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Review Article

Penetration Enhancers for TDDS

Increasing Efficiency of Transdermal Drug Delivery Systems Using Some Novel Penetration Enhancement Techniques - A Critical Review

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Abstract: The transdermal route has drawn considerable attention and has emerged as a solid alternative to mimic the drawbacks of drug delivery through the oral and parenteral routes. However, the effectiveness of TDDS is often limited by the skin's outermost layer, the stratum corneum (SC), which acts as a barrier to drug diffusion. In addition, the drug molecule's molecular weight, hydrophilicity, and ionic nature can also impact its transdermal delivery. Various methods have been developed to overcome these limitations to facilitate drug penetration across the SC, including nano-carriers, wearable delivery systems, and combination-based approaches. The use of nano-carriers, such as dendrimers, liposomes, niosomes, and micro sponges, has shown promise in enhancing the efficacy of TDDS. Another emerging innovation for TDDS is wearable delivery systems, which offer non-invasive, convenient, and extended drug administration. Additionally, combination-based approaches, such as ultrasound and microneedle-based systems or ultrasound and electrical-based techniques, are also being investigated and are the center of attraction in the research of TDDS approaches. This review summarizes a combination of all different novel penetration enhancement techniques used to enhance the efficacy of transdermal drug delivery systems that were not precisely captured by other review articles. Most of the review articles emphasized these penetration enhancement techniques separately. However, a careful review of all the penetration enhancement techniques in one article is missing. Thus, the purpose of this article is to comprehensively review and summarize the recently used penetration enhancement techniques along with the possible mechanism of action in a single article. Our primary aim is to collect relevant reviews and research articles by searching various databases to provide a comprehensive overview of the field. By providing a comprehensive overview of the available techniques, this review article will help students and researchers stay up-to-date with the latest developments in the field of novel penetration enhancement techniques used to increase the efficiency of TDDS.

Keywords: Transdermal delivery system, Nano-carriers, Microneedles, Wearable transdermal drug delivery, Sonophoresis, Penetration enhancement technique

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1. INTRODUCTION

Skin represents the most essential and influential organ of the body. It is a long-ago practice to deliver pharmacological agents through the skin. Furthermore, its utilization is confined to treating local diseases only. Since the first transdermal patch of scopolamine was authorized in 1979, transdermal drug delivery began to be encouraged as a systemic mode of drug administration. Significant research has been conducted in this field. It has been proven beneficial in reducing the dose frequency, attaining target delivery, and avoiding hepatic first-pass metabolism.[1] Transdermal drug delivery offers numerous benefits to cope with problems related to oral delivery and hypodermic injections by applying medicated patches onto the skin.[2] However, some constraints are related to transdermal drug delivery systems. The physical structure of the skin helps it act as a barrier and further limits the efficacy and application of drugs through the transdermal route. The human skin maintains a complex system fabricated with numerous stratum layers containing keratinocytes. The outermost layer of the skin, named stratum corneum (SC), consists of highly thick corneocytes, which act as the main barrier for the drug molecules to penetrate.[3] The complex anatomy of the skin does not allow the diffusion of drugs through the skin without any structural intervention, which hampers the effectiveness of the transdermal delivery. Drugs like rapid clearance and cutaneous first-pass effects may also have adverse pharmacokinetic or pharmacodynamic properties. These biopharmaceutical properties of certain drug molecules further complicate the effectiveness of TDDS.[4] Due to the above restrictions and problems, only a few categories of drug molecules could be suitable for transdermal delivery. Hence, the most fundamental challenge for transdermal delivery is increasing the number of drug molecules transported through the skin. Various studies show that novel flux development strategies can help maintain the transdermal delivery of different drug molecules. Further works have been performed to increase the flux in the transdermal area by using novel techniques. Some methods involve third-generation methods like permeation enhancers, electric devices, wearable devices, ultrasound, and nano-carriers.[5] Out of all the methods available, combining ultrasound techniques, microneedles, electrical techniques (iontophoresis/ electroporation), and wearable transdermal devices integrated with suitable electrical device/s is gaining popularity among researchers. However, the popularity of wearable transdermal drug delivery systems has increased tremendously. Wearable electronic devices have pulled special attention over the last few years.[5] Skin-mountable sensors are preliminary used in wearable technology, and such sensors have potential applications like health nursing, human motion detection, and intelligent human-machine interface.[6] New advances in wearable technology are exploring new opportunities in transdermal delivery.[7-8] Wearable clinical devices are being actively used due to their perfect ability to assimilate with the human body, record physiological signals over a long time with minimum error, and ease of use for everyone.[9-11] Remarkable advances in biotechnology, nanotechnology, and material science further led to advanced wearable medical systems for the transdermal delivery of active drug molecules.[12-14] In this review, the writers first explain the basics of skin structure to understand the theoretical application and then focus on improving drug administration techniques by TDDS. The study then moves forward to figure out the latest development, limitations, and future challenges within this field of research. We classify the current approaches used to achieve improved skin penetration of drugs and especially survey the recent developments in transdermal formulations based on new available technologies. This review further explores different physical methods, such as iontophoresis, electroporation, sonophoresis, and microneedles, to enhance the skin's permeability. It also highlights the most up-to-date evolution in the design of wearable and multifunctional therapeutic delivery systems. While various articles describe any other specific approach, this review focuses on wearable systems as the most relevant and essential technique to illustrate comparisons and distinctions.

2. CHARACTERISTICS OF DRUG MOLECULES SUITABLE FOR TRANSDERMAL PATCHES

It has been widely investigated to deliver different therapeutic agents through transdermal delivery. There are many advantages of administering therapeutic agents transdermally, including ease of administration and avoiding problems associated with oral delivery, such as first-pass metabolism. However, many drugs cannot be administered transdermally as it is very difficult to disrupt the SC and penetrate the skin using conventional patches. The limitation is mainly due to the drug molecules' constraining pharmacokinetic parameters and physicochemical properties. Mitragotri et al.[15] emphasized some important characteristics such as low molecular mass (<400 Da), solubility, crystallinity, high lipophilicity (oil soluble) and small required dose (up to milligrams), and partition coefficient Log P (octanol-water) between −1.0 to 4. In Table 1, we have summarized the factors to be evaluated for a drug candidate for transdermal drug delivery as well as the ideal physicochemical properties of the potential drug molecule. Moreover, the pharmacokinetics properties of a drug molecule need to be evaluated carefully. Those play a crucial role in determining its suitability for delivery by the transdermal route.

Table 1. An outline of physicochemical properties and factors to be considered for a potential drug molecule suitable for TDDS [16]

Factor	Value for a Drug to be an Ideal Candidate for TDDS
Physico-Chemical	
Solubility	
Crystallinity	
Molecular weight	400 or Less
Polarity (Partition Coefficient)	Log P (octanol-water) between -1 and 4
Melting point	
Pharmacokinetic	

Dose	Less than 2 mg/Day
Half-life	10 Hours or Less
Volume of distribution	
Total body clearance	
Therapeutic plasma concentration	
Bioavailable factor	
Biological	
Skin toxicity	Non-irritating and non-sensitizing
Site of application	
Allergic reactions	
Skin metabolism	
Skin permeability (Permeability Coefficient)	>0.5 × 10^{-3} cm/h

3. ROUTES AND BARRIERS TO DRUG DELIVERY IN THE TRANSDERMAL DRUG DELIVERY SYSTEM

The intracellular pathway is the most appropriate channel for the transfer of drugs in TDDS. The skin mainly comprises three layers, i.e., epidermis, dermis, and hypodermis. The epidermis consists of five layers. Out of this stratum corneum (SC) is the outermost layer of the skin (Fig. 1). The intracellular pathway involves disruption of the lipid membrane of the SC layer. Thus, all advanced techniques and approaches mainly focus on either improving the lipophilicity of the drug molecule within the SC environment or modifying the structure of the SC.[17-18]

