Beyond Pills: The Future of Cardiovascular Disease Treatment Through Transdermal Delivery

Divyansh Singh[1], Shweta Mishra[2], Gopal Rai[2]

[1,2] Guru Ramdas Khalsa Institute of Science & Technology (Pharmacy)

Barela, Kukrikheda, *Jabalpur* (M.P.), 483001

Abstract

The management of hypertension necessitates long-term treatment since it significantly contributes to morbidity and mortality on a global scale. The therapeutic potential of antihypertensive medications is constrained by their frequent administration, inconsistent bioavailability, and significant first-pass metabolism. Transdermal drug delivery systems (TDDS), which offer a continuous and controlled release of medications with enhanced bioavailability and patient compliance, have emerged as a successful strategy to address these constraints.In this review, we emphasise the most recent advancements and breakthroughs in the field of TDDS usage for antihypertensive medication delivery. We present a comprehensive overview of various antihypertensive transdermal patches, including timolol maleate, nicardipine hydrochloride, captopril, atenolol, metoprolol tartrate, clonidine, indapamide, labetolol, pinacidil, verapamil hydrochloride, nitrendipine, nifedipine, nicorandil, propranolol hydrochloride, diltiazem hydrochloride, amlodipine besilate, carvedilol, and lisinopril.Overall, this study offers a thorough viewpoint on the newest transdermal drug delivery methods for the treatment of hypertension. With better patient outcomes and quality of life, the use of TDDS for antihypertensive medications has the potential to revolutionise the management of hypertension.

Keywords: *Transdermal drug delivery systems, TDDS, antihypertensive drugs, hypertension, sustained release, bioavailability, patient compliance, transdermal patches.*

Introduction

Historical Background of transdermal drug delivery system- Transdermal medication delivery has undergone substantial investigation throughout the years and has made great strides recently. Transdermal drug delivery's major goal is to administer medications to the bloodstream via the skin at a predefined pace while minimising patient variance. This delivery approach provides a number of benefits over conventional oral administration, including less stress on the liver and digestive system, improved patient compliance, and less unpleasant side effects brought on by transient overdose.[1] Transdermal delivery enables the consistent provision of medications with brief biological half-lives and delivers regulated and continuous drug administration. Additionally, this method of distribution prevents medications from entering the circulation pulsatilely, which frequently has unintended adverse effects.[2] The skin functions as a permeability barrier that limits the transdermal absorption of several chemical and biological substances since it is the biggest organ in the body. It separates the surface environment from the underlying blood circulation system and is thin (a few millimetres), making it easily accessible. The skin's roles include protecting against UV light penetration, physical, chemical, and microbiological assaults, controlling blood pressure, and more. Diffusional resistance of the skin is strongly influenced by its ultrastructure and morphology.[3]

The term "drug delivery system" (DDS) refers to a collection of technologies that control the distribution and release of substances that are pharmacologically active into cells, tissues, and organs in order to maximise their efficacy while minimising side effects [4, 5]. DDS focuses on drug formulations and delivery techniques that can efficiently carry drugs. There are several administration techniques, including as oral administration, transdermal administration, lung inhalation, mucosal administration, and intravenous injection, depending on the delivery route. Transdermal drug delivery system (TDDS) stands up as a potential approach among these techniques.

A non-invasive drug delivery technique that has undergone substantial investigation is TDDS. It has had a significant influence on how various medicinal chemicals are distributed, particularly in the treatment of cardiovascular and central nervous system illnesses, hormone therapy, and pain management [6–9]. Due to TDDS's ability to bypass the digestive tract, drugs can be delivered without being impeded by intestinal flora, pH, or enzymes. Additionally, TDDS can control medicine release in accordance with consumption restrictions. The fact that TDDS is a painless and practical method of giving drugs to patients, especially those who are elderly and young, is one of its many advantages.[10–12]

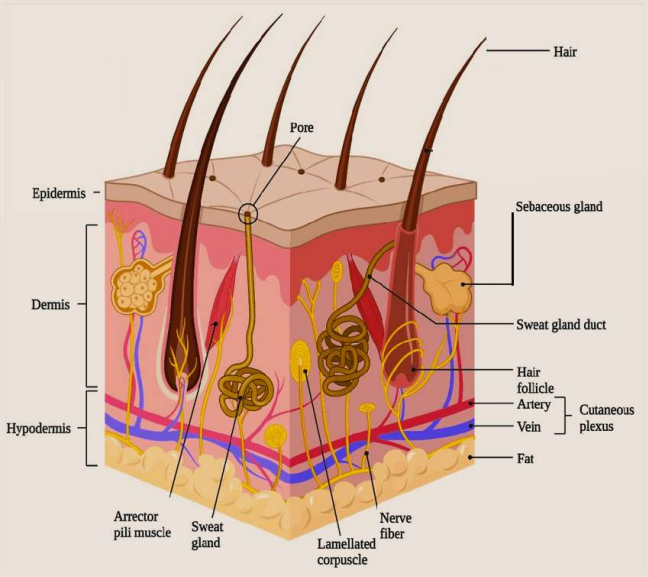


Figure-1 –Structure of the skin

However, due of the skin's natural barrier, TDDS still does not function to its full capacity. The skin, the body's largest organ that is located on the outside, has several layers that shelter us from the elements by insulating us from toxins, heat, and chemicals [13, 14] (Fig. 1). Each skin layer has elements that prevent transdermal distribution, such as the epidermis' function as a barrier and the dermis' capacity to produce skin cells and blood vessels.

The stratum corneum, the skin's outermost layer, is crucial to the epidermis' ability to act as a barrier by blocking the entry of outside elements. For the transport of substances with high molecular weights in the transdermal drug delivery system (TDDS), the barrier effect is particularly crucial. Although it is generally known that the intracellular pathway is used for medications with small molecular weights, other mechanisms and techniques, such as the intercellular pathway, have been developed and used for substances with high molecular weights [15–17].

