concerns over the use of extreme • temperatures and the logistics of these devices.

Passive delivery	Vesicles	• Achieve behavior related to sustained drug release. • Manage the rate of absorption using a multilayered • framework	• Prone to chemical instability. • High cost of formulation. • Restricted capacity for drug loading.
	Polymeric nanoparticles	• Achieve controlled and targeted release behavior • High non-deformability and mechanical strength • A variety of biodegradable materials can be used to make it. • Both hydrophilic and hydrophobic medications can be loaded. • Because of its small size, it can evade the immune system.	• Difficult to break down • Not enough toxicological assessment has been done • Some processes are difficult to scale up
	Nanoemulsion	• Long-term thermodynamic stability. • Excellent wettability. • High solubility and physical stability. • • It is possible to formulate it in a variety of ways.	• Necessitates the use of high amounts of emulsifying agents. • Shows poor solubilization efficiency for substances with high melting points. • Exhibits inconsistent distribution kinetics and clearance patterns.

APPLICATIONS

Cancer

The global incidence of cancer continues to rise, with an estimated 193 million new cases and 9.9 million deaths reported in 2020. Among these, breast cancer was the most prevalent, accounting for 2.3 million new cases. This trend underscores the increasing health burden of cancer and the pressing need for improved strategies in its prevention, diagnosis, and treatment. One promising avenue is transdermal drug delivery, which offers the potential to enhance cancer therapy by enabling the efficient administration of novel agents and improving the effectiveness of existing chemotherapeutics [29].

Biodegradable carriers have attracted significant interest for their role in eliminating residual cancer cells and preventing tumor spread when applied to treated sites. Many FDA-approved therapies incorporate biodegradable materials, such as bacterial cellulose (BC), due to their advantageous features—high porosity, biocompatibility, and purity. These materials can be customized using encapsulation methods or cross-linking techniques to enable controlled and sustained drug release, thereby minimizing systemic toxicity.

By facilitating localized delivery of anticancer agents directly into tumors, biodegradable carriers reduce the need for repeated invasive procedures, improving patient comfort and overall quality of life. In brain cancer therapy, for instance, embedding chemotherapy drugs into the tumor site allows for precise, gradual drug release as the carrier degrades, maintaining therapeutic concentrations in tumor cells while limiting damage to healthy tissues. This targeted approach enhances treatment efficiency, lowers the risk of recurrence, and provides a less invasive, more patient-friendly alternative to traditional methods.

Breast cancer

Transdermal drug delivery (TDD) offers targeted administration of anticancer drugs directly to tumors, reducing side effects and enabling combination therapies to overcome drug resistance. For example, curcumin-loaded nanomaterials combined with drugs such as tamoxifen, letrozole, anastrozole, imatinib, or vemurafenib show enhanced efficacy against breast and skin cancers. These nanomaterials improve drug uptake by cancer cells, boost inhibition of cell growth, and help counter resistance by acting on multiple pathways [29].

Studies with nanostructured lipid carriers (NLCs) and bacterial cellulose (BC)-based hydrogels have shown significant tumor reduction in mice without toxicity or inflammation, confirming their biocompatibility and therapeutic potential. Additionally, electrospun cellulose acetate fibers integrated into BC scaffolds provide a stronger model for studying breast cancer cell growth and evaluating new treatments, further supporting the role of BC-based systems in safe and effective cancer therapy.

Diabetes therapy

Elevated blood glucose levels (BGLs) are a defining feature of diabetes, a serious condition caused by either insufficient insulin production or impaired insulin absorption. Insulin, secreted by pancreatic β-cells, lowers glucose levels by binding to specific receptors on target cells and facilitating metabolic processes. Traditional diabetes management typically involves finger-prick testing and the administration of insulin or GLP-1 injections. While effective, these approaches are often inconvenient, painful, carry risks of infection, and fail to provide continuous monitoring of glucose fluctuations.

Closed-loop diagnostic systems have emerged as a promising alternative, as they continuously track glucose levels and adjust insulin delivery in real time to maintain stable BGLs. Among these, glucose-responsive microneedle (MN) patches have gained significant attention because they offer painless, drug-compatible, and real-time monitoring and treatment options. Recent progress in wearable MN-based systems combined with iontophoresis has further advanced diabetes care by improving glucose detection and enhancing the transdermal delivery of therapeutic molecules. Integrating electronic control into these platforms allows for precise, on-demand drug release, presenting an advanced strategy to optimize both glucose monitoring and treatment outcomes [34].

