Advances in Bioresearch
Adv. Biores., Vol 17 (5) May 2026: 98-107

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.17.5.98107

Advances in Bioresearch

REVIEW ARTICLE

Recent Advances in Transdermal Drug Delivery

Uma Rajendra Wagh[1], Dattatraya Manohar Shinkar[1*], Prashant Laxman Pingale[1], Sahebrao Sampat Boraste[1], Sunil Vishwanath Amrutkar[2]

[1*]Department of Pharmaceutics, Gokhale Education Society's Sir Dr. M.S. Gosavi College of Pharmaceutical Education and Research, Nashik-422005 (M.S.), India.

[2]Department of Pharmaceutical Chemistry, Gokhale Education Society's Sir Dr. M.S. Gosavi College of Pharmaceutical Education and Research, Nashik-422005 (M.S.), India.

***Corresponding author**: E-mail: dattashinkar@gmail.com

ABSTRACT

Many non-invasive treatments have recently evolved as an alternative to traditional needle injections. Because of its low cost, a transdermal drug delivery system (TDDS) is the most appealing approach among them. The rejection rate is low, administration is simple, and patients find it convenient and persistent. TDDS might be used not just in medicine but also in the skin care sector, including cosmetics. Since this method mostly involves local administration, it can prevent local drug concentration development and nonspecific delivery to areas not specifically targeted by the medicine. However, the physicochemical features of the skin translate into several hurdles and limitations in transdermal distribution, necessitating numerous studies to address these bottlenecks. In this study, we detail the many types of accessible TDDS approaches, as well as merits and limitations, characterization methodologies, and potential. Progress in research on these alternative technologies has proved TDDS's high efficiency, which is likely to find applications in a wide range of sectors. Drug/vehicle interactions, vesicles and particles, stratum corneum alteration, energy-driven approaches, and stratum corneum by passing techniques are among these strategies.

Keywords: *Transdermal drug delivery, Active delivery, Passive delivery, Stratum corneum, Iontophoresis, Sonophoresis*

Received 24.02.2026 Revised 08.04.2026 Accepted 14.05.2026

How to cite this article:
Uma Rajendra W, Dattatraya Manohar S, Prashant Laxman P, Sahebrao Sampat B, Sunil Vishwanath A. Recent Advances in Transdermal Drug Delivery . Adv. Biores., Vol 17 (5) May 2026: 98-107.

INTRODUCTION

Drug delivery systems are designed devices that convey a pharmaceutical component throughout the body in order to manage the release of its medicinal contents. Potential physical-chemical or enzymatic disruptions of the active ingredient are reduced by enclosing the molecules within a protective shell-like structure [1]. As a consequence, not only is the active compound's bioavailability raised, but also the unwanted side effects associated with unspecific systemic distribution are decreased. Drug delivery systems (DDS) use a variety of drug carriers to transport pharmaceuticals to specific cells, tissues, organs and subcellular organs for drug release and absorption. Its typical purpose is to improve therapeutic medicines' pharmacological activities and overcome difficulties such as restricted solubility, low bioavailability, drug aggregation, poor bio distribution, lack of selectivity, or to reduce the undesirable effects of therapeutic medications [2]. In drug delivery systems (DDS) therapeutic medications are carried in the body as needed to accomplish the intended therapeutic impact in a safe manner. Such systems are often developed to i) improve active ingredient water solubility and chemical stability, ii) boost pharmacological effectiveness, and iii) limit adverse effects. Any medication delivery system's purpose is to provide and maintain therapeutic drug concentrations at the target biological site. There are several administration modes available depending on the route of administration, including oral administration, mucosal administration, lung inhalation, intravenous injection, and transdermal administration [3].

TRANSDERMAL DRUG DELIVERY

A transdermal patch is put to the skin to deliver medication through the skin and into the bloodstream. A transdermal patch uses a special membrane to control the rate at which the liquid medicine contained in the patch's reservoir passes through the skin and into the circulation. Some drugs, such as alcohol, must be coupled with substances that increase their ability to permeate the skin before being utilized in a skin patch [4]. Patches placed to the skin reduce the requirement for syringe or pump vascular access. Transdermal patches were developed in the 1970s, with the first FDA approval for motion sickness therapy in 1979. Depending on the prescription, patches might last anywhere from one to seven days. Transdermal drug delivery offers the following significant advantages: improved bioavailability, more uniform plasma levels, and longer duration of action, resulting in reduced dosing frequency, fewer side effects, and improved therapy due to plasma level maintenance up to the end of the dosing interval versus a decline in plasma levels with conventional oral dosage forms [5].

ADVANTAGES:

1) They have the potential to reduce drug absorption issues caused by stomach pH, enzymatic activity, and drug interactions with food and other orally administered medications.
2) They offered longer treatment with a single application, which is an advantage over alternative dosage forms that needed more frequent dose administration.
3) They can be used as an alternative to traditional delivery when the oral route is ineffective, such as with vomiting and diarrhea [6].

DISADVANTAGES:

1) Because of the physical limitations on drug entry imposed by the skin's permeability, only potent medications are suitable candidates for transdermal patches.
2) Some individuals have contact dermatitis at the site of application as a result of one or more system components, prompting cessation.
3) Long-term adhesion is challenging [7].

MECHANISM OF DRUG ABSORPTION THROUGH SKIN:

The skin works as the body’s primary layer of barrier against the outer world and being the largest organ of the body, prevents it from outer hazards such as chemical, physical and mechanical impacts. Also, researchers have employed it as the principal location for absorption of number of drugs by local and systemic routes, due to the profusion of blood capillaries in the dermis [8].