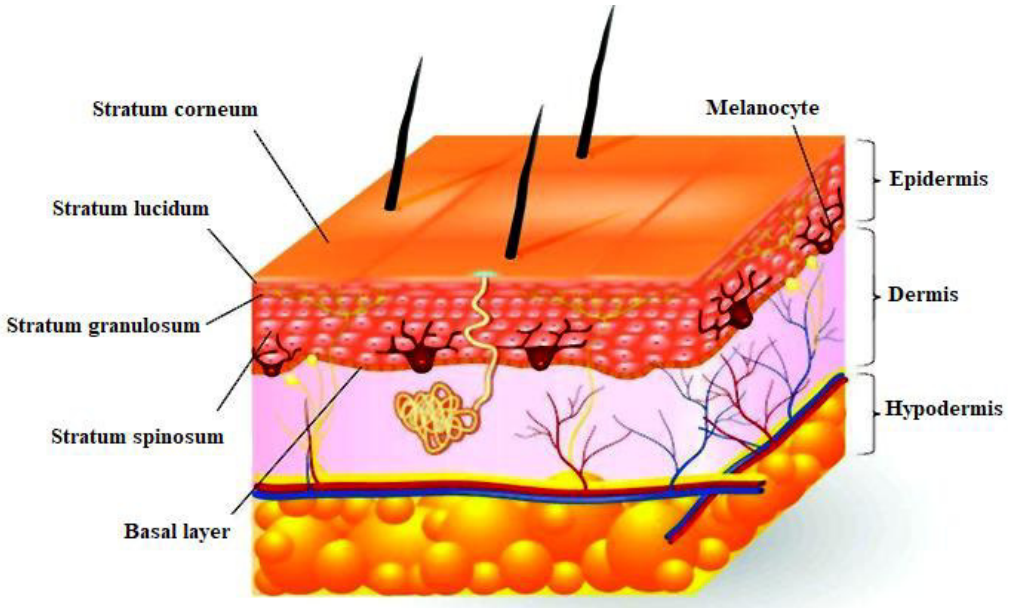


Fig.1.Schematic illustration of the three layers of skin[18].

Fig 1 presents the different skin layers. The skin mainly comprises three layers, i.e., epidermis, dermis, and hypodermis. The epidermis contains five layers, i.e., basal layer, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum. The stratum corneum is the outmost layer. Most of the advanced TDDS techniques are based on the principle of disruption of the SC layer.

3.1. Techniques for enhancement of skin permeation

The change in skin structure due to disruption of the stratum corneum allows for a more comprehensive class of materials transported across the skin. The standard methods used to increase skin permeability by utilizing this technique are ultrasound-based systems, microneedles (MNs), electrical techniques (Iontophoresis and Electroporation), and combination methods.

3.1.1. The ultrasound-based system

For several decades, various studies have been performed on using ultrasound-based systems in TDDS. However, the exact transport mechanism and delivery action need to be clarified. It is believed that the ultrasound-based system mainly works on the sonophoretic mechanism. The sonophoresis technique comes under third-generation energy-driven methodology. The sonophoretic system primarily works on the formation of microjets from the acoustic cavities (Fig. 2). This microjet forms the passage of small channels, permits the transportation of molecules, and finally helps to enhance skin permeability.[19] The current review focuses on low-frequency sonophoresis (LFS). It mainly emphasizes the perspective, basic mechanisms, and suitable examples, citing the successful transportation of drug molecules transdermally using the LFS approach.

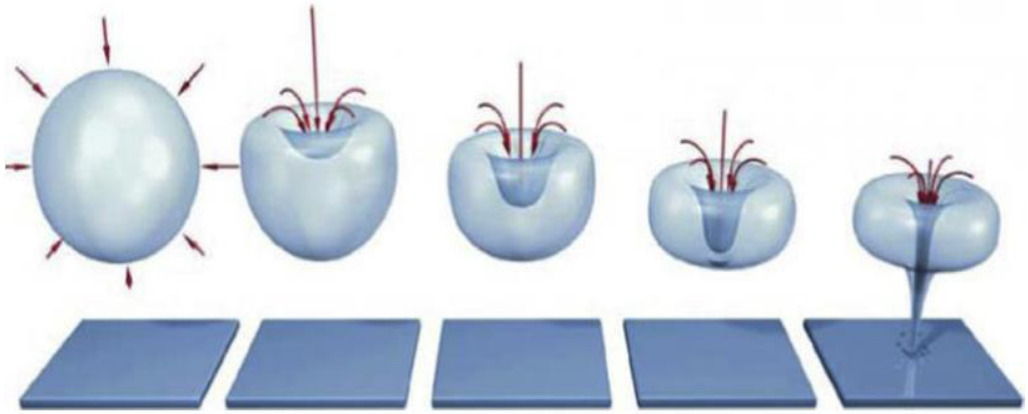


Fig.2. The mechanism of cavitation collapse near the skin surface, which creates a micro-jet. Reproduced with permission from.[19]

Copyrights 2014 Elsevier BV. The mechanism of sonophoresis has been briefly demonstrated in Figure 2. The sonophoresis system primarily works on the formation of microjets with the help of cavitation collapse near the skin surface. LFS utilizes ultrasound (US) to permeabilize the SC. Ultrasound is a high longitudinal frequency (with frequencies > 20 kHz) sound wave corresponding to a maximum hearing limit.[20] Ultrasounds are usually divided into three frequency ranges: low frequency (< 100 kHz), therapeutic (0.7 to 3 MHz), and high frequency (> 3 MHz).[19,21] The principal mechanism is primarily based on the induction of transient cavitation in the coupling media, which allows cavitation bubbles. The cavitation theory was well conversed by Park et al. [19], where they summarized the cavitation mechanism, the bubble formation, inertial cavitation, and the role of shear in cavitation formation and transmission. The bubbles become unsteady due to enormous local pressure and gradually collapse, producing a streamlined liquid jet that helps to pierce the SC.[23] The permeabilization efficiency of LFS is strong and inversely correlated with ultrasound frequency. In a study, Ashok et al. highlighted the spatial distribution of acoustic cavitation bubbles at different ultrasound frequencies.[23] Usually, LFS is applied to the skin along with a chemical penetration enhancer (CPE). Tezel et al., in a study, presented that the practice of CPE together with LFS showed a synergistic effect. 24 The study concluded that the synergistic effect of surfactants possessing anionic and cationic head groups in increasing skin conductivity in ultrasound was significant compared to those possessing nonionic head groups. Two discrete regions are produced in the skin due to LFS treatment: i.e., "localized transport regions" (LTRs) and "non-localized transport regions" (non-LTRs). The two transport regions have different degrees of permeability. The LTR regions are the locales in the skin in which a high level of fluidization has occurred due to high concentrations of CPE.[25] The skin surface physically ruptures due to cavitation formation close to it, which aggravates the permeation of CPEs into the skin in those regions. The permeability capacity of both areas mainly depends on the formation of the cavity near the skin surface. In Non-LTRs, cavitation events are formed less, leading to lower CPE content and lower permeability than LTRs.[26-27] The roles of CPE, particularly sulforhodamine B (SRB), a fluorescent hydrophilic permeant, and Rhodamine B hexyl ester (RBHE), a fluorescent hydrophobic permeant, were discussed by Joseph K et al. The study concluded that the chemical enhancer is required in the coupling medium during ultrasound treatment to obtain two significant levels of increased penetration of SRB and RBHE in US-treated skin relative to US-untreated skin.[25] Numerous studies in ultrasound-mediated transdermal transport have been carried out using various therapeutic compounds. Several have tested the ability to administer transdermal insulin because of the high incidence, cost, and difficulty of diabetes treatment.[27] One of the current insulin-related studies by Feiszthuber et al. [28] explained the feasibility of transdermal transportation of insulin in skin agar models and porcine skin.

3.1.2. Microneedles (MNs)

Intradermal injections are currently being utilized to address the issues related to transdermal delivery. However, the popularity of intradermal injections decreased due to certain limitations like needle injuries, needle phobia, requisites of specially qualified staff, and increased delivery costs. The microneedle drug delivery system is one of the best conventional intradermal injection dosage forms. Microneedles have been figured out to deliver small molecules [29] and various macromolecules.[30-31] These also deliver cosmeceuticals [31] and micro-/nano-particles. 32 Implementing diversified microneedles via the transdermal system has been evaluated by Du G et al. for diagnostic applications, patient surveillance, and advanced vaccination.[33] Research on microneedles has reached considerable progress in transdermal drug delivery and ascertains their place in other ocular, oral, and diagnostic fields. In similar studies, Prausnitz et al. and Jung et al. reported using microneedles in guts and cosmetics. Because of its popularity, significant emphasis has been given to the commercialization of this technology. For a better understanding of the reader, we have differentiated the traditional injection system from the microneedles in Fig.3**.** Micron-sized needling system is a microneedle, a painless technique in which MNs penetrate the outermost epidermal layer, making a small route to penetrate the skin without causing any bleeding or infection.[34] In a recent review of advancement in microneedle technology; Nagrakar et al. demonstrated the possible mechanism of penetration and emphasized that the microneedles mainly penetrate the outermost dermal layer by diffusion mechanism. Based on their diffusion mechanism, the therapeutic agents penetrate the dermal layer, which is very much impregnated with blood vessels.[35-36] The length of the microneedles is an important criterion to evaluate, and the length can change to ascertain epidermal penetration while preventing any damage to nerve fibers or blood vessels. Based on their molecular size, the microneedle delivery system does not show limitations since the channels are bigger than the ordinary therapeutic agents. In their research, Alderman et al. and Park et al. constructed

microneedles (MNs) with an extensive collection of microfabrication techniques.[37-38] Different materials, geometries, and dimensions (50–900 μm height, 2000 mm^2 surface area) are usually used to prepare microneedles.