The lipid layer, which is positioned erratically yet often, contains cells as well as hydrophilic and hydrophobic materials that make up the skin. The difficulty of transporting substances with high molecular weights via the skin is influenced by this structural characteristic of the skin. [18]

Given the structural qualities of the skin, the physicochemical properties of pharmaceuticals are crucial for enhancing drug transport through the skin. Transdermal medication distribution may potentially be hampered by the vascular system of the dermal layer. A layer of endothelial cells one cell thick, which culminates in the papillary loops of the superficial arteriovenous plexus close to the dermal-epidermal junction in the upper dermis, represents the interface between the tissues encircling the skin and the human vascular. Similar to how the endothelium functions throughout the body, the endothelium in the skin changes permeability and induces vasodilation or constriction in response to pressure, shear, osmotic pressure, heat, chemokines, and cytokines. To transmit medications to skin tissue and pass through cellular and vascular tissue to reach the target tissue, the stratum corneum's barrier effect must be overcome. It is difficult to give more than a little dose of medication through skin

tissue [19–21]. To get through the skin barrier and increase medication delivery effectiveness, active and passive transdermal drug delivery methods have been developed. Transdermal distribution is facilitated by passive approaches that take use of the drug's physicochemical characteristics, such as size and solubility. Iontophoresis, electroporation, and sonophoresis are examples of active procedures that employ outside energy sources to increase medication penetration [25–28]. These techniques offer the potential to increase the number of medications that can be given via the skin while also increasing the efficiency of drug administration. In addition to these approaches, innovative TDDS products have been created, such as hydrogels, nanoparticles, and microneedles, to enhance drug delivery effectiveness and get through the skin barrier [29]. Drugs can permeate the skin more readily thanks to microneedles, which are small needles. Drugs can be enclosed in carriers like nanoparticles and liposomes and delivered via the skin. Drugs may be released under regulated conditions using hydrogels, which are water-swollen networks. These innovations have the potential to completely transform the transdermal medication delivery industry and have demonstrated encouraging signs of increasing drug delivery effectiveness.nFuture forecasts predict that the market for transdermal medication delivery will expand due to the development of personalised medicine and tailored drug delivery systems.[30] According to a patient's genetic make-up, lifestyle, and other circumstances, personalised medicine includes treating them differently. To minimise negative effects and increase therapeutic efficacy, targeted drug delivery systems administer medications to certain cells or tissues. As they provide a non-invasive and tailored medication delivery technique, transdermal drug delivery systems have the ability to satisfy these objectives. [31] Contrary to topical administration, it has been demonstrated that external stimuli like electrical, mechanical, or physical stimulation improve the skin's permeability for drug transport. Active transdermal administration is a method that improves medication absorption via the skin by using specialised equipment. When compared to passive transdermal administration, which just depends on diffusion, this approach is different. Active transdermal delivery can transport drugs into the skin more quickly and reliably by applying external stimulation, potentially hastening the commencement of their therapeutic effects. This method has been thoroughly researched in the literature and shown to be efficient in delivering drugs and biomolecules. [73, 75-77]

Basic Principal of Transdermal permeation: Passive diffusion is essential for transdermal permeation, and the skin is a highly accessible organ because just a little layer of tissue separates its surface from the capillary network underneath it. A medicinal substance must go via a complicated, multi-step procedure from a formulation applied to the skin's surface to the body's circulatory system.

Advantages of transdermal drug delivery:

- Transdermal drug delivery enables the avoidance of gastrointestinal absorption with its associated pitfalls of enzymatic and pH associated deactivation.
- Avoidance of first pass metabolism.
- The lack of peaks in plasma concentration can reduce the risk of side effects, thus drugs that require relatively consistent plasma levels are very good candidate for transdermal drug delivery.
- As a substitute for oral route.

- The patch also permit constant dosing rather than the peaks and valley in medication level associated with orally administered medication.
- Rapid notifications of medication in the event of emergency as well as the capacity to terminate drug effects rapidly via patch removal.
- Avoidance of gastro intestinal incompatibility.

Convenience especially notable in patches that require only once weekly application, such a simple dosing regimen can aid in patient adherence to drug therapy.

- Minimizing undesirable side effects.
- Provide utilization of drug with short biological half lives, narrow therapeutic window.
- Avoiding in drug fluctuation drug levels.
- Inter and intra patient variation.
- Termination of therapy is easy at any point of time.
- Provide suitability for self administration.
- They are non invasive, avoiding the inconvenience of parentral therapy.

The drug reservoir in the therapeutic delivery system and its regulated release help prolong the action of medications with a short half-life.It has significant benefits for people who are queasy or unconscious. Transdermal patches are a superior delivery method for medications that are significantly destroyed by the liver, poorly absorbed from the gut, or broken down by the stomach.

The price of transdermal patches is reasonable.

Disadvantages of transdermal drug delivery:

- Transdermal drug delivery system cannot deliver ionic drugs.
- It cannot achieve high drug levels in blood.
- It cannot develop for drugs of large molecular size.
- It cannot deliver drugs in a pulsatile fashion.
- It cannot develop if drug or formulation causes irritation to skin.
- Possibility of local irritation at site of application.
- May cause allergic reaction.
- Sufficient aqueous and lipid solubility, a log P (octanol/ water) between 1 and 3 is required for permeate to transverse stratum corneum and underlying aqueous layer.
- Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin’s impermeability.

TRANSDERMAL DELIVERY ENHANCER

Table 1 The advantages and disadvantages of various transdermal delivery system.

Method	Advantages	Disadvantages	Ref.
Active Delivery	Iontophoresis	• Risk of burns if electrodes are used improperly	[25–29]
	• Improving the delivery of polar molecules as well as high molecular weight compounds	• Difficulty stabilizing the therapeutic agent in the vehicle	
	• Faster and easier administration	• Complexity of the drug release system	
	• Enabling continuous or pulsatile delivery of drug		
	Sonophoresis	• Can be prolonged to administer	[30–33]
	• Allows strict control of transdermal diffusion rates	• Minor tingling, irritation and burning	
	• In many cases, greater patient approval	• SC must be unbroken for effective drug penetration	
	• Less risk of systemic absorption		
	• Helpful to break up blood clots		
	Electroporation	• Impossible to use on a large area	[34–36]
	• Highly effective, reproducible, directed drug transfer	• Can disturb the cargo if high voltage is used	
	• Permits rapid termination of drug delivery through termination	• Possibility of cell damage	
	• Not immensely sensitizing	• Relatively nonspecific	
	Photomechanical waves	• Can improve transfer of molecules across the plasma membrane of cells in vitro without loss of viability	[37–40]
	• Not appear to cause injury to the viable skin	• Lack of human clinical data	
	• Do not cause pain or discomfort		
	Microneedle	• Painless administration of the active pharmaceutical ingredient	[41–54]
	• Faster healing at injection site	• Lower dosing accuracy than hypodermic needles	
	• No fear of needle	• Penetration depth of various particles depending on the skin layer	
	• Specific skin area can be targeted for proper drug delivery	• Possibility of venous collapse due to repeated injections	
	Thermal ablation	• Avoid the pain, bleeding, and infection	[55–59]
	• Can remove SC selectively without damaging deeper tissues	• Structural changes in the skin must be evaluated	
	• Better control and reproducibility	• Existing concerns about the use of extreme temperatures and the logistics of such devices	
	• Low cost and disposable device		
Passive Delivery	Vesicles	• Chemically unstable	[60–63]
	• Accomplish sustained drug release behavior	• Expensive of formulations	
	• Control the absorption rate through a multilayered structure		

- **IONTOTHERAPY:**

Iontophoresis is a method of administering drugs that improves skin penetration and speeds up the release of substances from drugs with subpar absorption or permeation characteristics. This technique encourages ion migration across the membrane by employing a tiny externally applied potential difference (less than 0.5 mA/cm2). Using an electrochemical potential gradient, iontophoresis has been utilised to transport both ionic and nonionic medicines in vivo. The polarity, valency, and mobility of the therapeutic molecule, the kind of electrical cycle employed, and the drug formulation all have an impact on iontophoresis's efficacy. Iontophoresis relies more on the applied current than it does on biological variables, in contrast to other medication delivery techniques. To increase patient compliance, this method may also include electronic reminders. (Fig. 2 1, 2) [25-28].