The physiology of skin was shown in figure.1

The epidermis is the protective covering of human skin, measuring 50–100 m depending on where it is positioned on the body. The epidermis's most superior layer, the stratum corneum (SC), has a thickness of 10–20 m and is composed of 15–30 corneocyte cell layers. This layer regenerates every four weeks [9]. The stratum lucidum is a translucent and thin covering of skin that lies underneath the stratum corneum. The stratum lucidum, which is exclusively seen in the digits, palms, and soles, composed of few layers of corneocytes below which contains the layer called the stratum granulosum. The cells in this layer have a thicker membrane than the other two [10]. The stratum spinosum is a keratinocyte-rich epidermal layer that sits underneath the stratum granulosum. Langerhans cells are antigen-presenting cells found in this layer. Furthermore, the stratum basale is the bottom layer of the epidermis, which has direct interaction with the dermis via interwoven collagen fibres [11]. The second skin layer in the integumentary system, positioned underneath the epidermis, is the dermis. It has two layers, which include papillary and reticular layers. Additionally, as a response to its role in sweating and sebum production, the dermis has a large number of hair follicles along with sebaceous and sweat glands. The hypodermis, being the lowest layer of skin, is high in proteoglycans and glycosaminoglycaecans because it connects skin, muscle, and bones. It is located underneath the dermis and is known as the superficial fascia, or subcutaneous layer. Medication absorption via the skin, on the other hand, is difficult owing to the barrier layer that can be passed, the SC [12]. The Subcutaneous is formed from dead cells that, when combined with lipid bilayer lamellae constituent, making a thick structure which is known as a "brick-and-mortar" configuration. Medication must first reach the epidermis along with its molecular architecture before being taken into the bloodstream [13].

Drug absorption via the skin's surface (SC) has been divided into two separate routes, including transepidermal and transappendageal routes. Drugs from transdermal patches can spread over the surface of skin and enter through cells and interspaces between cells because of the SC's massive surface area [14].

Mechanism of absorption in Transdermal drug delivery was shown in figure.2

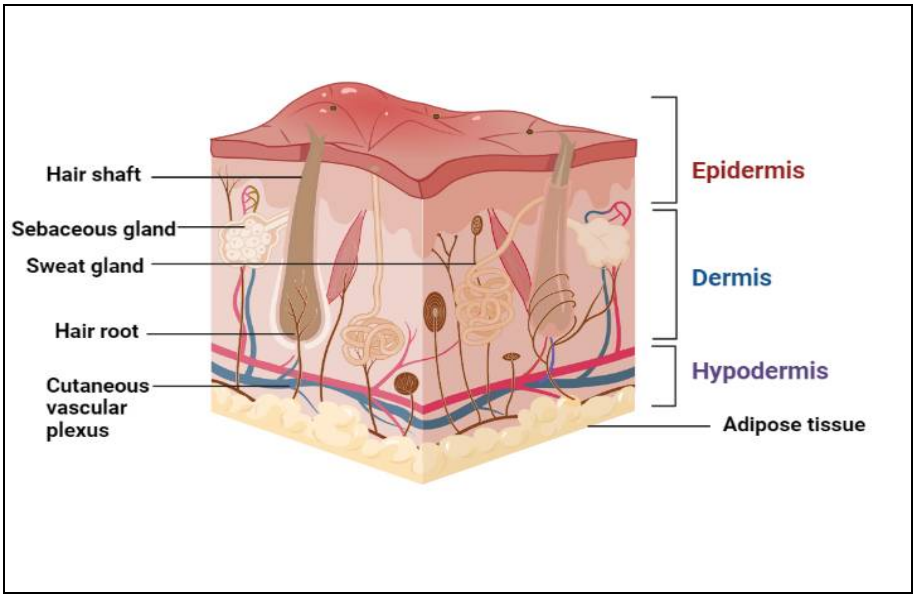

Figure 1. Diagrammatic representation of the physiology of the skin.

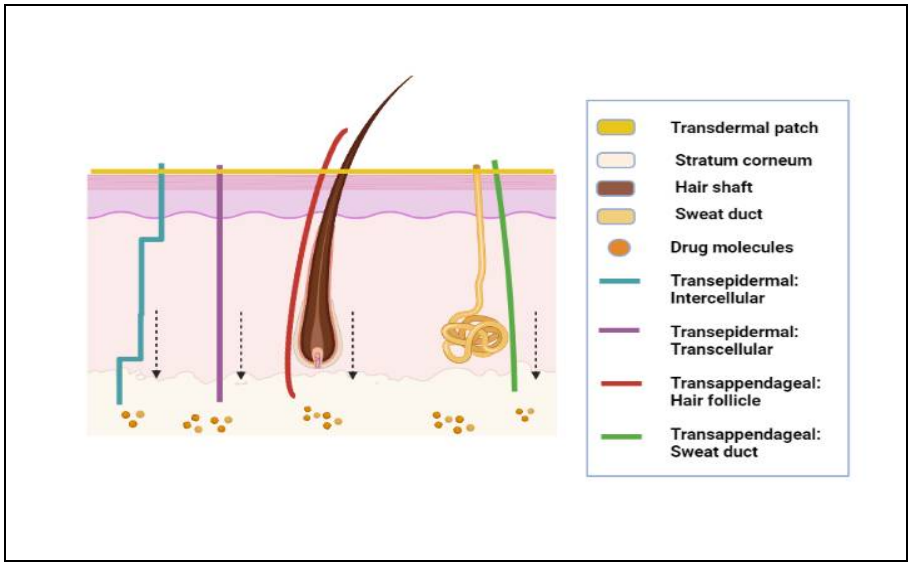

Figure 2. Diagrammatic illustration of mechanism of absorption in Transdermal drug delivery.

BARRIER EFFECT BY SKIN:

The stratum corneum has long been considered as the primary skin barrier. It is a cellular tissue, a fabric of cornified cells that forms a strong, flexible, cohesive membrane that works as a two-way barrier, limiting water loss, electrolytes, and other bodily components while reducing the entrance of harmful chemicals from the external environment. Physical, chemical, and pathological variables can all disrupt barrier function; variations in ambient humidity, for example, can cause pathophysiologic abnormalities [15]. As a result, the main challenge of TDDS is to overcome the stratum cornea's barrier effect, transport the medication to the skin tissue, and pass through the cellular and vascular tissue to reach the target tissue. The difficulty is that just a small quantity of medication can be administered via skin tissue. To address this issue, a number of unique TDDS systems have been studied and have emerged as appealing administration solutions [16].

