



Review Article A small review on recent advances in transdermal drug delivery system

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ARTICLE INFO	A B S T R A C T
Article history: Received 24-02-2024 Accepted 09-03-2024 Available online 07-05-2024	Transdermal drug delivery devices (TDDS), often known as "patches," are dosage forms designed to transfer a therapeutically effective amount of medicine over a patient's skin. Transdermal distribution establishes one of the most important channels for a revolutionary medication delivery method. Transdermal drug delivery has various advantages over traditional delivery methods, such as oral and injection; however, its efficacy is restricted. Transdermal administration traditionally entails pushing a
<i>Keywords:</i> transdermal delivery prolonged period of time painless conventional delivery methods	 patch containing a medicinal substance onto the skin, which is both convenient and painless, as well as therapeutic first-pass metabolism. It can deliver medications through the skin portal to systemic circulation at a predefined rate while maintaining therapeutically efficacious concentrations for an extended period of time. Around 74% of medications are taken orally, and one has been discovered to be less effective than expected. In this present review article, it covers a brief outline of various recent approaches in their development for transdermal patches.
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1. Introduction

Transdermal Drug Delivery Systems, or "patches," are discrete, self-contained dosage forms that, when placed on undamaged skin, transfer drugs to the systemic circulation at a controlled rate through the skin. Transdermal patches are essential for reducing patient noncompliance that was previously brought on by traditional dose forms, such as first-pass metabolism and medication breakdown from the presence of enzymes or changes in pH in the gastrointestinal tract. The goal of creating a transdermal drug delivery system was to boost the drug's bioavailability and enable a regulated release of the medication into the bloodstream through the skin. The transdermal drug delivery method involves the incorporation of the drug to be delivered into

polymeric membranes, which then diffuse the drug to the skin at a controlled and planned rate. It requires fewer doses than oral dosage forms, which lessens the chance of a medication being overdosed into the systemic circulation and hence causes fewer negative effects.

First-generation delivery methods do not include a patch; instead, lipophilic medications are delivered to the skin via a gel, liquid spray, or other topical formulation. These drugs evaporate or absorb into the stratum corneum, which serves as a reservoir for the drug's prolonged release into the epidermis over several hours. Example: Transdermal sprays containing estradiol were recently licensed; however, testosterone gels had been used for many years prior. Skin permeability is critical for the development of the second generation of transdermal delivery devices. By temporarily modifying the structure of the stratum corneum, the enhancers were able to boost skin permeability while

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avoiding injury to deeper living tissues. This generation of delivery methods focuses primarily on enhancing the dispersion of small molecules for localized and other systemic applications, hence advancing therapeutic treatment. However, it is less effective at delivering macro molecules.

The third generation of transdermal delivery systems is designed to target the stratum corneum and its effects. By shielding deeper tissues, this breakdown of the stratum corneum barrier results in more efficient transdermal transport.

With scopolamine as its active ingredient, Transderm-SCOP was the first transdermal patch for motion sickness to be authorized by the US FDA in 1979. These days, the most effective way to provide medications such as fentanyl, lidocaine, estradiol, and other combination patches containing multiple pharmaceuticals is through the transdermal administration system. On average, every 2.2 years, a new patch was approved between 1979 and 2002. That rate more than tripled to a new transdermal delivery technology every 7.5 months between 2003 and 2007.¹

2. Skin

With a surface area of 1.7 m2, the skin is the largest and most accessible organ in the body, accounting for 16% of the average person's total body mass (Figure 1). The skin's principal function is to act as a protective barrier between the body and the outside world, preventing pathogens, poisons, allergies, ultraviolet (UV) radiation, and water loss. There are three main sections of skin:

The stratum corneum is found in the outermost layer and the epidermis.

The dermis, the intermediate layer

The hypodermis, the outermost layer

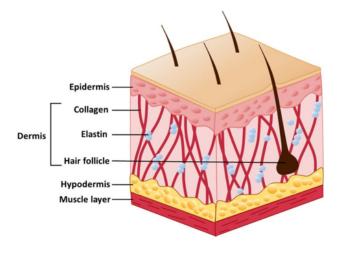


Figure 1: Schematic representation of the human skin structure.²

3. Epidermis

The epidermis, or skin's outermost layer, varies in thickness, measuring approximately 0.8 mm on the palms and soles of the hands and feet. The viable epidermis is frequently referred to as the epidermal layers underneath the stratum corneum. It is composed of multi-layered regions of epithelial cells.