The experimental setup for skin permeation testing using iontophoresis is presented in Figure 2.

Figure 2 shows the in vitro drug release profiles of drug-loaded AuNP oleogels (d-AuNP) on skin.

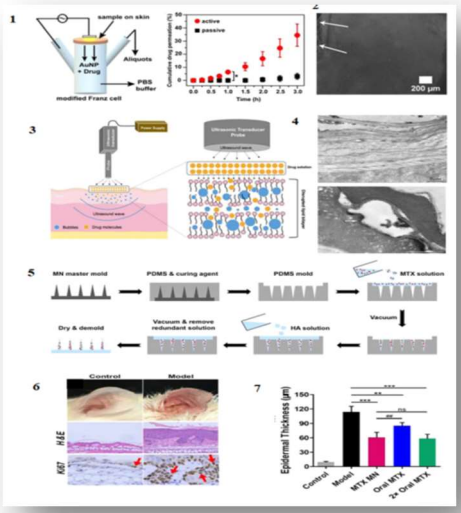
Figure 3 displays fluorescence spectroscopy images obtained from a skin permeation experiment after 1 hour of application, with arrows marking the top surface of the skin segment treated with d-AuNP.Figure 4 provides a schematic illustration of sonophoresis-assisted transdermal drug delivery.

Figure 5 demonstrates the penetration pathways of LaNO3 after treatment with low-frequency sonophoresis, along with TEM images of SC before and after treatment.

Figure 7 presents a schematic illustration of the fabrication process of the MTX-loaded HA-based dissolving MN patch.

Finally, Figure.6 provides a quantitative analysis.

The figures illustrate various aspects of transdermal drug delivery, including iontophoresis, sonophoresis, and microneedle-based systems. The images show drug release profiles, penetration pathways, and fabrication processes for drug delivery patches. The quantitative analysis in Figure 6 provides additional data on the effectiveness of the drug delivery system.



- **ULTRASOUND-MEDIATED DRUG DELIVERY**

Ultrasonic devices that generate the necessary range of ultrasound frequencies can improve transdermal medication administration [30,31]. Low-frequency ultrasound is more effective because it establishes an aqueous route in the disrupted bilayer through cavitation (Fig. 2C). To create an aqueous route, the drug is combined with a specialized coupler, such as a gel or cream, which couples ultrasonic waves to the skin and disrupts the skin layers. Typically, drugs move through channels created by applying ultrasonic waves with energies ranging from 20 kHz to 16 MHz. Ultrasound also increases the local temperature of the skin, producing a thermal effect that aids in the uptake of drugs. This technique has been used to deliver various medications from different classes, including those with poor solubility, dissociation and ionisation constants, and electrical characteristics (including hydrophilicity), such as mannitol and high molecular weight (MW) drugs like insulin. However, there are still challenges to overcome, such as device accessibility, maximizing exposure time and treatment cycles for delivery, and unfavorable side effects like burns. The exact mechanism of drug penetration using this approach is still not fully understood.

ELECTROPERMEABILIZATION

The process of electroporation includes delivering high-voltage electric pulses to the skin for milliseconds at a time. As a result, the stratum corneum (SC) develops tiny holes that increase permeability and aid in drug diffusion [34, 35]. Using sparsely spaced electrodes, electric pulses are administered in a pleasant and secure manner. Both low and large molecular weight medicines, such as oligonucleotides, the negatively charged anticoagulant heparin, and antiangiogenic peptides, have been effectively delivered using this method. The poor delivery capacity, considerable cellular disturbance, including cell death, drug degradation owing to heating, and denaturation of therapeutic proteins and other biomacromolecules are some drawbacks of this approach, which is normally painless and safe.

PHOTOMECHANICAL WAVES

Drugs can enter via temporary channels in the skin that can be created by photodynamic waves [37, 39]. With a modest radiation dose of just 5-7 J/cm2, the incident wave generates limited ablation that can penetrate the skin to a depth of 50–400 m. The parameters of the photodynamic wave need to be precisely adjusted in order to guarantee that the medication is delivered to the desired depth in the skin. Compared to earlier direct ablation methods, this restricted ablation has a longer peak and duration. Skin permeability increases minutes after a single laser pulse, enabling macromolecules to diffuse into the skin. 40 kDa macromolecules and 20 nm latex particles may be supplied with a single 23 ns photodynamic laser pulse.

- **MICRONEEDLE**

The microneedle drug delivery system is a cutting-edge strategy that administers medicine into the circulatory system using a needle [41]. One of the most popular approaches of transdermal medication administration, it is being further refined via continuous study. This method includes puncturing the epidermal layer of the skin with tiny needles to allow the drug to diffuse. Since microneedles are small and delicate, they provide the least amount of discomfort for patients while still delivering medicine straight to the blood capillary region for active absorption [42]. The geometric dimensions required for effective insertion of microneedles into human skin are the main areas of research attention. In-depth research has been done on the development of microneedle devices, taking into account the intended usage, drug kind, and dose [43]. Currently, photolithography and laser-mediated procedures are the two most widely utilised processes for making microneedles. To construct the 3D structure of the microneedle, laser-mediated processes entail cutting or ablating a flat metal or polymer surface. However, using etched photoresist to create an inverse mould of the microneedle structure, photolithography makes it possible to construct microneedles made of silicon or hydrogel that dissolve when exposed to water. The production of different microneedle systems also makes use of 3D printing, microstereolithography, and two-photon polymerization. There are several different kinds of microneedles that can be made, including hollow microneedles for drug storage and administration (such as syringes) and solid microneedles that provide a physical pathway for drug absorption. Drug-coated microneedles also deliver drugs as they penetrate the skin. The design, size, and form of these microneedles may be tailored for different drug types and administration sites utilising a range of production methods, including laser-mediated fabrication, photolithography, and 3D printing. [44-49]