HISTORY OF TRANSDERMAL DRUG DELIVERY SYSTEM:

For many years, researchers have analyzed the role of the skin to transport numerous sorts of substances. Transdermal delivery systems for many medications can decrease the number of dosing [17].

The first scopolamine-containing transdermal product (Transderm Scp®) was introduced in 1979. This medicine was used to cure motion sickness at sea for three days. In comparison to oral therapy, the development of Transderm Scp® shows that scopolamine delivered by transdermal route may alleviate

few side effects of drug. Following the introduction of scopolamine-containing medicine, Catapressts®, Transdermal patch of clonidine, an antihypertensive drug was introduced in 1984. Contraceptives such as norelgestromine, testosterone, levonorgestrel, oestradiol, norelgestromine, and ethynyl estradiol dominated the market from 1991 to 2004 [18].

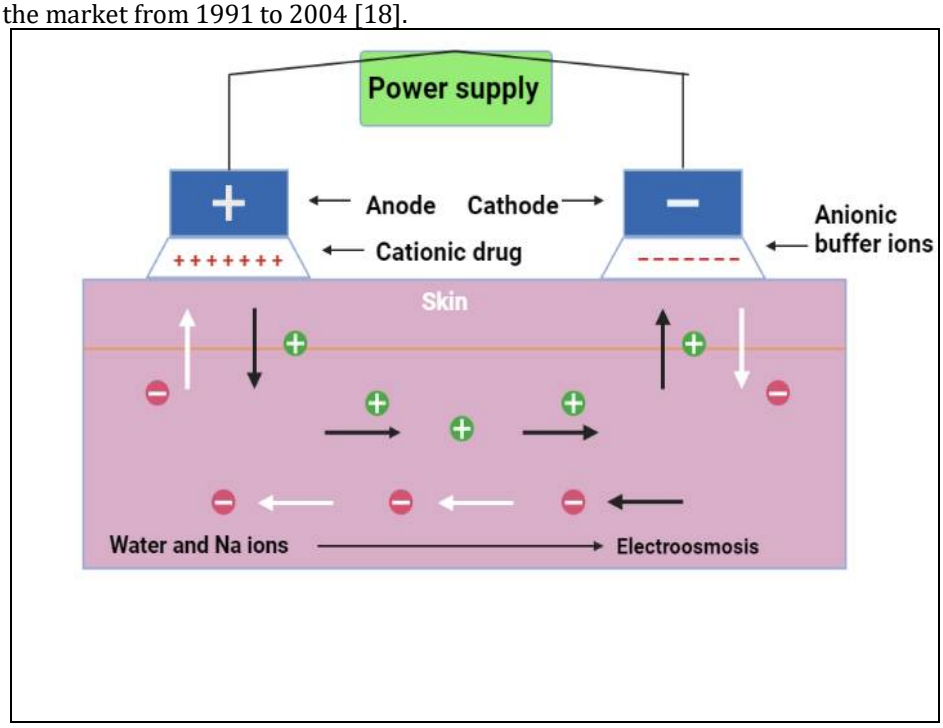

Figure 3. Representation of Iontophoresis process in Transdermal Drug Delivery

RECENT ADVANCES IN TRANSDERMAL DRUG DELIVERY

TECHNOLOGY FOR ENHANCING TDDS – ACTIVE DELIVERY:

Various drugs were made into transdermal formulations between 2005 and 2013. Fentanyl (Ionsys), Selegiline (Emsam), Diclofenac epolamine (Flector), Methylphenidate (Daytrana), and Sumatriptan are some of the examples. Iontophoresis has been utilized with transdermal goods such as Ionsys® and Zecuity® to enhance drug absorption from transdermal patches. Each transdermal product's development has been influenced by developments in understanding [19].

When compared to topical medication administration on the skin, external stimuli such physical, mechanical or electrical stimulation have been demonstrated to improve pharmaceutical and biomolecule skin permeability. Active transdermal delivery is TDDS, improved by appropriate equipment meant to deliver drugs into the skin in fast and efficient way. Electrical (iontophoresis and electroporation), acoustic (sonophoresis), laser, and magnetic energy-based indirect physical enhancement systems have evolved from experimental testing to commercialization. These methods will increase the therapeutic efficacy of the Transdermal delivery [20].

IONTOPHORESIS:

Iontophoresis is a technique for enhancing medication absorption through the skin by utilising tiny electrical currents. Being the application of an electrical potential, Iontophoresis maintains steady current over skin and improves the delivery of ionised and unionized moieties. This approach has the potential to broaden the variety of substances that can be administered transdermally [21]. The iontophoretic approach works according to the principle that opposite charges repel one another. After distribution of a cationic drug (DC) intended during iontophoresis, the charged drug will be dissolved in the electrolyte close to the electrode of identical polarity. After applying electromotive force the drug will be rejected and travelled through the stratum corneum in the direction of cathode. Interaction between electrodes along the skin's surface has been demonstrated to be insignificant, implying that drug ion transport happens through the skin rather than on the surface. When provided with an electric current, neutral molecules will travel due to electro-osmotic and osmotic forces [22].