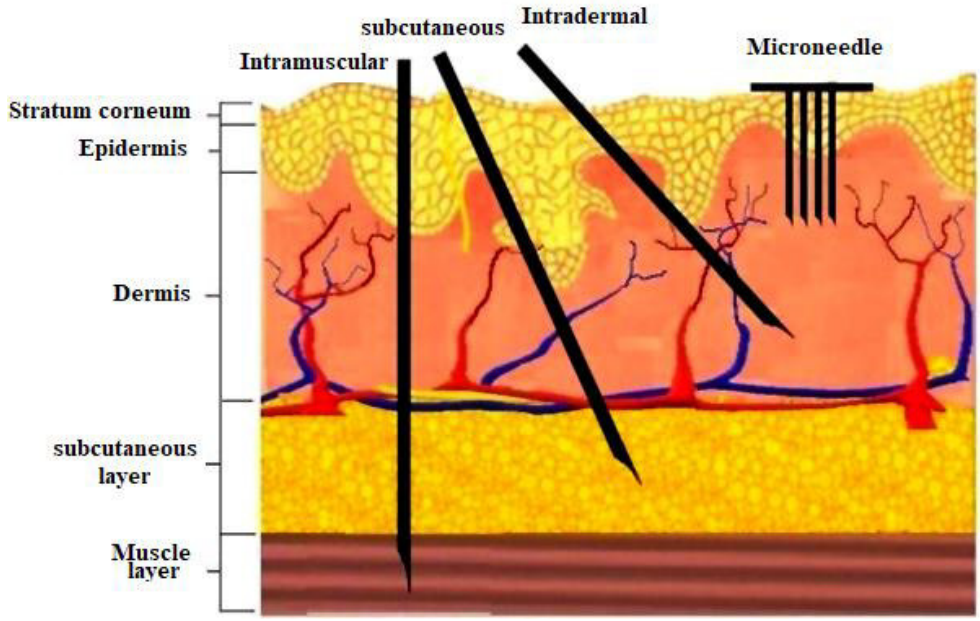


Fig.3.Comparison of microneedles with a traditional injectable form of delivery. It is reproduced with permission from.[36] Copyrights 2020 Elsevier B.V. [34]

Fig 3 illustrates the difference in administration of traditional injection systems such as intradermal, subcutaneous, and intramuscular with microneedle injection systems. MNs length is measured in microns, and the tip is slightly projected to penetrate the SC. Due to their correct size, the needles do not enter much deep inside the skin, not affecting the nerves, making them painless. MNs are available in 4 variants, i.e., solid, hollow, coated, and dissolving. The use of hollow microneedles for minimally invasive insulin delivery in subjects with type I diabetes was studied by Gupta et al.[40] Solid one has been widely applied for the pretreatment of the skin after applying a topical cream.[39] The hollow MN delivers a larger drug directly inserted into the skin.[40] Zhu et al. [41] demonstrated the use of coated MNs. The coated MNs have the medicament coated onto the surface of solid MNs.[41] In the dissolving MNs, the needle is a dissolvable substance containing the medication.[42] Lee et al.[42]prepared dissolving microneedles for transdermal drug administration prepared by step -wise controlled drawing of maltose. There are two main barriers associated with the clinical use of microneedles. The first is the scale-up production, and the second is the delivery of a limited amount of drug substance and the scope of services for a range of molecules. The former issue has received tremendous attention, and different new strategies have been developed to increase the delivery of MNs. However, the common factors associated with all MNs are their drug-loading capacity and the ability to penetrate the skin. The use of dissolving MNs has been considerably increased in recent times. For dissolving MNs, the critical parameter that needs consideration is dissolution time. A shorter dissolution time can deliver fewer drugs through the patches, while a longer dissolution time can increase the biohazard effect. One recent method that handles both challenges is manufacturing water-soluble biocompatible polymeric MNs, as reported by Boks MA et al.[43]. The water-soluble patches are a unique pattern that dissolves in 5 minutes. As a result, the device does not need to be detached, and it ensures the required dissolving time while reducing biological dangers to the skin.[43] The backings used in these microneedle patches are very flexible; consequently, these require small insertion forces or penetration, which ultimately increases the penetration ability of the MNs. The advancement in MNs technology allows the user to deliver a variety of drug molecules. Researchers successfully delivered different metabolites, drug molecules, and vaccines using MN technology in TDDS. For the reader's understanding, we have summarized the products made with different microneedles in Table 2.

Table 2. An outline of products made with different types of microneedles

Product	Type of MN	Reference
Soluvia(Influenza vaccine)	Metal	Nagarkar et al. [36]
Micron jet(Influenza vaccine)	Silicon	Du et al. [33]
Macromolecules, such as BSA and insulin	Metal	McAllister et al. [44]
Diclofenac, ibuprofen, ketoprofen, and paracetamol	MN roller devices	Stahl et al. [45]
Desmopressin	Coated	Cormier et al. [46]
Caffeine, lidocaine, metronidazole	Dissolving	Garland et al. [47]
Insulin	Hollow	Roxhed et al. [48]
Influenza vaccine	Coated	Zhu et al. [49]
A combination vaccine against anthrax, botulism, plague	Hollow	Morefield et al. [50]
Doxorubicin	PVA micro mold	Nguyen et al. [51]

Lidocaine	Solid microneedle with PEG matrix	Ma et al. [52]
Calcein	Silicon MN	Henry et al. [53]

Table 2 summarizes the different microneedle-based TDDS with the type of MNs used in each product.

3.1.3. Electrical techniques

The two essential methods for electrically facilitated TDD are iontophoresis and electroporation. Iontophoresis involves a high-voltage electric gradient to drive charged permeants into the skin through electrostatic effects.[54-55] A typical current-voltage in an iontophoresis system ranges from 0.1 to 1.0 mA/cm^2.[56] The only limitation of this method is the observed low electric fluxes in the uncharged species, which restrained the effectiveness of this method.[55] Herr NR et al.[55] studied the electro-osmotic flow and its contribution to iontophoretic delivery. The study showed that the ejections observed are due to the sum of iontophoretic and electro-osmotic forces. Moreover, the results illustrated that capillary electrophoresis (CE) could be used to predict the ejection percentage due to electroosmotic flow. Electroporation also utilizes electricity to disrupt cellular membranes.[57] This system works on a typical electrical pulsation of 10 µs - 10 ms volts. Denet et al. [58] presented a transdermal topical delivery system by the skin - electroporation. The study emphasized that the formation of an electric pulse produces aqueous pores in the lipid bilayer of the SC and disrupts cell membranes.[58-59] The electric field does provide a thrust to the system; however, delivery is governed by passive diffusion through the pores generated primarily due to the short period of the pulses (typically milliseconds).[60]However, the role of the duration of application of pulse (longer pulse and shorter pulse) had a significant role in the transport of active substance by TDDS. This assumption was proved by Zorec et al.[60] by experimenting, and they identified that the longer LV pulses significantly increase subsequent passive transport of calcein through dermatomed pig skin. In contrast, short HV pulses alone result in negligible passive transdermal transport of calcein. Compared to electroporation, iontophoresis has an insignificant effect on the cutaneous architecture because of the low gradient voltage electric current application for a short period. Because of resistive heating, a significant morphological modification can be observed after a long treatment process. 61 Due to the unique effect of electroporation, it comes under the third-generation technique, whereas iontophoresis comes under the second-generation technique. However, these two concurrent methods help attain superior drug delivery. The iontophoresis technology can be used to deliver proteins by transdermal iontophoretic mechanism. Dubey et al.[56] demonstrated the delivery of a ribonuclease by using a transdermal iontophoretic system. The study also demonstrated the feasibility of using transdermal iontophoresis to deliver a functional protein, ribonuclease A (RNAse; 13.6 kDa), non-invasively across the skin. Despite its ease of application, numerous concerns arise in the clinical applicability of electrical techniques. The main concern is the application and the beneficial effect of electrical techniques mainly confined to charged molecules. The iontophoresis application can quickly modify the electrical resistance of the SC as compared to electroporation.[60] All these issues have tempered research into electroporation for TDDS. At the current time, it has a significant role in the field of vaccination research. Its use in accomplishing intracellular uptake of DNA-based vaccines by skin-resident dendritic cells is an active area of research. [58] Denet AR et al., in their research, highlighted the delivery of DNA-based vaccines using electrical techniques. Phoresor®, Lidosite®, and E-trans® are examples of three commercially available products based on iontophoresis delivery systems. However, Phoresor® and Lidosite® are currently discontinued from the market by FDA.[62] Different transdermal patches available in the market function by modulating the skin structure by disrupting the stratum corneum (SC) by different techniques are listed in Table 3.