ABLATION THROUGH HEAT

Thermophoresis, sometimes referred to as thermal ablation, is a procedure that has the potential to develop skin microchannels for more effective drug administration by selectively destroying the stratum corneum's structural integrity with focussed heat [55]. A temperature above 100°C is necessary to thermally ablate the stratum corneum because it warms and vaporises keratin. The degree of the stratum corneum's structural alteration is closely correlated with the area's raised temperature, which makes thermal ablation the perfect technique for precisely controlling medicine delivery. The thermal exposure must be short (microseconds or fewer), producing a high enough temperature gradient throughout the skin, in order to selectively ablate the stratum corneum without harming

the healthy epidermis. As long as deeper tissue cells are uninjured, the ensuing micron-scale defects (50–100 nm in diameter) are too tiny to cause pain, bleeding, irritation, or infection. Thermal ablation is more repeatable and controlled than other techniques like mechanical abrasion, chemical etching, or tape-stripping. Both tiny and big molecules may be delivered successfully using this technique. When employing additional energy to hasten the diffusion of drug molecules, it is crucial to take into account the structural changes to the skin. Radiofrequency technology can also be used to create thermal ablation procedures. A tiny electrode is introduced into the skin during radiofrequency thermal ablation, which produces a high-frequency electric current that warms the skin and enlarges the pores. Additionally, this method may be utilised to enhance medication distribution and promote skin diffusivity. By altering the electrode size, temperature, and exposure time, the depth of ablation may be managed. It has been demonstrated that radiofrequency thermal ablation enhances the transport of medicines, including macromolecules like proteins and peptides, that are both hydrophilic and lipophilic [57, 59]. The development of microneedle-based drug delivery systems can be facilitated by the use of laser and radiofrequency thermal ablation, both of which have the potential to improve drug delivery. An array of metallic microelectrodes that are directly applied to the skin during radiofrequency thermal ablation produce channels in the stratum corneum that are a few nanometers wide. The skin is exposed to high-frequency electric current, which results in ionic vibrations and the generation of heat in certain skin areas. As a result, the heat produced by the water evaporation ablates the epidermis cells underneath each filament and creates microchannels that can be up to 50 m deep. In a matter of seconds, the procedure is finished, and fluid-filled microchannels are created, allowing hydrophilic molecules to flow through. The depth of the ablated skin is determined by the size and density of the microchannels, which are inversely correlated with the rate of drug transport. With a low-cost, disposable device, radiofrequency thermal ablation can increase the transport of numerous hydrophilic medicines, including macromolecules, and prolong drug release [59]. The use of chemical substances that can boost drug penetration via the skin is known as passive administration of chemical enhancers. The majority of these enhancers are tiny compounds with a high lipophilicity, which enables them to dissolve in the stratum corneum and produce transient fluid-filled channels that allow medicines to flow through. By lessening the cohesive forces between skin cells and so increasing the permeability of the skin barrier, chemical enhancers can also alter the stratum corneum's structural integrity [64].

There have been studies on a variety of chemical enhancers, including surfactants, fatty acids, alcohols, and terpenes. To boost medication distribution, these enhancers can be employed separately or in combination. For instance, it is possible to reduce the melting point and improve the solubility of medications in the skin by combining two or more chemicals in a eutectic mixture. Similar to this, medications can be enclosed in self-assembled vesicles comprised of nanoparticle composites to improve their distribution through the skin [65, 66].

Researchers have studied the skin lipid barrier and the transport of penetration enhancers using molecular modelling approaches in order to better understand the processes that control drug penetration across the skin. These techniques can aid in the prediction of the effectiveness and safety of various transdermal drug delivery schemes by modelling the interaction of medicines and enhancers with skin lipids and proteins.

VESICLES

The use of chemical substances that can boost drug penetration via the skin is known as passive administration of chemical enhancers. The majority of these enhancers are tiny compounds with a high lipophilicity, which enables them to dissolve in the stratum corneum and produce transient fluid-filled channels that allow medicines to flow through. By weakening the forces that hold skin cells together, chemical enhancers can also change the structure of the stratum corneum, increasing the permeability of the skin barrier. [64]. There have been studies on a variety of chemical enhancers, including surfactants, fatty acids, alcohols, and terpenes. To boost medication distribution, these enhancers can be employed separately or in combination. For instance, it is possible to reduce the melting point and improve the solubility of medications in the skin by combining two or more chemicals in a eutectic mixture. Drugs can also be enclosed in self-assembled vesicles comprised of nanoparticle composites to improve their transport over the skin. [65, 66]. Researchers have studied the skin lipid barrier and the transport of penetration enhancers using molecular modelling approaches in order to better understand the processes that control drug penetration across the skin. These techniques can aid in the prediction of the effectiveness and safety of various transdermal drug delivery schemes by modelling the interaction of medicines and enhancers with skin lipids and proteins. Transfersomes are a type of vesicle that has been developed to improve drug delivery through the skin. They are also known as deformable liposomes or elastic liposomes, and their defining characteristic is their high flexibility. This flexibility is due to the inclusion of single-chain surfactants, which transform the phospholipid bilayer and make the vesicles highly malleable. There are three generations of transfersomes, each with different compositions. First-generation transfersomes are composed of phospholipids and single-chain surfactants. Second-generation transfersomes contain at least two or more polar lipophilic molecules and at least one basic bilayer building component, typically fluid-phase phosphatidylcholine lipids. Third-generation transfersomes are made up of amphiphilic surfactants, either alone or in combination with phospholipids. Transfersomes are highly deformable, which allows them to penetrate through small pores in the skin. This property makes them an excellent choice for delivering macromolecular medications such as peptides and proteins. Compared to liposomes, transfersomes have higher skin permeation properties, which leads to increased drug absorption and efficacy. Transfersomes have been shown to improve the skin penetration of a variety of drugs, making them a promising technology for transdermal drug delivery.[62] Ethosomes are composed of phospholipids, alcohols, and water, with a higher alcohol concentration compared to liposomes. Both phospholipids and ethosomal formulations are known to facilitate the percutaneous delivery of drugs. As ethanol molecules replace water molecules near the lipid headgroup, the structure of the ethosome becomes more fluid and elastic. Due to their small particle size, stable structure, and high drug capture efficiency, ethosomes are capable of delivering medications deeply into the skin and even through it, leading to increased drug absorption and efficacy. Ethosomes are a type of multiphase dispersion system for skin-penetrating drugs with a molecular weight of up to 1000 kDa. Moreover, TDDS using transfersomes can provide more stable and longer retention time for these vesicles, enhancing their effectiveness in drug delivery. [63].