Its low hydration level of 15%–20% and extremely high density (1.4 g/cm3 in the dry state) may contribute to its barrier properties because it is in direct contact with the outside environment. The majority of stratum corneum cells are composed of 20% lipid and 70% insoluble keratin. Keratin found in corneocytes is connected to water in the stratum corneum.

4. Dermis

The dermis, which provides the skin with strength and suppleness, is around 2–3 mm thick and composed of 70% collagen and elastin fibers. The dermal blood veins nourish both the epidermis and the dermis. The dermis layer also contains lymphatic veins, nerves, and macrophages.

5. Hypodermis

The hypodermis, also known as the subcutaneous layer, is the skin's lowest layer and is composed of fat cells. It acts as the interface between the skin and the body's underlying tissues, such as the bones and muscles. As a result, the hypodermis' principal functions are heat insulation, protection against physical stress, and support for the skin's vascular and neurological signals. About half of the body's fat is made up of fat cells found in the hypodermis, which is made up of two types of cells: macrophages and fibroblasts.

The medicine can only be administered through skin tissue in minute amounts, which is the difficulty. Many innovative TDDS approaches have been carefully designed as 5-ransdermal drug delivery systems to address this issue.³

6. Transdermal Patches

A medicated adhesive patch, known as a transdermal patch or skin patch, is put on the skin to deliver a predetermined dose of medication via the skin and into the bloodstream. This frequently encourages the body's wounded area to mend. A regulated distribution of the medication into the patient is one benefit of transdermal drug administration over other forms, such as oral, topical, etc. That being said, one drawback to development is the skin's strong barrier properties. Transdermal patches can be used to deliver a wide range of medications.

6.1. Transdermal patch's key components are:

Components of a transdermal patch could include the following:

- 1. Liner: shields the patch while it's being stored. Before being used, the liner is removed.
- 2. Substance: substance solution in close proximity to the release liner
- 3. Adhesive: This substance is used to attach the patch's components to one another and to the skin.
- 4. Membrane: Regulates the drug's release from multilayer patches and reservoirs
- 5. Backing shields the patch from its external surroundings⁴

7. Advantages of Transdermal Drug Delivery System

The following are some of the alleged benefits of transdermal drug delivery:

- 1. It replaces oral administration when it is not appropriate, such as when vomiting or diarrhea occurs.
- 2. It avoids parenteral therapy's hazards and drawbacks
- 3. It prevents the "first pass" effect in the liver
- 4. It prevents gastrointestinal absorption fluctuations caused by changes in pH, enzyme activity, drug-food interactions, and other factors.
- 5. It decreases the daily dosage, which enhances patient adherence
- 6. It prolongs the action of medications with brief plasma half-lives by utilizing the therapeutic delivery system's drug reservoir and its regulated release features.
- 7. It increases therapeutic efficacy and decreases adverse effects as a result of improving the blood concentration-time profile and preventing medication from entering the bloodstream by pulse entry.
- 8. It ensures consistent performance over a long period of time and the capacity to mimic zero-order kinetics.
- 9. In an emergency, quickly identify the drug. Removal of the risks and challenges associated with IV therapy (e.g., non-responsive, unconscious, or comatose patients), injectables, or I.M. injectables.⁵

8. Disadvantages of Transdermal Drug Delivery System

- 1. Medication that requires high blood levels cannot be given; only strong compounds, 10 mg or less per day, are allowed.
- 2. Transdermal administration is often intended to provide slow, sustained medication delivery; it is not a method for achieving quick bolus-type drug input.
- 3. The medication should have a reasonable molecular size so that it may be absorbed via the skin.
- 4. When it comes to this route of administration, tolerance-inducing drugs are not a wise choice unless

a suitable wash-out period is scheduled in between the dose schedules.