Table 3. Marketed products of ultrasound, microneedles, and electric-based transdermal drug delivery system

TDDS method	Brand Name	Manufacturer	Product
Micro projection	Macroflux	Alza Corporate	Vaccines, therapeutic proteins
Iontophoresis	E-Trans	Alza Corporate	Fentanyl
Ultrasound	Sonoprop®	Sontra Medical Corporation	Peptides and other large molecules
Ultrasound	SonodermTM	Imrax	Insulin
Microneedles	Intranet	Weston medial	Vaccine
Microneedles	Powder Ject	Powder Ject Pharmaceuticals PLC	Insulin
Heat	CHADD	Zars Inc.	Lidocaine and tetracaine
Laser radiation	Transdermal assisted delivery	Norwood Abey	Wide range of drug molecules

Source: Data obtained from [59,63]

The table presented the marketed transdermal patches prepared using ultrasound, microneedles, and electric-based mechanisms.

3.1.4. Combination methods or penetration enhancement techniques with synergistic effect

Current research also prioritized combinations of skin permeabilizing strategies. Most studies emphasized using a combination of microneedles and electric techniques, microneedles, ultrasound, or ultrasound pretreatment followed via iontophoresis. This review also discusses the combination strategies with synergistic effects of the TDD method. Therefore, we have assigned a section of this paper to discuss this point. Our review covered two critical aspects of combining different technologies used for transdermal drug delivery systems. We focused primarily on the operation process of the combination approach, with further studies performed on these techniques (Table 4).

Table 4. A summary of product developed based on a combination method approach for TDD

Drugs used	Types of needle	Frequency of ultrasonic wave	Skin model	Conclusion drawn	References
Transdermal delivery system with a combination of micro-needling and sonophoresis system					
Calcein and Bovine serum albumin(BSA)	Hollow	In between 20 kHz and 16 MHz	Pigskin	Large molecular weight compounds can be delivered by this method. Significant improvement in in-vitro release rate was observed for BSA.	Chen et al.[64]
Glycerol	MN roller devices	-	Porcine skin	The combination method demonstrated the reduction of transdermal diffusion time of topically applied glycerol and the feasibility of dermatological application established in an in vivo study involving mice.	Yoon et al. [65]
Bovine serum albumin(BSA)	Solid	20 kHz, 9–18 W	Porcine ear skin	This combination technique successfully delivers large molecular weight molecules. Combining microneedles and ultrasound may become a painless alternative to hypodermal injections for delivering large molecules.	Han and Das [66]
Lidocaine	Stainless steel	20 kHz, 4 W and 400 W	Porcine ear skin	A stable formulation was prepared with a combination method of the micro-needle and sonophoretic system. This method is painless and promising.	Nayak et al. [67]
Fluorescein isothiocyanate-dextran	Homemade MN array	20 kHz	Porcine skin	The combined method shows good permeation enhancement of medicament without damaging the skin. However, the study proposed a combination of three techniques like microneedle, electroporation, and sonophoresis.	Petchsangsai et al. [68]
Transdermal delivery system with a combination of micro-needling and electrical driving forces					
Drugs used	**Types of needle**	**Duration of electrically modulated device application**	**Skin model**	**Conclusion drawn**	**References**
Ropinirole hydrochloride	Admin Patch®	Iontopho resist– 4 hr	Porcine ear skin	Modulated iontophoresis can control the release of ropinirole hydrochloride and may increase active substance administration.	Singh and Banga [69]
Propanolol Acetabutanol Atenolol Sotalol	Solid metallic	Iontophoresis– 6 hr	Dermatom-ed human skin	The study demonstrated that the dual iontophoresis method coupled with solid metallic microneedles is more effective for hydrophilic than lipophilic compounds. Based on this assumption, it was concluded that propranolol showed less flux and release than the other three drug molecules.	Pawar et al.[70]
Methotrexate	Solid tetrahedron	Current density 0.4 mA cm2	Male hairless rats	The study concluded that in vivo, there is a 25-fold increase in methotrexate delivery with a	Vemulapalli et al. [71]

		applied for 60 min		combination approach compared to a single method. Further, it proposed the local use of methotrexate using a combination method with better patient compliance and therapeutic activity.	
D_2O and Fluorescein isothiocyanate(FITC)-dextrans	Homemade MN array	Iontophoresis– 5 hr	Hairless rat skin	The study results indicated that the combination technique of iontophoresis and microneedle could be used as a potential method for permeation enhancement of high molecular compounds.	Wu et al. [72]
Insulin	Solid stainless	Iontophoresis, 0.2 mA cm^2 applied for 5 hr	The male guinea pigs	The nanovesicle of insulin with a combination of iontophoresis and microneedles showed a significant increase in permeability. This approach suggested a new method for delivering peptides with large molecular weights.	Chen et al. [73]
Prochlorperazine edisylate	Stainless steel	Iontophoresis-0.4 mA/cm2	Dermatomed human skin	The study concluded that microneedles, when combined with iontophoresis, significantly enhanced the transdermal delivery of prochlorperazine edisylate. In addition, the in-vitro flux obtained due to iontophoresis and microneedles is sufficient to get the desired plasma concentration of prochlorperazine edisylate.	Kolli et al. [74]

Table 3 keeps the information regarding the drug molecules delivered successfully by combining the various penetration enhancement techniques having synergistic effects. The outcome of each research was presented precisely with the technique or device used for the study.

3.1.4.1. Microneedles combined with electrical driving forces

Combining MNs with electrical techniques (electroporation or iontophoresis) is simple. The electrical driving forces' current is transmitted in the skin through the aqueous pores created by the MNs. Usually, skin is pretreated with MNs, after which the drug of interest is implemented with instantaneous iontophoresis for 4-6 hours.[69-70] Singh and Banga successfully delivered ropinirole hydrochloride using modulated iontophoresis and microneedles through the skin.[69] Two benefits of this combination delivery system are; the capacity to govern the flux of drugs through control of the applied current and a diminution in the lag time needed for drug molecules to infiltrate the skin.[69-75] This method yields the best results at a faster rate for small molecules than any single method. The combination method merits a little disruption of the SC layer, which is essential for delivering small molecules.[69] Ultimately, the technique's sequential process and awkward nature minimize its use. However, the lipophilicity of the drug molecule can vary the transportation across the incorporated skin. The above-said result aligned with the study conducted by Pawar et al.[70], reporting a relationship between the lipophilicity of the molecule and electrically assisted transdermal delivery of drugs across the incorporated skin.

3.1.4.2. Microneedles combined with ultrasound for transdermal drug delivery

Several scientific works exist on the combined use of MNs and ultrasonic for drug delivery; however, the major consideration is given to the concomitant use of these two methods.[64-66] In this method, the microneedles pierce the SC layer of the skin, and the ultrasonic system is used for drug permeation and penetration into the skin.[64-69] Efforts have already been made to consolidate both mechanisms. A study group by Singh and Banga [69] created an MN device with a 20 kHz piezoelectric crystal so that each MN could carry ultrasound into the skin.[69] The instantaneous use of treatments and assimilation into a single device simplifies this method's use. In another study by Chen B et al., the simultaneous treatment improved the transdermal delivery of calcein and bovine serum albumin over either method.[64] One can also use a combination of solid MNs with ultrasound cavitation. Solid MNs can help in permeability enhancement by creating visible holes. An enhancement in permeability can be significant by applying high-intensity ultrasound on the MN's pretreated base. This arrangement is beneficial for delivering large molecules and can be a superior preparation for a long-term transdermal drug delivery system.