- **HYBRID NANOPARTICLES**

Nanoparticles (NPs) are nanocarriers with diameters ranging from 1 to 1000 nm that can be classified into different types based on their composition. Drug delivery using NPs provides targeted and controlled release, modifications to drug dynamics in vivo, and prolonged drug circulation, all of which enhance medication bioavailability and reduce toxicity and adverse effects. Traditional methods for manufacturing NPs involve polymerization and crosslinking, with biodegradable polymeric materials such as gelatin and polylactic acid (PLA) commonly used [67, 69, 70]. Polymeric NPs are gaining popularity in transdermal drug delivery systems because they can overcome the limitations of lipid-based systems. For instance, they can protect unstable drugs from degradation and denaturation, and facilitate continuous drug release to minimize side effects. The concentration gradient of drug permeation across the skin is enhanced by transdermal delivery. Depending on their structure and manufacturing process, polymeric NPs can be classified as nanospheres, nanocapsules, or polymer micelles. Chitosan, gelatin, alginate, poly(D,L-lactide-co-glycolide) (PLGA), polycaprolactone, and polyacrylic acid are among the commonly used natural polyesters and polymers. In certain conditions where a synthetic membrane resembling the cellular lipid bilayer membrane exists, these polymer chains can be formed by covalently linking two or more single polymeric units. Due to their high molecular weight, these polymers can form complex structures. However, the polymer membrane is highly structured, making it impossible for polymeric NPs, which have high mechanical strength and non-deformability, to pass through pores smaller than or equal to their size. Nevertheless, medications can be stored for a prolonged period before being released from the NPs and diffused into the deeper layers of the skin because these NPs can be difficult to degrade[68, 78-80].

- **NANOEMULSION**

Nanoemulsions are a type of mixture that exhibit low viscosity, isotropy, thermodynamic, and dynamic stability [71]. They consist of tiny, transparent or translucent oil droplets that are dispersed in an aqueous phase and stabilized by a surfactant or co-surfactant layer. The droplet size of nanoemulsions ranges from 100 to 1000 nm, with an upper limit proposed due to its nanoscale dimensions. Nanoemulsions have a high specific surface area, low surface tension, and small particle size, which make them highly wettable and provide close contact with the skin. They offer several advantages over other topical skin therapies, including great solubilization capacity, physical stability, enhanced bioavailability, simplicity of manufacture, low energy requirement, and long shelf life. Additionally, nanoemulsions have a shorter transdermal time and greater transdermal absorption compared to other topical therapies. They can be classified into oil-in-water (O/W) nanoemulsions, water-in-oil (W/O) nanoemulsions, and bicontinuous/multiphasic nanoemulsions, with O/W nanoemulsions being more commonly used in pharmaceuticals due to their ability to encapsulate lipophilic components [58, 68]. These unique characteristics make nanoemulsions a promising candidate for use in transdermal drug delivery systems and could lead to significant advancements in pharmaceutical applications.

- **CHARACTERIZATION TECHNIQUES FOR TDDS**

To ensure that TDDS is effective and efficient, an important step is to evaluate the delivery of the medication. Different techniques are used depending on the type and purpose of the medication. Three popular techniques for evaluation are microscopic and spectroscopic examination, tape stripping, and diffusion cells. Each technique uses a different method of analysis, but all are based on the principle of measuring drug concentration in each layer of the surface as it is absorbed, or using an imaging material instead of the drug to visually confirm the absorption pattern. These techniques are well documented in the literature, with references provided for further reading [81, 82].

When it comes to evaluating TDDS efficiency, diffusion cell tests are considered the standard method, with Franz diffusion cells being the most commonly used configuration (Fig. 4) [84, 85]. This technique enables critical links to be established between the skin, active pharmaceutical ingredients, and formulation characteristics. The diffusion cell comprises an application chamber for the drug, a membrane for the drug to diffuse through, and an acceptor media chamber from which samples can be examined. Two main types of diffusion cells exist, namely static and flow-through cells. In static cells, such as the widely used Franz diffusion cell, the donor, membrane, and acceptor modules can be arranged vertically or horizontally. Some Franz cells open upward, using ambient pressure for measurement. However, most cells are top-closed, resulting in higher pressure that could lead to overestimated penetration values. Recently, automated samplers have replaced Franz diffusion cells used in "hand-sampler" experiments. These automated devices simplify researchers' work and reduce experimental errors.

- **TAPE STRIPPING**

Tape stripping is a minimally invasive method to evaluate the penetration of topically applied formulations through the SC layer. This technique involves removing a layer of the SC with an adhesive tape and then analyzing the skin layer on the tape [74, 83, 86, 87]. After applying the test formulation topically and allowing it to incubate for a specific time, the tape is removed. The composition can be removed or left on the skin to provide the initial quantity of components for measurement. The adhesive tape is applied to the skin surface and removed from the same area to avoid creases and recesses affecting the results. The elimination rate is also a critical factor. The amount of skin removed from the patch increases proportionally to the slow removal of the adhesive tape because the SC layer adheres to the patch with more strength. The sticky tape removed contains both the SC layer and the mixture present in use. Various techniques can be used to analyze samples collected with adhesive tape. Spectroscopic techniques provide semiquantitative insights, whereas results from high-performance liquid chromatography (HPLC) analysis are quantitative. During HPLC analysis, the test substance on the adhesive tape is extracted and subjected to chromatographic separation for analysis. Active compounds can also be identified using atomic absorption spectroscopy.[88]

The analysis of skin obtained via tape stripping is commonly performed using attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR), which is based on changes in oscillations and atom-bonding angles resulting from the absorption or scattering of infrared light. The measurement involves plotting the transmitted

radiation as a function of wavelength/wavenumber to determine the change in radiation as it passes through the sample. The resulting spectrum provides both qualitative and quantitative data. The depth of penetration is influenced by the infrared radiation's wavelength, the refractive index of the ATR crystal, the material being measured, and the angle of reflection. The use of tape stripping in conjunction with ATR-FTIR spectroscopy enables the detection of various exogenous compounds in particular layers of the SC. However, the technique has limitations, such as overlapping peaks between the drug and skin characteristic peaks, which may hinder detection.

CONCLUSION AND PROSPECTIVE FUTURE

TDDS technology has revolutionized drug delivery, becoming the preferred method for transdermal delivery across different skin types, while avoiding first-pass metabolism and other issues associated with alternative drug administration routes. TDDSs offer consistent and secure drug administration, with stable drug formulation until they reach the target area. They allow for controlled and uniform drug distribution, making them noninvasive, nonallergenic, and easy to administer. New and old formulations have improved bioavailability for drugs with low absorption rates, with simple administration routes allowing for larger dosages over an extended period. TDDS technology is expanding rapidly in the pharmaceutical industry and gaining critical value in biomedical applications, due to its ability to enhance drug delivery through topical channels.

Despite years of research, passive approaches such as chemical enhancers have only provided moderate improvements in the transdermal transport of small molecules and slightly improved transport of macromolecules in potentially clinically acceptable situations. Active transport methods using external devices have significantly improved the transdermal delivery of medicines and macromolecules, but their effectiveness is partially offset by their dependency on electronic control systems, which require energy sources and have limited usefulness and expense. Microneedle-based techniques can greatly increase transdermal distribution, but further research is needed to ensure increased safety, minimal skin injury, and cost-effectiveness. The TDDS technology has witnessed significant growth in recent years, as indicated by the rise in research studies, patents, and available products from various firms and research institutions. Among the different TDDS modalities, microneedles have gained significant attention due to their ability to combine the benefits of existing simple application and patch-type needles with the advantages of microneedles to enhance treatment effectiveness and outcomes. To achieve this, production and commercialization techniques are being developed, leveraging cutting-edge technologies such as 3D bioprinting. Advancements in TDDSs have the potential to drive progress in vaccination and encourage patient self-administration of medications for long-term treatment. Furthermore, they could serve as a means of reducing the prevalence of various diseases, including those related to the cardiovascular and central nervous systems, diabetes, neuromuscular diseases, genetic diseases, and infectious diseases.

CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REFERENCES:

1. Jalwal P, Jangra A, Dhaiya L, Sangwan Y, Saroha R. (2010). A review on transdermal patches. Pharmaceutical Research Journal, 3, 139-149.
2. Bhowmik D, Chiranjib, Chandira M, Jayakar B, Sampath KP. (2010). Recent advances in transdermal drug delivery system. International Journal of Pharmaceutical Technology Research, 2(1), 68-77.
3. Kumar A, Pullankandam N, Prabhu SL, Gopal V. (2010). Transdermal drug delivery system: an overview. International Journal of Pharmaceutical Sciences Review and Research, 3(2), 49-54.
4. Divya A, Rao MK, Gnanprakash K, Sowjanya A, Vidyasagar N, Gobinath M. (2012). A review on the current scenario of transdermal drug delivery systems. International Journal of Research in Pharmaceutical Sciences, 3(4), 494-502.
5. Vega-Vásquez P, Mosier NS, Irudayaraj J. Nanoscale drug delivery systems: from medicine to agriculture. Front Bioeng Biotechnol. 2020;8:79. doi: 10.3389/fbioe.2020.00079.
6. Vargason AM, Anselmo AC, Mitragotri S. The evolution of commercial drug delivery technologies. Nat Biomed Eng. 2021. doi: 10.1038/s41551-021-00698-w.
7. Mali AD, Bathe R, Patil M. An updated review on transdermal drug delivery systems. Int J Adv Sci Res. 2015;1(6):244-54. doi: 10.7439/ijasr.v1i6.2243.
8. Li C, Wang J, Wang Y, Gao H, Wei G, Huang Y, et al. Recent progress in drug delivery. Acta Pharm Sin B. 2019;9(6):1145-62. doi: 10.1016/j.apsb.2019.08.003.
9. Kumar JA, Pullakandam N, Prabu SL, Gopal V. Transdermal drug delivery system: An overview. Int J Pharm Sci Rev Res. 2010;3(2):49-54.
10. Roohnikan M, Laszlo E, Babity S, Brambilla DA. Snapshot of transdermal and tropical drug delivery research in Canada. Pharmaceutics. 2019;11(6):256. Available from: https://doi.org/10.3390/pharmaceutics11060256.
11. Peña-Juárez MC, Guadarrama-Escobar OR, Escobar-Chávez JJ. Transdermal delivery Systems for Biomolecules. J Pharm Innov. 2021;6:1–14.
12. Ali H. Transdermal drug delivery system & patient compliance. MOJ Bioequiv Availab. 2017;3(2):47–8.
13. Leppert W, Malec–Milewska M, Zajaczkowska R, Wordliczek J. Transdermal and Topical Drug Administration in the Treatment of Pain. Molecules. 2018;23(3):681.
14. Akhter N, Singh V, Yusuf M, Khan RA. Non-invasive drug delivery technology: development and current status of transdermal drug delivery devices, techniques and biomedical applications. Biomed Tech. 2020;65(3): 243–72. Available from: https://doi.org/10.1515/bmt-2019-0019.
15. Pires LR, Vinayakumar KB, Turos M, Miguel V, Gaspar J. A perspective on microneedle-based drug delivery and diagnostics in Paediatrics. J Pers Med. 2019;9(4):49. Available from: https://doi.org/10.3390/jpm9040049.
16. Ruby PK, Pathak SM, Aggarwal D. Critical attributes of transdermal drug delivery system (TDDS) – a generic product development review. Drug Dev Ind Pharm. 2014;40(11):1421–8. Available from: https://doi.org/10.3109/03639045.2013.879720.

17. Ali, S., Shabbir, M., & Shahid, N. (2015). The structure of skin and transdermal drug delivery system - a review. Research Journal of Pharmaceutical Technology, 8(2), 103-109. https://doi.org/10.5958/0974-360X.2015.00019.0
18. Wang, M., Luo, Y., Wang, T., Wan, C., Pan, L., Pan, S., et al. (2020). Artificial skin perception. Advanced Materials, 33, e2003014.
19. Hutton, A. R., McCrudden, M. T., Larrañeta, E., & Donnelly, R. F. (2020). Influence of molecular weight on transdermal delivery of model macromolecules using hydrogel-forming microneedles: potential to enhance the administration of novel low molecular weight biotherapeutics. Journal of Materials Chemistry B, 8(19), 4202-4209. https://doi.org/10.1039/D0TB00021C
20. Andrews, S. M., Jeong, E. H., & Prausnitz, M. R. (2013). Transdermal delivery of molecules is limited by full epidermis, not just stratum corneum. Pharmaceutical Research, 30(4), 1099-1109.
21. Chaulagain, B., Jain, A., Tiwari, A., Verma, A., & Jain, S. K. (2018). Passive delivery of protein drugs through transdermal route. Artificial Cells, Nanomedicine, and Biotechnology, 46(1), 472-487. https://doi.org/10.1080/21691401.2018.1430695
22. Uchechi, O., Ogbonna, J., & Attama, A. A. (2014). Nanoparticles for dermal and transdermal drug delivery. In A. D. Sezer (Ed.), Application of Nanotechnology in Drug Delivery (pp. 193-235). InTech.
23. Zhou, X., Hao, Y., Yuan, L., Pradhan, S., Shrestha, K., & Pradhan, O. (2018). Nanoformulations for transdermal drug delivery: a review. Chinese Chemical Letters, 29(12), 1713-1724. https://doi.org/10.1016/j.cclet.2018.10.037
24. Kováčik, A., Kopečná, M., & Vávrová, K. (2020). Permeation enhancers in transdermal drug delivery: benefits and limitations. Expert Opinion on Drug Delivery, 17(2), 145-155. https://doi.org/10.1080/17425247.2020.1713087
25. Pawar, P. M., Solanki, K. P., & Mandali, V. A. (2018). Recent advancements in transdermal drug delivery system. International Journal of Pharmacy and Clinical Research, 10(3), 65-73.
26. Mujoriya, R., & Dhamande, K. A. (2011). Review on transdermal drug delivery system. Research Journal of Science and Technology, 3(4), 227-231.
27. Mujoriya R, Dhamande KA. Review on transdermal drug delivery system. Res J Sci Tech. 2011;3(4):227–31.
28. Patel R, Patel A, Prajapati B, Shinde G, Dharamsi A. Transdermal drug delivery systems: A mini review. Int J Adv Res. 2018;6(5):891–900. doi: 10.21474/IJAR01/7109.
29. Kakar S, Singh R, Rani P. A review on transdermal drug delivery. Innoriginal Int J Sci. 2016;3(4):1–5.
30. Wang Y, Zeng L, Song W, Liu J. Influencing factors and drug application of iontophoresis in transdermal drug delivery: an overview of recent progress. Drug Deliv Transl Res. 2021. doi: 10.1007/s13346-021-00898-6.
31. Dhal S, Pal K, Giri S. Transdermal delivery of gold nanoparticles by a soybean oil-based oleogel under iontophoresis. ACS Appl Bio Mater. 2020; 3(10):7029–39. doi: 10.1021/acsabm.0c00893.
32. Moarefian M, Davalos RV, Tafti DK, Acheniec LE, Jones CN. Modeling iontophoretic drug delivery in a microfluidic device. Lab Chip. 2020;20(18):3310–21. doi: 10.1039/D0LC00602E.