- 5. The drug's difficulty passing through human skin and the skin's barrier function.
- 6. Another significant drawback is dermatitis, or skin irritation, brought on by enhancers and excipients in medication delivery systems that increase percutaneous absorption.
- 7. Not every skin type will adhere to the adhesive successfully 6

9. Limitations of Transdermal Drug Delivery System

- 1. Some of the limitations of TDDS can be addressed with innovative techniques, including electroporation, ultrasonography, and iontophoresis.
- 2. The skin permeability of transdermal medication delivery systems is restricted
- 3. It is limited to strong medications and long lag times
- 4. The presence of skin enzymes, such as peptidases, prior to systemic metabolism may metabolize drugs into inactive forms and decrease their potency.
- 5. Given that solute diffusivity is inversely correlated with molecular weight and that big molecules cannot be used, a molecular weight of less than 500 Dalton is necessary to guarantee easy diffusion over the SC.
- 6. When it comes to administering significant dosages of medication through the skin, transdermal administration is not only impractical but also costly.
- 7. Sensitization or irritation may result from a medication's composition
- 8. When a medicine is heavily metabolized in the skin and its molecular size is large enough to hinder its diffusion through the skin, it is not a realistic option.
- 9. It is not appropriate for a medication with an unfavorable o/w partition coefficient.
- 10. Transdermal drug delivery systems are only appropriate for very powerful medications because of the skin's intrinsic impermeability, which places constraints on drug entrance.
- 11. For a medicine to pass through the stratum corneum, it must possess certain desirable physicochemical qualities. Transdermal delivery will be extremely challenging if the drug dose needed for therapeutic benefit exceeds 10 mg/day.
- 12. It may be necessary to stop using one or more of the system components because some patients have contact dermatitis at the application site.
- 13. Another aspect that must be thoroughly considered before deciding to manufacture a transdermal medicine is clinical need.⁷

10. Various Techniques to Enhance Transdermal Permeation

10.1. Acoustic techniques

The use of ultrasonic waves and short-duration shock pulses has made transdermal distribution simpler. Through a process known as sonophoresis, ultrasound at different frequencies in the 20 kHz–16 MHz range has been used to improve skin permeability. Sonophoresis has historically been achieved with high-frequency ultrasound (f > 1 MHz, therapeutic ultrasound). Nevertheless, the augmentation of transdermal transport brought about by low-frequency ultrasound (f<100 kHz) is notably higher than that brought about by therapeutic ultrasound.

As a result, throughout the last 10 years, low-frequency sonophoresis has drawn special attention. Ultrasonic pressure fields are known to generate cavitation, which is the formation, oscillation, and collapse of bubbles. This phenomenon occurs in addition to heating. Cavitation occurs exclusively in specific settings (for example, low-frequency ultrasound) and is not synonymous with ultrasonic heating or imaging technologies. Cavitation bubbles concentrate ultrasonic energy, enabling targeted effects at the location of bubble activity and transdermal medication delivery.⁸

10.2. Microneedle

The unique microneedle drug delivery device uses a needle to deliver medication to the circulatory system. This is a common method of transdermal drug delivery that is currently being researched. This method involves puncturing the skin's surface layer with micron-sized needles, allowing the drug to spread throughout the epidermal layer. These tiny, thin microneedles aid in alleviating discomfort by delivering medication directly to the blood capillary area, allowing active absorption. Researchers have attempted to use a variety of approaches to reach the appropriate optimization and geometric measures required for the successful insertion of microneedles into human skin, which also represents the overarching goal of microneedle research.

Numerous studies have been undertaken to develop microneedle systems, taking into account the intended use, drug kind and dosage, and objective. To date, microneedles have been produced using photolithography and lasermediated techniques. Laser-mediated manufacturing procedures produce metal or polymer microneedles. A laser is used to cut or ablate a flat metal or polymer surface, resulting in the three-dimensional structure of a microneedle. Photolithography is the method of intricately producing microneedles, and it has the advantage of being able to produce needles in a range of shapes and materials. This technology, which uses photoresist etching to build an inverse mold based on the microneedle structure, is most commonly employed to generate hydrogel, dissolving, or silicon microneedles. Furthermore, the technologies of 3D printing, microstereolithography, and two-photon polymerization are being investigated in order to create various microneedle systems. A variety of types of prepared microneedles are available, including solid microneedles that act as a physical conduit for drugs to be absorbed; drug-coated microneedles that help administer drugs coated on the needles' surfaces as they penetrate the skin; dissolving microneedles composed of drug formulations that dissolve in the body; and naturally delivered melting needles that involve the storage of drugs in hollow needles and then administration.⁹

10.3. Thermal ablation

Thermal ablation selectively heats the skin's surface to create micron-sized pores in the stratum corneum. When the skin's surface is heated to hundreds of degrees for milliseconds to microseconds, heat is localized and does not spread to the live tissues beneath. This prevents injury or irritation to these tissues. In terms of mechanics, thermal ablation may entail rapidly vaporizing water in the stratum corneum, resulting in volumetric expansion and micronscale ablation of surface craters. A more recent study has revealed that temperatures far higher than the boiling point of water are necessary, as well as the possibility of other processes such as tissue burning.