3.2. Modification of drug formulation enabling passage through the SC using chemical penetration enhancers (CPEs)

Chemical penetration enhancers (CPEs) belong to specialized chemicals that disturb the lipid bilayer within the subcutaneous layer. The CPEs are mainly coming under the second generation of transdermal delivery systems. Chemical enhancers alone have had limited success in transdermal formulations, but combinations have been more successful. The lack of mechanical information on how the individual chemical enhancers interact with stratum corneum substantially limits the rational combinations of penetration enhancers. [15] This bottleneck can be directly addressed by high-throughput screening of transdermal formulations, which could lead to the breakthrough of a previously unidentified combination of penetration enhancers. However, the combinations of CPEs are coming under the third generation of transdermal delivery systems.[5] Unlike physically enhanced delivery methods discussed above, chemical penetration enhancers (CPEs) ensure advantages such as ease of application and design flexibility. Recent studies have focused more on the (CPEs) and introduced several classes of penetration enhancers, including surfactants, fatty acids/esters, terpenes, and solvents. However, most effective, a small number of chemical enhancers have been reported to enhance drug transport.[76] The CPEs mainly consist of three primary groups: H-bond acceptor solvent, pure fatty acid, and alcohols or surfactants with large polar groups. Pathan et al. [76] described the possible mechanism of enhanced drug penetration using CPEs. Detailed mechanistic studies have revealed that the cleavage of the hydrogen bonds between the ceramides is responsible for the enhanced penetration activity of CPEs. It penetrates the tight lipid layer quickly, reducing the resistance of the critical skin barrier. A large amount of water in the drug formulation further increases penetration into the cell. Inflammation of the cells inside corneocytes occurs due to amino acids. It augments the water content inside the intercellular space and primarily disrupts the lipid plane. However, the patients sometimes feel discomfort due to associated side effects such as a bad and burning sensation in the skin.[76]

4. MODIFICATION OF THE DRUG FORMULATION USING NANO-CARRIERS

In TDDS, the penetration capacity of pharmacological substances through the skin can be increased by altering the drug substance's physicochemical properties (i.e., prodrugs approach) or modifying drug formulation using nano-carriers. The prodrug approach changes the physicochemical properties of the drug substance, which is mainly related to manufacturing an active substance with an adduct or with a new salt form to get the desired modified physicochemical properties. However, nano-carriers are a new scientific approach that prepares different formulations of the pharmacologically active substance with desired quality attributes. In this review, we have emphasized more on nano-carriers due to their versatile use in the health and pharmaceutical industries.[77] The use of lipophilic nanoparticles for drug delivery, such as liposome and its derivatives, liquid crystals, solid lipid nanoparticles, and nanoemulsion, has a wide application in the health and cosmetic industries. Nanoparticles can be applied in gels, creams, lotions, and solutions. The use of the nanoparticles has been elaborately discussed by Escobar-Chavez et al. The mechanism of action used by these systems involves perturbing the stratum corneum, contravening the tight junctions, and disturbing the cell membrane structure, thereby expediting drug penetration.[78] The NPs have incredible potential to improve drug penetration across the skin. One can use NPs for both hydrophilic and hydrophobic drugs. The benefits associated with nano-transporters increase drug stability by preventing the breakdown of the skin microflora, ascertaining site-specific targeting, which covers a large portion of the skin area, and ensuring controlled release delivery.[77-78]The most notable features accompanying the nanoparticles include, these are non-invasive and are beneficial for controlled release formulations.

4.1. Liposome and its derivative

Liposomes consist of phospholipids containing a hydrophilic head and a hydrophobic tail (Fig. 4). Liposomes and their analogs can carry both hydrophilic and hydrophobic drugs inside the aqueous phase, and the membrane bilayer of the liposome, respectively. The interaction between the positive charge of cationic liposomes and the negative charge on the skin surface manifests higher penetration for cationic liposomes. If small peptides are functionalized on the surface of the liposome, they may serve to increase cellular absorption and penetration into the skin layers. The penetration ability of liposomes can further be enhanced by using edge activators. Edge activators consist of a chain of surfactants that helps increase liposomes' elasticity, fluidity, and deformability. These unique characteristics of liposomes help constrict themselves through the intracellular space and support diffuse through the skin easily.[78-79] A derivative of liposome containing novel vesicles named transfer some encompasses edge activators in their vesicular arrangement. These properties of liposomes attracted various researchers, and different molecules are targeted in the dermal route as a liposomal-based transdermal patch (Table 5).

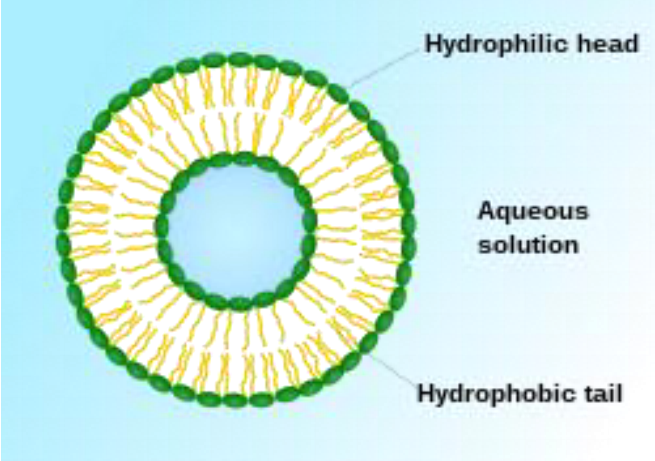


Fig.4.Structure of liposome containing the hydrophilic head, hydrophobic tail, and aqueous solution.[79]

Figure 4 presented the structural illustration of a liposome containing the self-assembled structure of the amphiphilic lipid molecules containing the hydrophilic head and hydrophobic tail and entrapping the aqueous solution inside the cavity the structured formed. It briefly explains the scheme of liposomes formed by phospholipids in an aqueous solution. Many factors, including the drug molecule's physicochemical and characteristic properties, can affect the liposome's transdermal penetration. However, the liposomal formulation and selection of suitable polymers can successfully help the drugs transport via liposomal vesicles across the skin. Researchers widely use liposomes as a carrier for transdermal drug delivery systems for successful transdermal application of antibiotics, NSAIDs, sex hormones, and anticancer molecules. To highlight the success stories of liposomal TDDS, we have tabulated some of the active molecules along with the liposome vesicle composition in Table 5.

Table.5. Studies of active ingredients based on liposomes as a carrier for transdermal drug delivery system

Active Ingredient	Therapeutic category	Polymers used	Study outcome	Reference
Amphotericin B	Antifungal	Hydrogenated soy phosphatidylcholine/ cholesterol	The most stable form of amphoteric B compared to the reported powder and solution form.	Manosroi et al. [80]
Ketoprofen	NSAIDs (Non-steroidal anti-inflammatory drugs)	Hydroxy propyl-Beta cyclodextrin, phosphatidylcholine, and cholesterol	The authors investigated the ideal operative condition for the ketoprofen–cyclodextrin–liposome system for permeation and encapsulation efficiency.	Maestrelli et al. [81]
Melatonin	Neurohormone responsible for sleep	Soya phosphatidylcholine	Improved transdermal application of melatonin with enhanced transdermal flux, higher entrapment efficiency, and low skin irritant potential	Foldvari [82]
Vitamin E Acetate	Vitamin	Coat some MC-6081 (POPC), cholesterol, and stearic acid	The study developed a new formulation with improved skin deposition of vitamin E acetate compared to the marketed formulation.	Sharma et al.[83]
Avanafil	Erectile dysfunction	phospholipid, lecithin, and cholesterol	An improved permeable transdermal formulation and bioavailability of avanafil developed.	Hosny and Aldawsari [84]
Aceclofenac	NSAIDs (Non-steroidal anti-inflammatory drugs)	Soybean lecithin	The author developed an alternate route for oral administration of aceclofenac with improved patient compliance and controlled absorption through the skin.	Gupta et al. [85]
Tamoxifen	Estrogen receptor modulator	Eudragit-RL, hydroxypropyl methylcellulose K-50, and ethyl cellulose	Greater bioavailability compared to the existing commercial formulation of tamoxifen was proposed.	Adhyapak and Desai [86]
Tretinoin	Anti-acne	Soy phosphatidylcholine (PhospholiponR90, P90)	Researchers evaluated liposomal trétinoin based carriers for the	Sinico et al. [87]