Charges that are similar repel each other. With similarly charged electrode a charged ion will be repelled into skin. Because of the negative charge at physiological ph, skin will behave as a cation selective membrane by promoting cation transport via anodal iontophoresis. Anodal iontophoresis also induces

convective motion of the solvent in reaction to counterion movement. This electro-osmosis mechanism involves the passage of both neutral molecules and positively charged ions [23].
Iontophoresis process in Transdermal Drug Delivery was shown in figure.3

ADVANTAGES OF IONTOPHORESIS TECHNIQUE:

1. Ionized and unionized medication delivery.
2. Depending on the current applied Continuous or pulsatile drug delivery.
3. Making it easier to stop medication delivery.
4. Providing more control on the amount of medicine administered since the amount of chemical supplied is dependent on applied current, its duration and area of skin that has been exposed to current.
5. Restored skin barrier function without causing significant irritation to skin.
6. Improving the delivery of polar compounds and molecules of high molecular weight [24].

SONOPHORESIS:

Ultrasound at frequencies ranging from 20 kHz to 16 mhz is used in this approach to modify the lipid bilayer structure of the SC. Cavitation Thermal effects are two potential increased sonophoresis processes. Sonophoresis is also known as Phonophoresis [25]. When ultrasound is applied to the skin, the temperature rise results in more drug permeation into the skin. The cavitation process causes cavities and bubbles to form in the SC. Once ultrasound is employed, it produces a continuous pulsation and a sustained cavitation, causing bubbles to develop around the application site [26]. Sonophoresis enhances skin permeability and effectively transfers medicines. Ultrasound waves of varying frequency are used in this procedure. In general, low-frequency ultrasound (khz) is thought to generate more transdermal enhancement than high-frequency ultrasound [27]. Inertial cavitation can be defined as the formation of tiny bubbles inside a suitable solvent as a response of the use of ultrasound in one or several cycles. Sonophoresis is the procedure of placing a pharmaceutical solution beneath a sensor device and then delivering a specific ultrasonic signal to the drug solution and skin [28].
The mode of ultrasound, frequency, and intensity are all factors which impact sonophoresis-based medication delivery systems. Sonophoresis efficiency may also be affected by coupling medium, ultrasonic probe distance from the skin and ultrasound application time [29]. Sonophoresis is a medication delivery technique that includes the transfer of molecules such as small molecules and macromolecules. Various types of medications have been administered successfully with this strategy. This implies that it might be utilized to enhance the transfer of hydrophobic and hydrophilic medications. But, there are some disadvantages to sonophoresis, including the lengthy duration of the treatment, the necessity for specialized equipment, and the requirement for healthy skin during exposure [30].
Sonophoresis process in Transdermal Drug Delivery was shown in figure.4

ELECTROPORATION:

Electroporation, a method used to produce pores on the skin by briefly applying a high voltage (10–1000 V) to the skin. It involves exposing a medicinal solution to pulse waves after it has been administered to the skin. Then the pulse wave will form hydrophilic holes in the bilayer of the SC, allowing drugs to penetrate deeper in the skin layers through the holes generated [31]. Electric pulses are delivered using tightly spaced electrodes for the safe and painless drug administration. This is a highly noninvasive process that has been used to successfully transport not just low Molecular weight medications like mannitol, calcein, or doxorubicin but also high Molecular weight pharmaceuticals such as antiangiogenic peptides, oligonucleotides, and the negatively charged anticoagulant heparin [32].
Electroporation method in Transdermal Drug Delivery was shown in figure.5
Several factors influence drug distribution by electroporation, including the physicochemical qualities of the drug, the voltage utilized, the duration of the pulse, and the number of pulses. Various medicines, including calcein, insulin, tetracaine, alniditan, timolol, fentanyl, and alniditan have been enhanced in vitro transdermal absorption via electroporation [33]. Some disadvantages of electroporation include the need for complicated instrumentation, tedious application methods, the need for skilled professionals, less drug delivered due to the restricted area of water - soluble pores created, and the chance of cell injury owing to the high voltages used [34].

PHOTOMECHANICAL WAVES:

Photomechanical waves will penetrate the SC, letting the medication flow via the transiently formed channel. The incident wave causes limited ablation, which is done by exposing the incident wave to a low radiation dose of around 5–7 J/cm2 in order to expand the depth to 50–400 m for effective transmission. The limited ablation treatment had a longer rise and duration than earlier direct ablation operations, requiring the management of photodynamic wave properties to ensure product delivery to the right depth in the skin. The wave created by single laser pulse improved the skin permeability, letting

macromolecules to penetrate through the skin. Latex particles having a diameter of 20 nm and dextran macromolecules with a molecular weight of 40 kda might be given [35].

MICRONEEDLE

Microneedles (mns) are needles with micron-sized needle heights ranging from 25 to 2000 m on a solid support. Following implantation into the skin, these needles can puncture the SC and form micro conduits [36]. Microneedles are needles that are micron-sized and can penetrate the SC after being implanted into the skin, causing in greater electrical activity. In the patent, titled 'Drug Delivery Device,' Gerstel and Place proposed the first MN idea. Zahn et al. created hollow microneedle, a technique that uses MN's ability to penetrate the skin to inject a medicinal solution into the skin via the hollow needles [37].

MN's are commonly used to improve the transdermal delivery of a number of medications. MN's may travel through the skin's surface layer and into the dermis without hurting blood vessels or nerve endings. As a result, mns are painless and more convenient to deliver than hypodermic injections. Secondly, hydrogel-forming mns minimize the requirement for sharps sewage disposal and will not contribute to the spread of blood-borne illnesses like regular needle and syringe devices do [38]. MN's are frequently made from biodegradable polymers or biocompatible chemicals. The benefits outlined above demonstrate that mns are a potential technique for improving medication penetration into the skin [39].