33. Byrne JD, Yeh JJ, DeSimone JM. Use of iontophoresis for the treatment of cancer. J Control Release. 2018;284:144–51. doi: 10.1016/j.jconrel.2018.06.020.
34. Sloan JB, Soltani K. Iontophoresis in dermatology: a review. J Am Acad Dermatol. 1986;15(4):671–84. doi: 10.1016/S0190-9622(86)70223-5.
35. Park J, Lee H, Lim GS, Kim N, Kim D, Kim YC. Enhanced transdermal drug delivery by sonophoresis and simultaneous application of sonophoresis and iontophoresis. AAPS PharmSciTech. 2019;20(3):96. doi: 10.1208/s12249-019-1309-z.
36. Seah BC, Teo BM. Recent advances in ultrasound-based transdermal drug delivery. Int J Nanomedicine. 2018;13:7749–63. doi: 10.2147/IJN.S174759.
37. Nguyen HX, Banga AK. Electrically and ultrasonically enhanced transdermal delivery of methotrexate. Pharmaceutics. 2018;10(3):117. doi: 10.3390/pharmaceutics10030117.
38. Escobar-Chávez JJ, Díaz-Torres R, Domínguez-Delgado CL, Rodríguez-Cruz IM, López-Arellano R, Hipólito EAM. Therapeutic applications of sonophoresis and sonophoretic devices. In: Percutaneous Penetration Enhancers Physical Methods in Penetration Enhancement. Springer-Verlag Berlin Heidelberg; 2017. p. 31–58.
39. Charoo NA, Rahman Z, Repka MA, Murthy SN. Electroporation: An avenue for transdermal drug delivery. Curr Drug Deliv. 2010;7(2):125–36. doi: 10.2174/156720110791011765.
40. Chen X, Zhu L, Li R, Pang L, Zhu S, Ma J, et al. Electroporation-enhanced transdermal drug delivery: effects of logP, pKa, solubility and penetration time. Eur J Pharm Sci. 2020;151:105410. doi: 10.1016/j.ejps.2020.105410.
41. Sokołowska E, Błachnio-Zabielska AU. A critical review of electroporation as a plasmid delivery system in mouse skeletal muscle. Int J Mol Sci. 2019;20(11):2776. doi: 10.3390/ijms20112776.
42. Dermol-Černe J, Pirc E, Miklavčič D. Mechanistic view of skin electroporation – models and dosimetry for successful applications: an expert review. Expert Opin Drug Deliv. 2020;17(5):689–704. doi: 10.1080/17425247.2020.1745772.
43. Escobar-Chávez JJ, Bonilla-Martínez D, Villegas-González MA, Revilla-Vázquez AL. Electroporation as an efficient physical enhancer for skin drug delivery. J Clin Pharmacol. 2009;49(11):1262–83. doi: 10.1177/0091270009344984.
44. Lin CH, Aljuffali IA, Fang JY. Lasers as an approach for promoting drug delivery via skin. Expert Opin Drug Deliv. 2014;11(4):599–614. doi: 10.1517/17425247.2014.885501.
45. Lee S, Kollias N, McAuliffe DJ, Flotte TJ, Doukas AG. Topical drug delivery in humans with a single photomechanical wave. Pharm Res. 1999;16(11):1717–21. doi: 10.1023/A:1018954015441.
46. Agrawal S, Gandhi SN, Gurgar P, Saraswathy N. Microneedles: An advancement to transdermal drug delivery system approach. J Appl Pharm Sci. 2020;10(3):149–59.
47. Zhao Z, Chen Y, Shi Y. Microneedles: a potential strategy in transdermal delivery and application in the management of psoriasis. RSC Adv. 2020;10(24):14040–9. doi: 10.1039/D0RA00735H.
48. Jung JH, Jin SG. Microneedle for transdermal drug delivery: current trends and fabrication. J Pharm Investig. 2021. doi: 10.1007/s40005-021-00512-4.

49. Shakya AK, Ingrole RSJ, Joshi G, Uddin MJ, Anvari S, Davis CM, et al. Microneedles coated with peanut allergen enable desensitization of peanut sensitized mice. J Control Release. 2019;314:38–47. doi: 10.1016/j.jconrel.2019.09.022.
50. Lim J, Tahk D, Yu J, Min DH, Jeon NL. Design rules for a tunable merged-tip microneedle. Microsyst Nanoeng. 2018;4(1):1–10.
51. Dardano P, Caliò A, Palma VD, Bevilacqua MF, Matteo AD, Stefano LD. A photolithographic approach to polymeric microneedles array fabrication. Materials. 2015;8(12):8661–73. https://doi.org/10.3390/ma8125484.
52. Han D, Morde RS, Mariani S, Mattina AAL, Vignali E, Yang C, et al. 4D printing of a bioinspired microneedle array with backward-facing barbs for enhanced tissue adhesion. Adv Funct Mater. 2020;30(11):1909197. https:// doi.org/10.1002/adfm.201909197.
53. Xiao Z, Li X, Zhang P, Wang Y. Research of polymeric microneedles for transdermal drug delivery. Progress Chem. 2017;29(12):1518.
54. Balmert SC, Carey CD, Falo GD, Sethi SK, Erdos G, Korkmaz E, et al. Dissolving undercut microneedle arrays for multicomponent cutaneous vaccination. J Control Release. 2020;317:336–46. https://doi.org/10.1016/j. jconrel.2019.11.023.
55. Kim HM, Lim YY, An JH, Kim MN, Kim BJ. Transdermal drug delivery using disk microneedle rollers in a hairless rat model. Int J Dermatol. 2012;51(7): 859–63. https://doi.org/10.1111/j.1365-4632.2011.05343.x.
56. Li K, Yoo KH, Byun HJ, Lim YY, Kim MN, Hong HK, et al. The microneedle roller is an effective device for enhancing transdermal drug delivery. Int J Dermatol. 2012;51(9):1137–9. https://doi.org/10.1111/ j.1365-4632.2010.04703.x.
57. Bariya SH, Gohel MC, Mehta TA, Sharma OP. Microneedles: an emerging transdermal drug delivery system. J Pharm Pharmacol. 2012;64(1):11–29.
58. Lee YS, Kang TG, Cho HR, Lee GJ, Park OK, Kim SY, et al. Localized delivery of Theranostic nanoparticles and high-energy photons using microneedleson-bioelectronics. Adv Mater. 2021;33(24):2100425. https://doi.org/10.1002/a dma.202100425.
59. Du H, Liu P, Zhu J, Li Y, Zhang L, Zzhu J, et al. Hyaluronic acid-based dissolving microneedle patch loaded with methotrexate for improved treatment of psoriasis. ACS Appl Mater Interfaces. 2019;11(46):43588–98. https://doi.org/10.1021/acsami.9b15668.
60. Alkilani AZ, Mccrudden MTC, Donnelly RF. Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics. 2015;7(4):438–70. https://doi.org/10.3390/pharmaceutics7040438.
61. Amjadi M, Mostaghaci B, Sitti M. Recent advances in skin penetration enhancers for transdermal gene and drug delivery. Curr Gene Ther. 2017;17(2):139–46.
62. Szunerits S, Boukherroub R. Heat: a highly efficient skin enhancer for transdermal drug delivery. Front Bioeng Biotechnol. 2018;6:15. https://doi.org/10.3389/fbioe.2018.00015.
63. Parhi R, Mandru A. Enhancement of skin permeability with thermal ablation techniques: concept to commercial products. Drug Delivery Translat Res. 2021;11:817-41.