Pain management and opioid-sparing analgesia

Matrix and reservoir transdermal patches (e.g., fentanyl, buprenorphine, lidocaine) provide sustained analgesia for chronic pain, reducing dosing frequency and gastrointestinal/hepatic side effects associated with oral routes. Iontophoretic and microneedle approaches allow more rapid or localized analgesic delivery when needed. Clinical and pharmacokinetic literature show improved adherence and steady plasma concentrations, but issues such as variable skin permeability, heat-induced overdose risk, and local skin reactions must be managed [36].

Neurological disorders and CNS delivery

TDDS strategies aimed at CNS disorders include nano-carriers designed to improve blood–brain barrier penetration, microneedle-assisted percutaneous delivery, and localized implants providing sustained release. While preclinical data show promise for levodopa, peptides and small molecules, robust demonstrations of improved brain bioavailability and clinical benefit in humans remain limited; safety and repeat dosing effects on neural tissue are active ñ areas.

Hormone replacement therapy (HRT) and contraception

Transdermal systems deliver sex hormones (estrogen, testosterone, progesterone) and investigational transdermal contraceptives to achieve steady systemic exposure while avoiding first-pass hepatic metabolism. These products generally improve pharmacokinetic profiles and adherence, but skin irritation, adhesive sensitivity, and individual variability in absorption require formulation and user-education strategies [28].

Cardiovascular therapeutics

Transdermal delivery of nitroglycerin, clonidine and other small-molecule cardiovascular drugs provides sustained hemodynamic control with improved compliance. Patches avoid first-pass effects and reduce peak–trough fluctuations, but dose titration during acute events and interactions with external heat remain concerns.

Vaccination and immunotherapy (needle-free)

Microneedle patches deposit antigen into the epidermis/dermis — regions rich in antigen-presenting cells — producing robust immune responses and enabling thermostable or dose-sparing formulations. Clinical studies, including phase I trials for influenza and other vaccines, show safety and immunogenicity for some MN vaccine candidates, highlighting potential for mass vaccination that is easier to deploy and acceptable to users [27].

Dermatological disorders and localized dermatotherapy

Advanced nanocarriers (liposomes, ethosomes, transfersomes, SLNs/NLCs), penetration enhancers and microneedles help deliver antifungals, corticosteroids, immunomodulators and anticancer agents deeper into skin layers, improving outcomes for psoriasis, eczema, fungal infections and superficial skin cancers. Careful excipient selection is needed to avoid irritation while ensuring consistent penetration.

Challenges and future directions

This review discusses the key limitations of transdermal drug delivery systems (TDDS), particularly those linked to restricted skin permeability and the physicochemical properties of drug molecules. Addressing these barriers could broaden the scope of TDDS applications, leading to improved therapeutic outcomes and enhanced patient quality of life. Current research focuses on technological innovations and novel formulation strategies designed to overcome these shortcomings and increase system effectiveness. Clinicians can apply these advancements to optimize treatment approaches by staying updated on emerging developments in the field.

A major emphasis is placed on the need for innovative delivery platforms and formulations that can resolve issues of drug stability and precise dose regulation. Technologies such as microneedles and nanoparticles are being investigated for their ability to achieve more efficient, targeted transdermal delivery by improving drug penetration and distribution across the skin layers. These innovations hold promise for expanding TDDS applications and introducing new treatment possibilities across multiple disease areas [39].

Notable progress includes the development of microneedle patches for insulin administration in diabetes management, which help minimize dosing errors and enhance therapeutic efficiency. Similarly, transdermal patches have been designed for localized analgesic delivery, offering effective pain control for chronic conditions. Such non-invasive alternatives provide greater patient comfort and adherence compared to conventional methods. In addition, they help maintain stable drug concentrations, avoiding the peaks and troughs often associated with oral therapy, while reducing gastrointestinal side effects. Consequently, transdermal systems present a reliable and patient-centered option for sustained pain relief and long-term disease management.

CONCLUSION

Transdermal drug delivery systems (TDDSs) are considered highly advantageous due to their ease of use, painless nature, and ability to provide sustained drug release. These features enhance patient adherence to therapy and ultimately improve clinical outcomes. By supporting individualized dosing, TDDSs also open possibilities for personalized medicine tailored to specific patient needs. Continuous research and innovation in this field are expected to revolutionize drug administration, particularly for chronic conditions such as diabetes, hypertension, and long-term pain management [40]. Various TDDS approaches—such as liquid jet injectors, microinjections, microneedles, transdermal patches, gene guns, and ultrasound-based systems—offer unique mechanisms and therapeutic benefits. Their extended-release properties ensure consistent and controlled drug absorption, maintaining stable plasma concentrations while reducing the frequency of dosing. This not only enhances treatment effectiveness but also ensures continuous therapeutic availability within the body.

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