THERMAL ABLATIONL:

Thermal ablation or Thermophoresis, which has a possible way of effectively modifying the SC structure with localized heat that allows for improved drug delivery via skin microchannels [40]. Thermal ablation of the stratum corneum necessitates a temperature greater than 100 °C, which induces heating and keratin vaporization. Thermal exposure should be short, lasting only a few microseconds, in order to establish a high enough temperature differential across the tissue to allow for accurate ablation of the stratum corneum without injuring the healthy epidermis. It can also transport tiny molecules as well as substances with a large molecular weight [41]. Laser thermal ablation techniques use a laser to produce skin micropore structure as well as a skin temperature increase that enhances skin diffusivity. Radiofrequency thermal ablation involves putting a network of needle-like metallic electrodes placed right onto the skin and delivering a radio frequency electric current (100–500 kHz) into the skin to form micron-scale channels in the stratum corneum. Radiofrequency thermal ablation, which uses a low-cost, disposable device, can keep the medication release and increase delivery of majority of hydrophilic medications, including macromolecules [42].

ENHANCEMENT USING CHEMICAL ENHANCERS - PASSIVE DELIVERY:

Application of chemical enhancers and hydration of skin were strategies for changing the SC by Morrow et al. Based on this classification, these approaches are classified as part of the second generation of transdermal administration. Chemical permeation enhancers can be used to modify the SC as well. These enhancers work by changing the partition coefficient of drug, denaturing the proteins or altering the lipid bilayer of the SC. These chemicals have been widely employed to promote medication penetration in numerous transdermal devices. These compounds must be inert, nonirritant, nonallergenic, nontoxic, be visually acceptable, elicit fast effects and most importantly, skin barrier function must recover rapidly once the chemicals are withdrawn [43].

Dimethyl sulphoxide (DMSO), for example, is widely used to increase absorption of drug by interfering with the lipid areas of the SC. DMSO also works by denaturing protein complexes and changing the keratin structure of the SC. Subsequently, DMSO was investigated for enhanced transdermal dispersion of polar medications by altering diffusivity in SC corneocytes. DMSO was seen to be an effective permeation enhancer in the transdermal distribution of numerous medications, including fenoterol hydrobromide, hydrocortisone, testosterone, and naloxone.

. Chemical enhancers with their mechanism of action used in TDDS was shown in figure.6

Azone (1-dodecylazacycloheptan-2-one), a class of chemical enhancers that could be employed as a penetration enhancer by connecting with SC lipids and altering the bilayer's lipid packing structure. Levamisole hydrochloride , ketoprofen, dimethyl fumarate, and 5-fluorouracil have all been delivered via a zone. Other pyrrolidone-based synthetic chemical permeation enhancers include n-methyl pyrrolidone and 2-pyrrolidone. These compounds could interact with the keratinised portion of the SC, altering its solubility. N-methyl pyrrolidone has been studied for transdermal administration of ketoprofen, lidocaine hydrochloride, bupranolol, and 5-hydroxymethyl tolterodine [44].

Fatty acids can also improve chemical permeability. As mentioned earlier, the SC is lipophilic and has hydrophobic properties. As a result, the use of fatty acids such as lauric acid and oleic acid would boost absorption of drug into the skin due to their comparable lipophilicity. Flurbiprofen, propranolol, theophylline, and donepezil are examples of medicines whose transdermal distribution was improved by the use of fatty acids [45].

Surfactants are amphiphilic compounds with polar as well as nonpolar functional groups. Surfactants have the ability to solubilize the SC lipids, disrupt the lipid and protein domains, and permeate the lipid bilayer . Surfactants such as sodium lauryl sulphate (SLS) and polysorbate 80 have been widely employed to improve medication transdermal absorption (Tween). Urea, like surfactants, is used to improve medication absorption through the skin by raising skin water content, initiating keratolytic action and by disrupting SC lipids [46].

CLINICAL TRIALS AND MARKETED DRUG PRODUCTS

Over 900 studies on ClinicalTrials.gov have the term "transdermal" in their description (search conducted December 2019). Unfortunately, there are many trials involving the same four drugs (testosterone, estradiol, nicotine and fentanyl), and the fact that the bulk of the trials pertain only a few drugs is not surprising given the exclusive character of marketed transdermal drugs, the selective nature of the skin as a barrier to diffusion, and the pharmacodynamics and pharmacokinetic properties of marketed transdermal drugs [46].

Table.1 covers several transdermal medications for systemic distribution that have been approved in the United States and the European Union recently

.

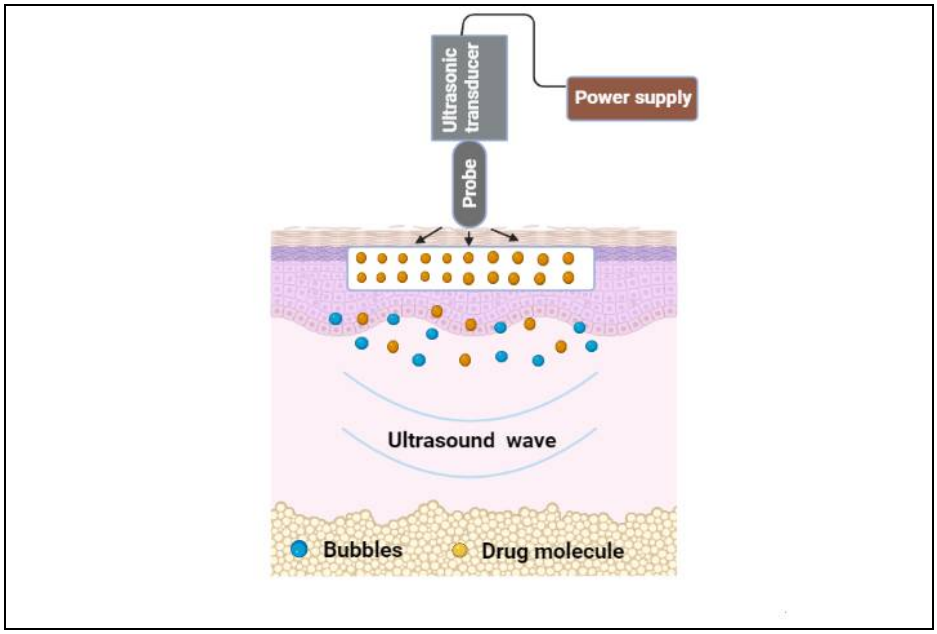

Figure 4. Representation of Sonophoresis process in Transdermal Drug Delivery.