64. Babaie S, Del Bakhshayesh AR, Ha JW, Hamishehkar H. Invasome: A novel nanocarrier for transdermal drug delivery. Nanomaterials. 2020;10(2):341. https://doi.org/10.3390/nano10020341.
65. Palac Z, Engesland A, Flaten GE, Škalko-Basnet N, Filipović-Grčić J, Vanić Ž. Liposomes for (trans)dermal drug delivery: the skin-PVPA as a novel in vitro stratum corneum model in formulation development. J Liposome Res. 2014;24(4):313–22. https://doi.org/10.3109/08982104.2014.899368.
66. Rajan R, Jose S, Mukund VP, Vasudevan DT. Transferosomes-a vesicular transdermal delivery system for enhanced drug permeation. J Adv Pharm Technol Res. 2011;2(3):138–43. https://doi.org/10.4103/2231-4040.85524.
67. Zhang Z, Liu Y, Chen Y, Li L, Lan P, He D, et al. Transdermal delivery of 5aminolevulinic acid by nanoethosome gels for photodynamic therapy of hypertrophic scars. ACS Appl Mater Interfaces. 2019;11(4):3704–14. https://doi.org/10.1021/acsami.8b17498.
68. Stanekzai A, Sudhakar CK, Zhakfar AM, Karan VS. Recent approaches in transdermal drug delivery system. Res J Pharm Tech. 2019;12(9):4550–8. https://doi.org/10.5958/0974-360X.2019.00783.2.
69. Hadgraft J, Lane ME. Passive transdermal drug delivery systems. Am J Drug Deliv. 2006;4(3):153–60. https://doi.org/10.2165/00137696-200604030-00003.
70. Gandhi K, Dahiya A, Monika LT, Singh K. Transdermal drug delivery – a review. Int J Res Pharm Sci. 2012;3(3):379–88.
71. Dhal S, Gavara RR, Pal K, Banerjee I, Mishra M, Giri S. Facile transdermal delivery of upconversion nanoparticle by iontophoresis-responsive magneto-upconversion oleogel. Nano Express. 2020;1(1):010012. https://doi.org/10.1088/2632-959X/ab81e1.
72. Jeong WY, Kim SD, Lee SY, Lee HS, Han DW, Yang SY, et al. Transdermal delivery of Minoxidil using HA-PLGA nanoparticles for the treatment in alopecia. Biomater Res. 2019;23(1):16. https://doi.org/10.1186/s40824-019-01 64-z.
73. Jijie R, Barras A, Boukherroub R, Szunerits S. Nanomaterials for transdermal drug delivery: beyond the state of the art of liposomal structures. J Mater Chem B. 2017;5(44):8653–75. https://doi.org/10.1039/C7TB02529G.
74. Ali A, Ahmad U. Nanoemulsion as a vehicle in transdermal drug delivery. Insights Biomed. 2018;3:15.
75. Ramadon D, McCrudden MT, Courtenay AJ, Donnelly RF. Enhancement strategies for transdermal drug delivery systems: current trends and applications. Drug Deliv Transl Res. 2021;20:1–34.
76. Lee HJ, Song CY, Baik SM, Kim DY, Hyeon TG, Kim DH. Device-assisted transdermal drug delivery. Adv Drug Deliv Rev. 2018;127:35–45. https://doi. org/10.1016/j.addr.2017.08.009.
77. Bird D, Ravindra NM. Transdermal drug delivery and patches - an overview. Med Devices Sens. 2020;3(6):e10069.
78. Hanbali OA, Khan HS, Sarfraz M, Arafat M, Ijaz S, Hameed A. Transdermal patches: design and current approaches to painless drug delivery. Acta Pharma. 2019;69(2):197–215. https://doi.org/10.2478/acph-2019-0016.
79. Escobar-Chávez et al. (2012) discuss the use of nanocarriers for transdermal drug delivery.
80. Patra et al. (2018) review recent developments and future prospects of nano-based drug delivery systems.

81. Buhecha et al. (2019) develop and characterize PLA nanoparticles for pulmonary drug delivery.
82. Raza et al. (2015) discuss approaches and evaluation of transdermal drug delivery systems.
83. Sheth and Mistry (2011) formulate and evaluate transdermal patches and study the permeation enhancement effect of eugenol.
84. Salamanca et al. (2018) use the Franz diffusion cell approach for pre-formulation characterization of ketoprofen semi-solid dosage forms.
85. Lee et al. (2019) study the percutaneous permeability of 1-phenoxy-2-propanol, a preservative in cosmetics.
86. Rajithaa et al. (2019) develop a chaulmoogra oil-based methotrexate loaded topical nanoemulsion for the treatment of psoriasis.
87. Ashtikar et al. (2013) use confocal Raman microscopy to perform non-invasive depth profile imaging of the stratum corneum.
88. Zhang, L. W., & Monteiro-Riviere, N. A. (2012). Use of confocal microscopy for nanoparticle drug delivery through skin. Journal of Biomedical Optics, 18(6), 061214. https://doi.org/10.1117/1.JBO.18.6.061214.