		and hydrogenated soy phosphatidylcholine (Phospholipon R90H, P90H), cholesterol trans-retinoic acid, diacetyl phosphate, and stearyl amine	treatment of various skin diseases.	
Methotrexate	Immuno-suppressant	Soybean lecithin (PC) or hydrogenated lecithin (HPC) and dipotassium glycyrrhizinate (KG) as surfactant	Researchers evaluated KG as a potential surfactant for methotrexate liposomes. In addition, they explored the topical use of methotrexate liposomes for psoriasis.	Trotta et al. [88]
Progesterone	Steroid and sex hormone	Egg-phosphatidyl -choline (EPC) Dimyristoylphosphati dyl-choline(DMPC) Dipalmitoylphosphati dyl-choline (DPPC) Dioleoylphosphatidyl-choline (DOPC) Oleic acid and stearic acid	The study proposed concomitant and controlled release of progesterone in hormonal therapy.	Knepp et al. [89]
Diclofenac sodium	NSAIDs (Non-steroidal anti-inflammatory drugs)	Soy lecithin (Lipoid S75) and egg phosphatidylcholine (Lipoid E80), cholesterol, cholesteryl sulfate, palmitic acid, sepharose CL-4B, Sephadex G-50 and sodium deoxycholate (SDCh)	Researchers developed a PVPA-based novel skin barrier model with a modified stratum corneum barrier for higher molecular weight drug molecules like diclofenac sodium.	Palac et al. [90]
Ketoconazole	Antifungal	Lipoid S phosphatidyl choline-3, containing not less than 98% phosphatidyl choline	Researchers evaluated the topical application of ketoconazole for fungal infection with a better stability profile.	Shaik[91]
Celecoxib	NSAIDs (Non-steroidal anti-inflammatory drugs)	Soya lecithin and cholesterol	The permeability of celecoxib release was increased in the liposomal formulation through rat skin using components such as lecithin and cholesterol.	Jeong et al. [92]
Lamivudine	Antiretroviral	Phospholipon® 90G, Phospholipon® 90H, DMPC, and DPPC	Researchers prepared the lamivudine liposome formulations with good stability and considerably controlled skin permeation with negligible retention of drugs in the skin.	Ogiso et al. [93]
Cyclosporin	Immuno-suppressant	Monoolein-monoacylglyceride as a penetration enhancer	Researchers explored a new topical treatment for skin diseases like psoriasis, atopic dermatitis, and some hair follicle disorders by using liposomal cyclosporin transdermal delivery system.	Lopes et al. [94]
Lidocaine hydrochloride	Anesthetics	Transactivation transcriptional activator (TAT) peptides were conjugated on the octadecyl-quaternized, lysine-modified chitosan to form polymeric liposomes (TAT-PLs) with cholesterol.	The study suggested an efficacious alternative dosage form, such as liposomal-based transdermal delivery of lidocaine hydrochloride.	Wang et al. [95]

Table 5 presents the success story of liposomes as carriers for transdermal drug delivery systems. It gives the different active ingredients successfully delivered using liposomes as a transdermal drug delivery system carrier. The table also includes different polymers used for designing the liposome vesicles and the research conclusion for ease of understanding to the reader.

4.2. Niosomes

During the past years, niosomes have undergone comprehensive research for transdermal drug delivery and are suitable vehicles for drugs meant for dermal targets. Niosomes are very popular among all topical drug delivery systems due to their inherent properties. Specific properties of the niosome formulations distinguished them from others, such as superior skin permeability, sustained drug release for a particular time, and modulation of systemic drug absorption through the skin.[79] The mechanism of niosomal drug delivery for transdermal targeting has been well explained by Rita et al.[96] The niosome mainly consists of non-ionic surfactant molecules having a hydrophilic head and a lipophilic tail (Fig. 5). The internal structure can accommodate both hydrophilic drug and lipophilic drug substances. The niosomes containing the pharmacological substance get adsorbed onto the skin surface by internalizing hydrophilic/aqueous or hydrophobic/lipid components. It may also result from special receptors or ligands binding on the skin surface. At the same time, the niosomes fuse with the skin cell membranes, resulting in the fusion of the niosomal content with the cell membrane. Ultimately, endocytosis occurs, and lysozymes in the cytoplasm absorb the niosome vesicle. Further, the niosomal membrane gets ruptured, facilitating the release of the entrapped drug substance inside the medium.[96-97] Niosomes were successfully implemented in the cosmetic industry. In a cosmetic application developed by L'Oreal, niosomal surfactant vesicles were first reported. Niosomal carriers can deliver several pharmacological agents, including NSAIDs, antihypertensive, antispasmodics, flavonoids, antioxidants, anticancer, antimicrobial, and other drugs. A summary of the findings of investigations over the past few years for transdermal niosomal drug delivery systems is given in Table 6.

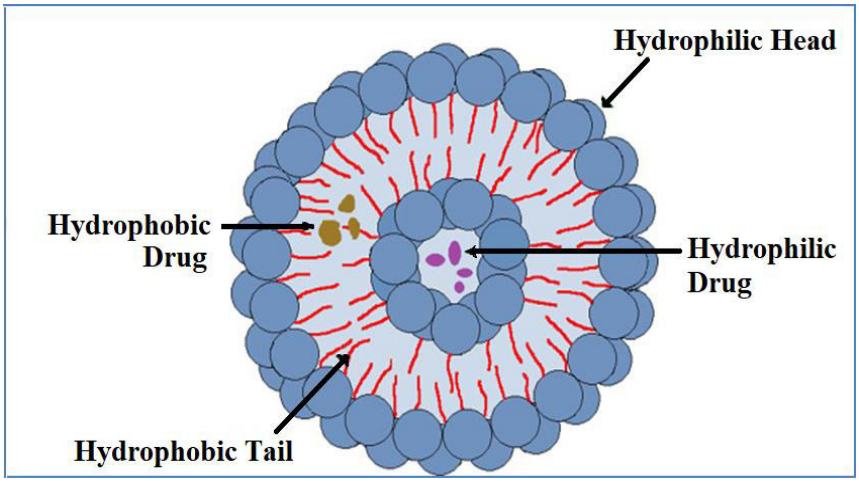


Fig.5. A typical structure of niosomes containing the hydrophilic head, hydrophobic tail, hydrophilic drug, and hydrophobic drug. It is reproduced with permission from.[97] Copyrights 2017 Elsevier BV.

Figure 5 presents the structural illustration of a niosome containing the main components such as the hydrophilic head, hydrophobic tail, hydrophilic drug, and hydrophobic drug embedded between the hydrophilic head and hydrophobic tail.

Table 6. Example of drug molecules delivered as niosomal carriers for transdermal drug delivery systems

Active Ingredient	Therapeutic Category	Polymers used	Study outcome	References
Bufomedil hydrochloride	A Vasoactive drug used in the treatment of vascular diseases	Cholesterol and span 60	Buflomedil hydrochloride is more effective and stable by transdermal administration than liposomal vesicles.	Akhtar et al. [98]
Minoxidil	Anti-hypertensive vasodilator	Cholesterol, BrijTM, and SpanTM	A promising approach to minoxidil niosomal formulations for topical administration in treating hair loss.	Balakrishnan et al. [99]
Meloxicam	NSAIDs (Non-steroidal anti-inflammatory drugs)	Cholesterol and span 60	Meloxicam was found to have higher stability in niosomal vesicles. [100] Researchers described an alternative of meloxicam gel in vehicles for transdermal delivery of meloxicam with increased permeation enhancement effects. [101]	El-Badry et al and El-Menshawe and Hussein [100-101]