Animal studies show that thermal ablation effectively distributes drugs such as interferon α -2b and human growth hormone. Radiofrequency ablation and ohmic microheaters have been utilized to heat the skin. The technique is well tolerated because of the minute-length scales of localized skin injury caused by thermal ablation. Unpublished publications describe clinical research concerning the delivery of different drugs, such as insulin and human growth hormone.¹⁰

10.4. Macroflux

It has a titanium microprojection array that breaks through the skin's outermost layer to form a superficial route. The titanium disc attached to the polymeric adhesive backing serves as the primary part of the microprojection patch. The titanium disc is made up of a variety of tiny, toothlike titanium microprojections that have been coated in therapeutic materials. A single microprojection can have up to 300 microprojections per centimeter and a length of less than 200 μ m. They only reach the stratum corneum's 10–25 μ m thin layer of dead cells, where they make "holes" or microchannels big enough to let big molecules pass through to the deeper, physiologically active layers of the epidermis. The microprojections made of titanium are too tiny to hurt. This method provides a pleasant and needle-free transdermal medication administration system for large molecular-weight molecules like vaccines, insulin, and numerous peptide hormones.

Patients can receive medication for 12 weeks under this new arrangement.

There are three different Macroflux designs. Among them are

- 1. The dry-coated macroflush system, which consists of a microprojection array coated with medication and affixed to an elastic polymer adhesive backing, is used for brief administration.
- 2. The D-TRANS macrofluid system, which combines a drug reservoir with a microprojection array, is likewise intended for short-term delivery.

Three. The E-TRANS macroflow system combines an electrotransport system with a microprojection array.¹¹

10.5. Microfibers and nanofibers

Because of these systems' capacity to have a local impact, there has been an increase in wound healing. One benefit of nanofibers is their large surface area, which promotes better medication solubility. The drug molecules are entrapped in the polymer framework to generate a better-regulated drug delivery system and an increased drug concentration in the carrier, hence increasing medicine flow into the skin. One way of producing nanofibers is by electrospinning various polymers to form nanofibers with a tiny diameter, a large surface area, and flexibility. Rancan and colleagues demonstrated how ciprofloxacin, an antibiotic with limited water solubility, can be given locally over an extended period of time using nanofiber mats to promote wound healing. In ex vivo human skin models, nanofiber devices were effective in treating pseudomonas aeruginosa. Moreover, Zhu and colleagues created coreshell nanofibers to treat melanoma. Their study showed that nanofibers could be used in cancer treatment with tailored medication delivery because of their excellent drug encapsulation efficiency.¹²

10.6. Electroporation

The temporary structural perturbation of lipid bilayer membranes with the application of a brief electric pulse (milliseconds or microseconds) is known as electroporation. It is widely accepted that for the electroporation of a single lipid bilayer, a transmembrane potential difference of 0.5 to 1.0 volts must be applied. The stratum corneum lipid domain has been demonstrated to be susceptible to modification using electroporation. As a result, macromolecules like calcitonin and medium-sized molecules like fentanyl. Additionally, there have been reports of increased transport for charged (like heparin), neutral (like mannitol), hydrophilic (like metoprolol), and lipophilic (like timolol) molecules. The magnitude of the applied voltage determined the flux. An in vivo investigation with hairless rats demonstrated that fentanyl reacted quickly to electrical pulses. Skin electroporation was used to quickly (within 15 minutes) distribute fentanyl transdermally at therapeutic doses, resulting in a deep analgesia that lasted for almost an hour.¹³

10.7. Nanoemulsions

A family of emulsions known as nanoemulsions is defined by the dispersion of minuscule droplets when combined. These formulations can be either oil-in-water or waterin-oil. Since they need certain manufacturing techniques, surfactants that can stabilize the nanodroplets, and unique thermodynamic circumstances, nanoemulsions cannot develop spontaneously. These are the main requirements for nanoemulsions. Since lipophilic compounds may be transported into the skin via nanoemulsions, they might be the perfect vehicle to use for treating acne by facilitating the penetration of active ingredients into the lipophilic environment of the pilosebaceous unit. Furthermore, nanoemulsion particles can have additional therapeutic effects, such as improved skin hydration and viscoelasticity, and they won't clog pores.¹⁴