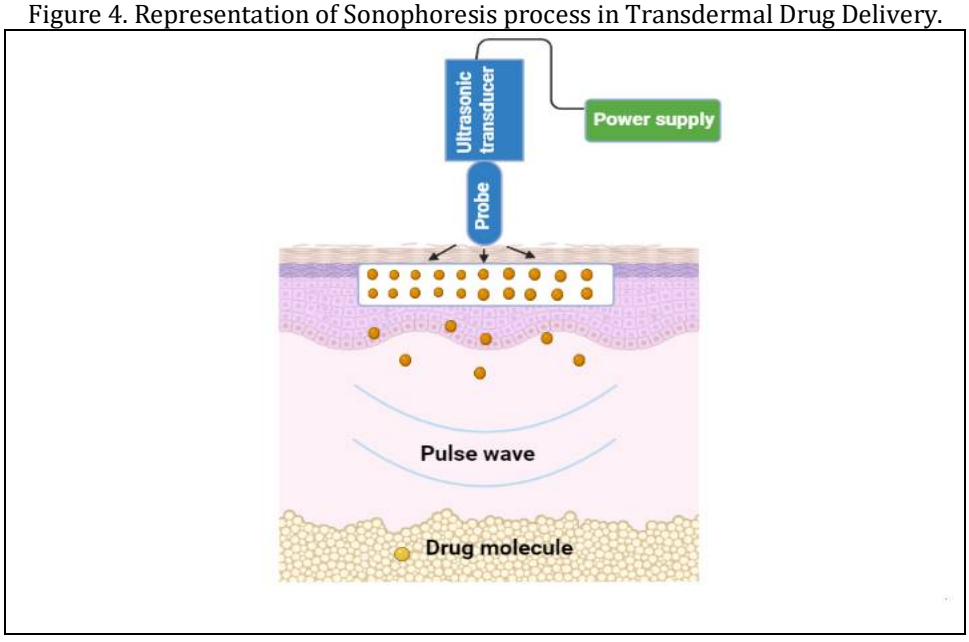

Figure 5. Representation Electroporation method in Transdermal Drug Delivery.

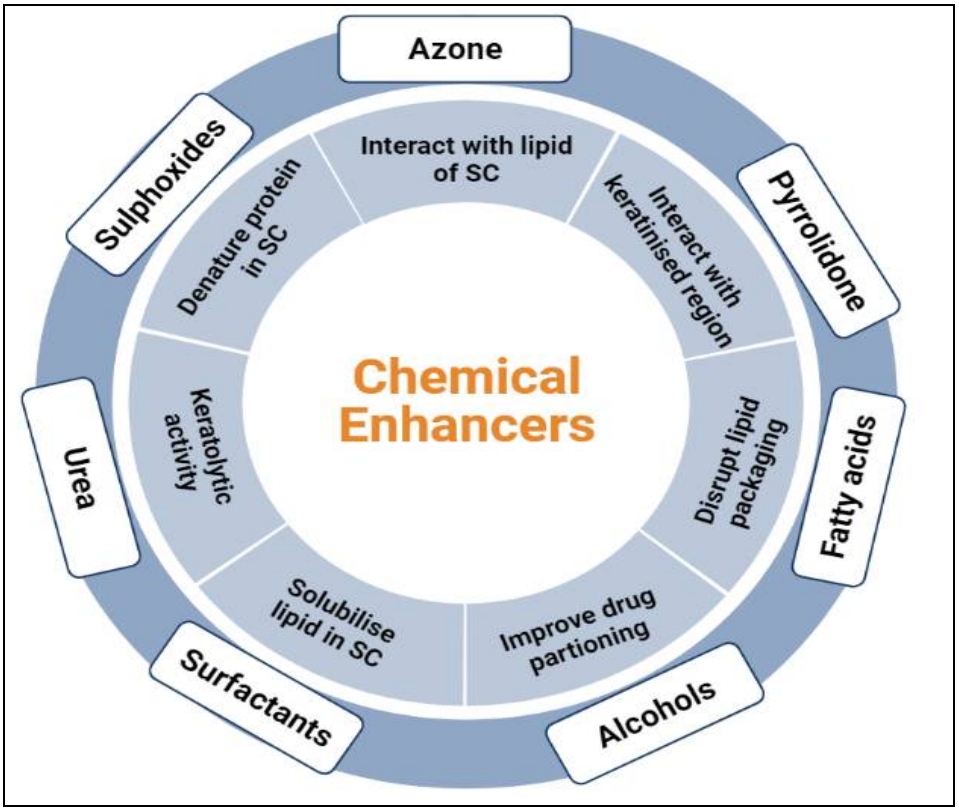

Figure 6. Chemical enhancers with their mechanism of action used in TDDS.

Table 1. Drugs approved in US and Europe recently for Transdermal delivery.

Drug (Trade name)	Year of FDA approval	Indication	Duration of application
Granisetron (Sancuso®)	2008	Nausea and Vomiting	Upto 7 days
Asenapine (Secuado)	2009	Antipsychotic	24 hrs
Selegiline (Emsam®)	2006	Major depressive disorder	24 hrs
Oxybutynin (Oxytrol®)	2003	Overactive bladder	3-4 days
Sumatriptan (Zecuity®)	2013	Migraine	4 hrs
Buprenorphrine (Butrans®)	2010	Chronic pain	7 days
Oestradiol (Menostar®)	2004	Female HRT	7 days
Lidocaine (L) (Synera®)	2005	Local dermal analgesic	20-30 min
Oestradiol (Minivelle®)	2012	Female HRT	3-4 days
Ethinyl oestradiol (Ortho Evra®)	2001	Female contraception	7 days
Methylphenidat e (Daytrana®)	2006	ADHD	Upto 9 hrs
Menthol (M) (Salonpas®)	2008	Muscle and joints pain	Upto 8-12 hrs
Rivastigmine (Exelon®)	2007	Alzheimers and Parkinson	24 hrs
Rotigotinec (Neupro®)	2007	Restless leg syndrome	24 hrs
Oestradiol E (Climara Pro®)	2003	Female HRT	7 days
Diclofenac epolamine (Flector®)	2007	Topical acute pain	12 hrs
Capsaicin (Qutenza®)	2009	Neuropathic pain	60 min
Oestradiol (Evamist®)	2007	Menopausal sysmptoms	2 pump action once
Testosterone (Axiron®)	2010	Hypogonads	One spray once