Papain	Digestive protein modulator	PLGA or poly(lactide-co-glycolic acid), Polyvinyl alcohol and tween 61	These enhance superior cutaneous permeation and reduction of hypertrophic scars of papain niosome.	Manosroi et al. [102]
Gallidermin	Chemical characterization of peptide antibiotics named lantibiotics	Cholesterol, dimethyl dioctadecyl ammonium bromide (DDAB), diacetyl phosphate (DP) and tween 61	Anionic niosomes loaded with gallidermin with a negligible risk of systemic effects were established. Researchers also investigated topical antibacterial gallidermin therapy.	Manosroi et al. [103]
Salidroside	A glucoside found in plant herbs is responsible for antidepressant and anxiolytic activity.	Cholesterol, and Span40	Improved permeation effect and reduction of salidroside cutaneous deposits by niosome carrier.	Zhang et al. [104]
Lornoxicam	NSAIDs (Non-steroidal anti-inflammatory drugs)	Cholesterol, and span 40	Lornoxicam niosomal formulations have improved anti-inflammatory efficacy.	El-Ridy et al.[105]
Lopinavir	Anti-HIV	Phospholipid (Phospholipon 90 H), pan 40, and cholesterol.	A novel transdermal niosomal carrier of lopinavir was reported with superior bioavailability, stability, and skin permeability.	Patel et al. [106]
Quercetin	A flavonoid used as an antioxidant and anti-tyrosinase	Span60 and RH40	Researchers prepared a niosome formulation of quercetin by using a nonionic surfactant with improved solubility, photostability, and skin penetration ability.	Lu et al. [107]
Diclofenac sodium	NSAIDs (Non-steroidal anti-inflammatory drugs)	Span 60, Tween 60, and pluronic F127	Researchers reported higher cumulative amounts of diclofenac sodium across rabbit skin after 24 hours.	Tavano et al. [108]
Baclofen	Antispasmodic	Cholesterol, and Span 20	In comparison to other formulations, baclofen-produced formulations have better muscle relaxant activity.	Keservani et al. [109]
Celecoxib	NSAIDs (Non-steroidal anti-inflammatory drugs)	Cholesterol, Span 60 or Span 40	A superior in vitro release, skin permeation, and anti-inflammatory effect of celecoxib niosomal gel	Auda et al. [110]
Hyaluronic acid	A naturally occurring polymer used for biomedical application	N-hydroxysuccinimide, Triton X-100, fluorescein isothiocyanate (FITC),span 20, and tween 80	Hyaluronic acid niosomal preparation was reported as a potential carrier for tumor therapy by percutaneous absorption.	Kong et al. [111]
Centella Asiatica Extract(CAE)	A plant extract used as an anti-tumor, anti-psoriasis, eczema, anti-inflammation, anti-aging, burn and wound healing formulae.	Cholesterol and span 60, and tween 60	A new topical formulation of CAE niosomal formulation was prepared using hyaluronic acid as a penetration enhancer with better-enhanced stability and penetration effect.	Wichayapreechar et al. [112]
Clomipramine	Antidepressant	Cholesterol and tween (20,60), and span (20,60)	Clomipramine was found to have improved bioavailability and patient compliance	Mohamed et al. [113]

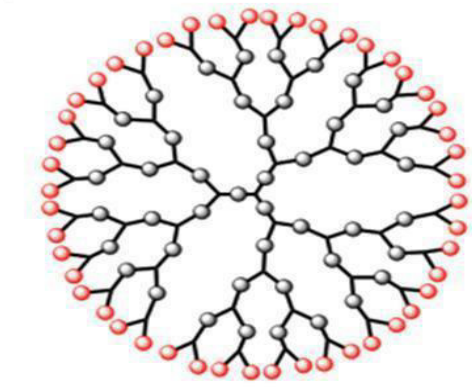
Enoxacin	Antibiotic	Dimyristoyil-phosphatidylcholine (DMPC), soybean phosphatidylcholine, egg phosphatidylcholine, cholesterol (CH), diacetyl phosphate (DCP), and span(40 and 60)	A topical niosomal formulation of enoxacin was developed with a less toxic effect and enhanced skin permeation properties.	Fang et al. [114]
Ketorolac	NSAIDs (Non-steroidal anti-inflammatory drugs)	Cholesterol, lecithin, span 20, and tween 20	A novel formulation of ketorolac in proniosome with higher entrapment efficiency was developed	Alsarra et al.[115]
Simvastatin	Dyslipidemic agent	Cholesterol, stearyl amine, diacetyl phosphate, and span (20 and 60)	The authors developed a simvastatin niosome transdermal formulation with enhanced bioavailability and hypolipidemic activity.	Zidan et al. [116]
Nifedipine	Anti-hypertensive	Cholesterol, Soya lecithin, span (20, 40, and 80), and tween (20 and 80)	Researchers developed a stable formulation of nifedipine with the highest entrapment efficiency and drug release	Yasam et al. [117]

TDDS: Transdermal drug delivery systems

Table 6 presents the example of drug molecules delivered using niosomal carriers for transdermal drug delivery systems. The different polymers used for designing the niosomal vesicles and the research conclusion were presented for easy understanding.

4.3. Dendrimers

Dendrimers can improve permeability and escalate the transport of lipophilic drugs through the skin. Generally, dendrimers comprise three elements, i.e., a core, an interior section called branched dendrons, and the terminal groups (Fig. 6A and 6B).[118] The dendrimers are generally prepared by two synthetic pathways, divergent or convergent. Cationic dendrimers can transport oppositely charged drug molecules, i.e., negatively charged on the skin surface at physiological pH. For example, peptidic dendrimers function as a chemical penetration enhancer and help disrupt the skin structure.[118] The mechanism of action of dendrimers varies based on their type. For example, polyamidoamine (PAMAM), a polymeric dendrimer, squeezes the lipid from the stratum corneum over prolonged contact with the skin, ultimately creating tiny holes in the skin surface and interacting with the phospholipid openings. An extensive review of the structure, method of preparation, limitations, and application of dendrimers is explained by Singh et al. [118.] The main advantage of the dendrimers system is that the skin irritation associated with TDDS is minimal. The dendrimers can enhance skin deposition and permeation. [118,119] The dendrimer carriers are suitable for delivering several pharmacological agents, including NSAIDs, vitamins, antifungals, etc. A summary of the findings of investigations over the past few years for transdermal dendrimers drug delivery systems is cited below for the reader. There are several drugs, including indomethacin[120], ketoprofen[121], diflunisal[122], diclofenac sodium[123], 5-fluoro uracil[124], 8-methoxy psoralene[125], tamsulosin[126], riboflavin[127], and dithranol[128] that have been shown to have a positive effect when used with dendrimers



(A)

Fig. 1 Basic structure of dendrimer

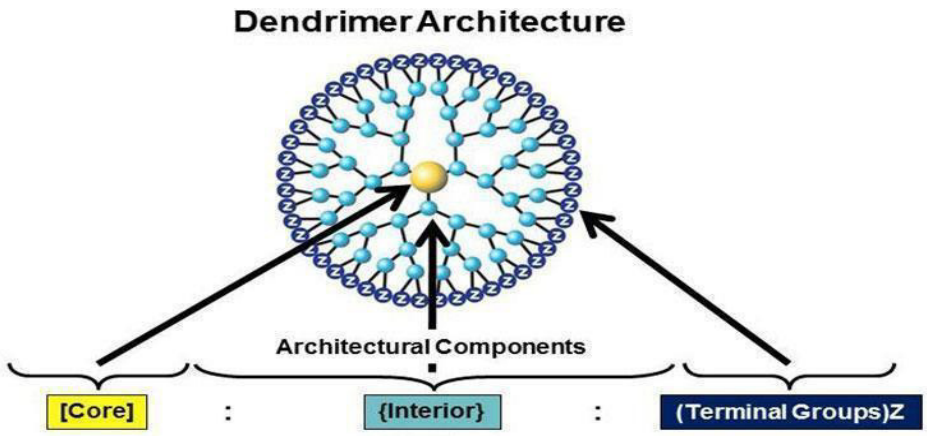


Fig. 6: Architectural components of dendrimers

(B)

Fig. 6. (A) Basic structure of dendrimers (B) Architectural components of dendrimers[118]

Figure 6 presents the schematic illustration of the basic structure of dendrimers. Next, the architectural components of dendrimers are presented in a graphic presentation.