10.8. Inotroporesi

Iontophoretic skin patches work by driving the medicines across the SC, mostly through the process of electrophoresis. They accomplish this by delivering low medically tolerable electrical currents (0.1-1 mA/cm2) from an external electrode for minutes to hours. To be successful, iontophoretic technologies must use the right chemical, which is difficult to give by conventional means, has poor gut absorption, and can benefit from the use of an electric current to increase the speed or rate of administration. Drugs that must be administered on a continuous basis-24 hours a day, for example-may not be ideal candidates for iontophoretic technology. In contrast to other approaches, a number of iontophoretic-based skin patches are available for pharmaceutical delivery, including fentanyl, lidocaine/epinephrine, and, more recently, sumatriptan, a migraine treatment marketed under the brand name Zecuity. Zecuity offers low patient variability and four-hour delivery of migraine medicine at a fixed rate. The microprocessors can change how recommended doses are administered while continuously assessing skin resistance. Because the transport rate is precisely proportional to the supplied constant current, the transdermal route provides for drug kinetic control and dose increases. The maximum current that may be applied before reaching the pain threshold dictates how much medication is given. Currently, this technique cannot transport larger molecules.¹⁵

10.9. Magnetophoresis

It was found that the magnetic field's influence on the drug substance's diffusion flow strengthened with increasing applied strength. A predetermined magnetic field strength is applied to aid in the medication's systemic circulation penetration. Lidocaine was administered using a magnetophoretic TDDS patch at magnetic field intensities of 30, 150, and 300 mT. The transport of drug molecules is aided by the magnetokinesis phenomenon.

Furthermore, the drug's octanol/water partition coefficient increased from 13.80 to 25.94 at 300 mT by magnetophoretic treatment. Improvements in skin bioavailability were shown in vivo investigations as compared to ordinary nonmagnetic patches. By increasing blood flow and absorption at the level of the skin's blood vessels via the use of a heat-controlled mechanism, TDDS and devices enhance drug distribution.

The device's micro-unit generates chemo-reactive oxidative responses, which deliver the heat in the appropriate amount and relay it in a time-fixed fashion. The drug distribution from a nicotine patch applied to the upper arm of ten healthy non-smokers increased up to thirteen times at a controlled heat application of 43°C. The same results were observed when patches containing nitroglycerine were subjected to high ambient temperatures. The controlled-heat-aided drug delivery (CHADD) system or device facilitates the easier absorption of medication into the bloodstream by applying heat to the skin. The CHADD systems consist of a small heating unit that uses oxidation reactions to produce heat with a limited intensity and duration.¹⁶

11. Discussions

So, I elaborated on the advanced techniques for easy penetration of drug formulations through a transdermal patch via skin. I believe that my study is useful, and it will have a great impact on novel drug delivery systems in future applications. Transdermal drug delivery systems (TDDS) transport medications through the skin and into the bloodstream. They have several benefits compared to traditional oral or injectable methods, including enhanced patient adherence, bypassing first-pass metabolism, and prolonged drug release. Transdermal drug delivery is a method of systemically administering medications by applying a drug formulation to unbroken and healthy skin. The medicine first enters the stratum corneum, then passes through the deeper epidermis and dermis without accumulating in the dermal layer.¹⁷

12. Conclusions

Transdermal drug delivery devices are a cutting-edge medical innovation, particularly for patients who struggle to remember to take their prescriptions on time. To guarantee optimal patient outcomes, physicians and other bioallied health professionals should be knowledgeable about the correct transdermal system administration procedures. Consequently, technology in the pharmaceutical sector is advancing more quickly. Medication delivery methods have advanced, resulting in rate-controlled delivery with fewer adverse effects and continuous medication delivery with higher efficacy. Transdermal delivery is regarded as one of the more ancient forms of technology. The transdermal route is increasingly becoming the most commonly used method of medication delivery as a result of recent technological advancements. With its expanded therapeutic potential, TDDS can be used to create promising, deliverable medications that include both hydrophilic and hydrophobic active ingredients. With its expanded therapeutic potential, TDDS can be used to create promising, deliverable medications that include both hydrophilic and hydrophobic active ingredients. As a result, one of the pharmaceutical industry's fastest-growing segments is this technology.

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14. Conflict of Interest

The authors whose names are listed immediately below certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or nonfinancial interest in the subject matter or materials discussed in this manuscript.

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