CONCLUSION AND FUTURE PERSPECTIVES

TDDS technology is the optimum medication injection medium for transdermal delivery across skin types. TDDS is noninvasive, nonallergenic, and has a predetermined duration and dosage administration technique, allowing for homogenous medication release at prescribed and regulated rates. Chemical enhancers, for example, have had minimal efficacy in enhancing transdermal transport. Methods for

piercing micron-sized holes into the skin can dramatically boost medication, macromolecule, or particle transdermal delivery.

Transdermal delivery devices were created to address issues with oral and injectable dose forms. There are several improvement options available for improving transdermal delivery systems. The majority of pharmaceutical products use passive transdermal drug delivery systems. The coupling of energy-driven technologies such as iontophoresis with regular transdermal patches (Zecuity®) has resulted in yet another technique for enhancing passive transdermal delivery systems.

Lately, significant work has been done in the domains of transdermal medication application and polymeric microneedle diagnostics. Microneedles might be used in the future to distribute cells locally, enabling cell-based treatment. In addition, the first transdermal prodrug product is expected to hit the market in coming years. Novel prodrugs might not only assist some drugs reach clinical efficacy, but they could also aid with skin problems. The frequency and severity of skin irritation reactions will diminish when physical diffusion enhancement technologies such as liposomes, microemulsions, nanoparticles, and evaporating gels become more widely available. Chemical permeation enhancer analogue innovations exhibit greater gains in minimising cutaneous irritation.

REFERENCES

1. Felice, B., Prabhakaran, M. P., Rodriguez, A. P., & Ramakrishna, S. (2014). Drug delivery vehicles on a nano-engineering perspective. *Materials Science and Engineering: C, 41*, 178–195.
2. Vega-Vásquez, P., Mosier, N. S., & Irudayaraj, J. (2020). Nanoscale drug delivery systems: From medicine to agriculture. *Frontiers in Bioengineering and Biotechnology, 8*, 79.
3. Li, C., Wang, J., Wang, Y., Gao, H., Wei, G., Huang, Y., ... & Jin, Y. (2019). Recent progress in drug delivery. *Acta Pharmaceutica Sinica B, 9*(6), 1145–1162.
4. Park, K. (2014). Controlled drug delivery systems: Past forward and future back. *Journal of Controlled Release, 190*, 3–8.
5. Wiechers, J. (1992). Use of chemical penetration enhancers in transdermal drug delivery—Possibilities and difficulties. *Acta Pharmaceutica Nordica, 4*(2), 123–130.
6. Lewis, S., & Udupa, N. (2006). Design and evaluation of matrix type and membrane controlled transdermal delivery systems of nicotine suitable for use in smoking cessation. *Indian Journal of Pharmaceutical Sciences, 68*(2), 179–184.
7. Naik, A., Pechtold, L. A., Potts, R. O., & Guy, R. H. (1995). Mechanism of oleic acid-induced skin penetration enhancement in vivo in humans. *Journal of Controlled Release, 37*(3), 299–306.
8. Berner, B., & John, V. A. (1994). Pharmacokinetic characterisation of transdermal delivery systems. *Clinical Pharmacokinetics, 26*(2), 121–134.
9. Reddy, K. R., Mutalik, S., & Reddy, S. (2003). Once-daily sustained-release matrix tablets of nicorandil: Formulation and in vitro evaluation. *AAPS PharmSciTech, 4*(4), 480–488.
10. Mali, A. D. (2015). An updated review on transdermal drug delivery systems. *Skin, 8*(9), 1–6.
11. Boer, M., Duchnik, E., Maleszka, R., & Marchlewicz, M. (2016). Structural and biophysical characteristics of human skin in maintaining proper epidermal barrier function. *Advances in Dermatology and Allergology, 33*(1), 1–5.
12. Sandby-Moller, J., Poulsen, T., & Wulf, H. C. (2003). Epidermal thickness at different body sites: Relationship to age, gender, pigmentation, blood content, skin type and smoking habits. *Acta Dermato-Venereologica, 83*(6), 410–413.
13. Böhling, A., Bielfeldt, S., Himmelmann, A., Keskin, M., & Wilhelm, K. P. (2014). Comparison of the stratum corneum thickness measured in vivo with confocal Raman spectroscopy and confocal reflectance microscopy. *Skin Research and Technology, 20*(1), 50–57.
14. Wickett, R. R., & Visscher, M. O. (2006). Structure and function of the epidermal barrier. *American Journal of Infection Control, 34*(10), S98–S110.
15. Jaitley, S., & Saraswathi, T. R. (2012). Pathophysiology of Langerhans cells. *Journal of Oral and Maxillofacial Pathology, 16*(2), 239–244.
16. Matsui, T., & Amagai, M. (2015). Dissecting the formation, structure and barrier function of the stratum corneum. *International Immunology, 27*(6), 269–280.
17. Lovászi, M., Szegedi, A., Zouboulis, C. C., & Törőcsik, D. (2017). Sebaceous immunobiology is orchestrated by sebum lipids. *Dermato-Endocrinology, 9*(1), e1375636.
18. Wong, R., Geyer, S., Weninger, W., Guimberteau, J. C., & Wong, J. K. (2016). The dynamic anatomy and patterning of skin. *Experimental Dermatology, 25*(2), 92–98.
19. Singh, I., & Morris, A. P. (2011). Performance of transdermal therapeutic systems: Effects of biological factors. *International Journal of Pharmaceutical Investigation, 1*(1), 4–9.
20. Michaels, A. S., Chandrasekaran, S. K., & Shaw, J. E. (1975). Drug permeation through human skin: Theory and in vitro experimental measurement. *AIChE Journal, 21*(5), 985–996.
21. Ramadon, D., McCrudden, M. T., Courtenay, A. J., & Donnelly, R. F. (2022). Enhancement strategies for transdermal drug delivery systems: Current trends and applications. *Drug Delivery and Translational Research, 12*(4), 758–791.

22. Kligman, A. M. (2000). Hydration injury to human skin: A view from the horny layer. In *Handbook of occupational dermatology* (pp. 76–80). Springer.
23. Zhai, H., & Maibach, H. I. (2002). Occlusion vs. skin barrier function. *Skin Research and Technology, 8*(1), 1–6.
24. 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. *Journal of Materials Chemistry B, 8*(19), 4202–4209.
25. Pawar, P. M., Solanki, K. P., & Mandali, V. A. (2018). Recent advancements in transdermal drug delivery system. *International Journal of Pharmaceutical and Clinical Research, 10*(3), 65–73.
26. Pastore, M. N., Kalia, Y. N., Horstmann, M., & Roberts, M. S. (2015). Transdermal patches: History, development and pharmacology. *British Journal of Pharmacology, 172*(9), 2179–2209.
27. Wiedersberg, S., & Guy, R. H. (2014). Transdermal drug delivery: 30+ years of war and still fighting! *Journal of Controlled Release, 190*, 150–156.
28. Kim, B., Seong, K. Y., You, I., Selvaraj, V., Yim, S. G., O'Cearbhaill, E. D., ... & Yang, S. Y. (2018). Touch-actuated transdermal delivery patch for quantitative skin permeation control. *Sensors and Actuators B: Chemical, 256*, 18–26.
29. Al Hanbali, O. A., Khan, H. M. S., Sarfraz, M., Arafat, M., Ijaz, S., & Hameed, A. (2019). Transdermal patches: Design and current approaches to painless drug delivery. *Acta Pharmaceutica, 69*(2), 197–215.
30. Benson, H. A., Grice, J. E., Mohammed, Y., Namjoshi, S., & Roberts, M. S. (2019). Topical and transdermal drug delivery: From simple potions to smart technologies. *Current Drug Delivery, 16*(5), 444–460.
31. Gangarosa, L. P., & Hill, J. M. (1995). Modern iontophoresis for local drug delivery. *International Journal of Pharmaceutics, 123*(2), 159–171.
32. Williams, A. C., & Barry, B. W. (1992). Skin absorption enhancers. *Critical Reviews in Therapeutic Drug Carrier Systems, 9*(3–4), 305–353.
33. Wang, Y., Thakur, R., Fan, Q., & Michniak, B. (2005). Transdermal iontophoresis: Combination strategies to improve drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics, 60*(2), 179–191.
34. Srinivasan, V., & Higuchi, W. I. (1990). A model for iontophoresis incorporating the effect of convective solvent flow. *International Journal of Pharmaceutics, 60*(2), 133–138.
35. Williams, A. C., & Barry, B. W. (1991). Terpenes and the lipid–protein–partitioning theory of skin penetration enhancement. *Pharmaceutical Research, 8*(1), 17–24.
36. Mitragotri, S., & Kost, J. (2004). Low-frequency sonophoresis: A review. *Advanced Drug Delivery Reviews, 56*(5), 589–601.
37. Park, D., Park, H., Seo, J., & Lee, S. (2014). Sonophoresis in transdermal drug delivery. *Ultrasonics, 54*(1), 56–65.
38. Amjadi, M., Mostaghaci, B., & Sitti, M. (2017). Recent advances in skin penetration enhancers. *Current Gene Therapy, 17*(2), 139–146.
39. Lin, C. H., Aljuffali, I. A., & Fang, J. Y. (2014). Lasers as an approach for promoting drug delivery via skin. *Expert Opinion on Drug Delivery, 11*(4), 599–614.
40. Donnelly, R. F., Singh, T. R. R., Morrow, D. I., & Woolfson, A. D. (2012). *Microneedle-mediated transdermal and intradermal drug delivery*. Wiley.
41. Larrañeta, E., Lutton, R. E., Woolfson, A. D., & Donnelly, R. F. (2016). Microneedle arrays as transdermal drug delivery systems. *Materials Science and Engineering: R: Reports, 104*, 1–32.
42. Zahn, J. D., Talbot, N. H., Liepmann, D., & Pisano, A. P. (2000). Microfabricated polysilicon microneedles. *Biomedical Microdevices, 2*(4), 295–303.
43. Moreira, A. F., Rodrigues, C. F., Jacinto, T. A., Miguel, S. P., Costa, E. C., & Correia, I. J. (2019). Microneedle-based delivery devices for cancer therapy. *Pharmacological Research, 148*, 104438.
44. Donnelly, R. F., Mooney, K., McCrudden, M. T., Vicente-Pérez, E. M., Belaid, L., González-Vázquez, P., ... & Woolfson, A. D. (2014). Hydrogel-forming microneedles increase in volume during swelling in skin. *Journal of Pharmaceutical Sciences, 103*(5), 1478–1486.
45. Ilić, T., Savić, S., Batinić, B., Marković, B., Schmidberger, M., Lunter, D., ... & Savić, S. (2018). Combined use of nanoemulsions and microneedles for NSAID transport. *European Journal of Pharmaceutical Sciences, 125*, 110–119.
46. Abiandu, I., & Ita, K. (2019). Transdermal delivery of potassium chloride with microneedles. *Journal of Drug Delivery Science and Technology, 53*, 101216.