4.4. Solid-in-oil dispersion

Another popular nanosystem for TDD is solid-in-oil (S/O) dispersion, which emerged as a novel method for administrating active ingredients through the skin. Solid-in-oil dispersion is an oil-based dispersion that carries hydrophilic molecules in solid powder form. The hydrophilic carrier in powdered form was prepared by Kitaoka et al. by separating the water and cyclohexane from water-in-oil (W/O) emulsion by lyophilization process.[129]A complex of drug-surfactant was prepared with the prepared dispersion and with another oil-based carrier. The diameter of an oil-based carrier plays a significant role, and preferably, a diameter less than 500 nm enhances the skin penetration capacity effectively. The preferable option for constructing the S/O dispersion is isopropyl myristate (IPM) due to its interaction with lipid layers within the skin proving to be biologically compatible. A potential example of solid-in-oil dispersion is an application in immune therapy by administering through the skin (Table 7).[129] More recently, Hirakawa et al. [145] investigated an oil-based solid-in-oil (S/O) nanodispersion of a hydrophilic drug that effectively enhanced the permeation of proteins into the skin. To achieve this objective, different model proteins like ITC-labeled insulin (MW ca. 6 kDa), enhanced green fluorescent protein (EGFP, MW ca. 27 kDa), and horse radish peroxidase (HRP, MW ca. 40 kDa), were taken as model molecules. Researchers successfully manufactured several pharmacological compounds employing a solid-in-oil nanosystem as a carrier in transdermal drug delivery systems. The application successfully implemented for drug molecules such as aceclofenac[130], ketoprofen[131], celecoxib[132], indomethacin[133], caffeine[134], triptolide[135], methotrexate[136], nifedipine[137], lidocaine and prilocaine[138], amlodipine[139], diclofenac sodium[140], and paclitaxel.[141]

Table 7. Studies conducted by using solid-in-oil (S/O) dispersions as a carrier of TDDS for protein, peptides, and antigens

Active substance	Description of study	Reference
Insulin	Developed transcutaneous delivery of fluorescein-isothiocyanate labeled insulin (6 kDa) using the Yucatan micro pig skin.	Tahara et al. [142]
Ovalbumin- An model antigen	Researchers attempted to increase the transcutaneous permeability of an antigen protein ovalbumin using a solid-in-oil (S/O) nanodispersion.	Kitaoka et al. [143]
Ovalbumin	Researchers achieved transcutaneous ovalbumin immunization using a solid-in-oil (S/O) nanodispersion, excluding any skin adjuvant.	Tahara et al. [144]
Ovalbumin	Researchers studied cancer immunity in mice by vaccinating them with S/O nanodispersion of ovalbumin.	Hirakawa et al. [145]
Peptide	Researchers prepared novel transcutaneous patches for a peptide (7crpR) solid-in-oil (S/O) nanodispersion delivery using the pollinosis model of mice.	Kitaoka et al. [146]

Table 7 presents the example of the active substances delivered using solid-in-oil (S/O) dispersions as a carrier of TDDS for delivering protein, peptides, and antigens.

4.5. Microsponge for TDD

A new drug delivery system known as microsponges is a sustainable option for TDD, which may conquer the drawbacks of nano and micro formulations. Specifically, microsponges diminish skin irritation, allergic reaction, and greasiness, increasing patient compliance.[147] Structurally, microsponges consist of microporous beads representing spherical particles ranging from 5 to 300 mm. The spherical particles tend to form bunches of smaller spheres (Fig. 7) and can effectively deliver low-dose drug molecules.[148]

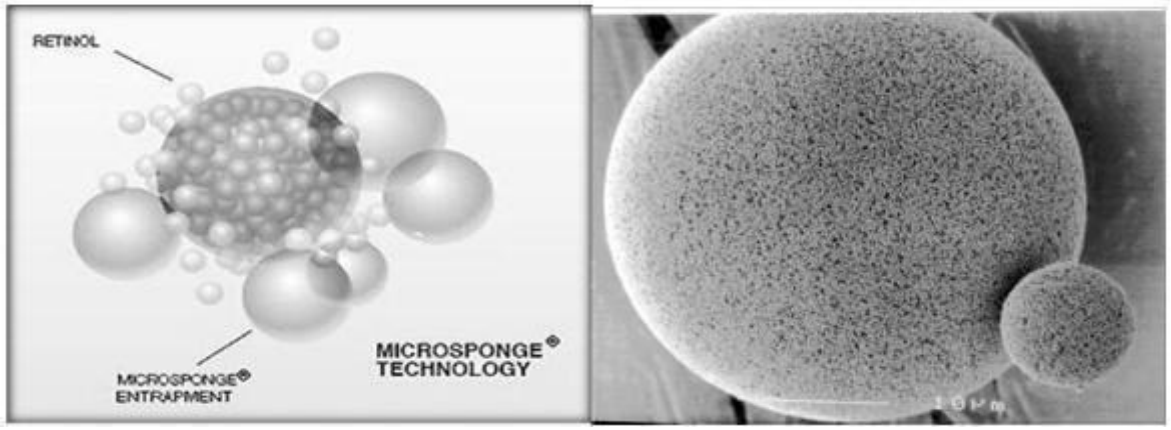


Fig. 7. Basic view of Microsponge [148]

Figure 7 shows the basic view of the microsponge with microporous beads representing spherical particles. It also elucidates a clear view of the formation of bunches of smaller spheres with the help of spherical particles. The advantages associated with microsponges increase their popularity among all transdermal drug delivery techniques. The beneficial properties of microsponges that stand out from other transdermal drug delivery systems include increased drug stability, sustained drug release mechanism, and minimum observed side effects. Microsponge, drug delivery systems also increase drug retention on the skin surface and within the epidermis.[148] In a recent development, a microscope technology of flurbiprofen was developed and tested for drug release and anti-inflammatory efficacy by Kadhim et al. [149]. In this technique, the drug was mixed in two phases. In phase I and phase II, polyvinyl alcohol (PVA) and Eudragit E100 were used, respectively, with different doses of flurbiprofen. Microsponges, drug delivery systems, are novel controlled pharmaceutical products that entrap various drug molecules. Research on microsponge delivery on skin diseases increase tremendously for different active substances such as flurbiprofen[149], benzoyl peroxide[150], hydroxyzine hydrochloride[151], oxybenzone[152], mupirocin[153], fluconazole[154], ketoconazole[155], eberconazole[156], diclofenac sodium[157], naproxen.[158]Similarly; some researchers explored the transdermal use of a microsponge delivery system for molecules like fluconazole [159] and meloxicam.[160]

4.6. Challenges of nano-carriers-based TDD

Several benefits are associated with applying nano-carriers in transdermal drug delivery. Despite these benefits, this method has significant concerns about drug delivery to the skin. The challenges liposomes pose are toxicity probability due to drug leakage inside the bloodstream due to vesicle bursting. The same type of problems can be seen with other nano-carrier systems also due to issues that arise for skin compatibility, drug loading capacity, and long-term stability.[148-161] The problem associated with oil in the dispersion system is the toxicity of surfactants. Likewise, the limited use of microsponges is because of their complex synthetic route. Another issue that raised serious concern for using almost all nano-carriers is the nano-carriers accumulation near hair follicles and glands. As a result, it restricts the continuous movement of drug substances from the epidermis to the delivery site, thus restraining consistent drug delivery. Many researchers highlighted the dark side of nanocarrier-based TDD. Similarly, Kurmi et al. discussed many disadvantages. One of the significant disadvantages of nanocarrier-based TDD is the scaling up of the technology from a lower scale to a larger scale and high production cost due to advanced technology and equipment.[162-163]

5. WEARABLE TRANSDERMAL DELIVERY SYSTEMS

Wearable and skin-attachable medical devices are being actively ensued because of their capability to assimilate with the human body, appropriately deliver the pharmacological substance, and record the physiological signals of body parameters for a long time flawlessly. Amjadi et al.[164] demonstrated the role of wearable medical systems in different fields. Remarkable advances in medical science, pharmaceuticals, biotechnology, and nanotechnology, have promoted the improvement of different wearable medical systems for real-time screening of human activities, as well as transdermal delivery of pharmaceutical agents.[164] Wearable transdermal drug delivery systems carry the pharmacologically active substances mountable to a flexible and resilient supporting material such as elastomers or hydrogels for percutaneous delivery of therapeutic agents, increasing patient compliance and satisfaction.[165]These specialized delivery systems are mainly useful for medical conditions for critical disease settings (cancer, diabetes) and long-term monitoring disease conditions.

5.1. Categorization of wearable transdermal delivery systems

There are four categories of wearable transdermal delivery systems, i.e., mechanoresponsive transdermal delivery systems, electrically activated transdermal delivery patches, light-responsive skin patches, and bioresponsive materials for wearable transdermal delivery (Fig. 8).

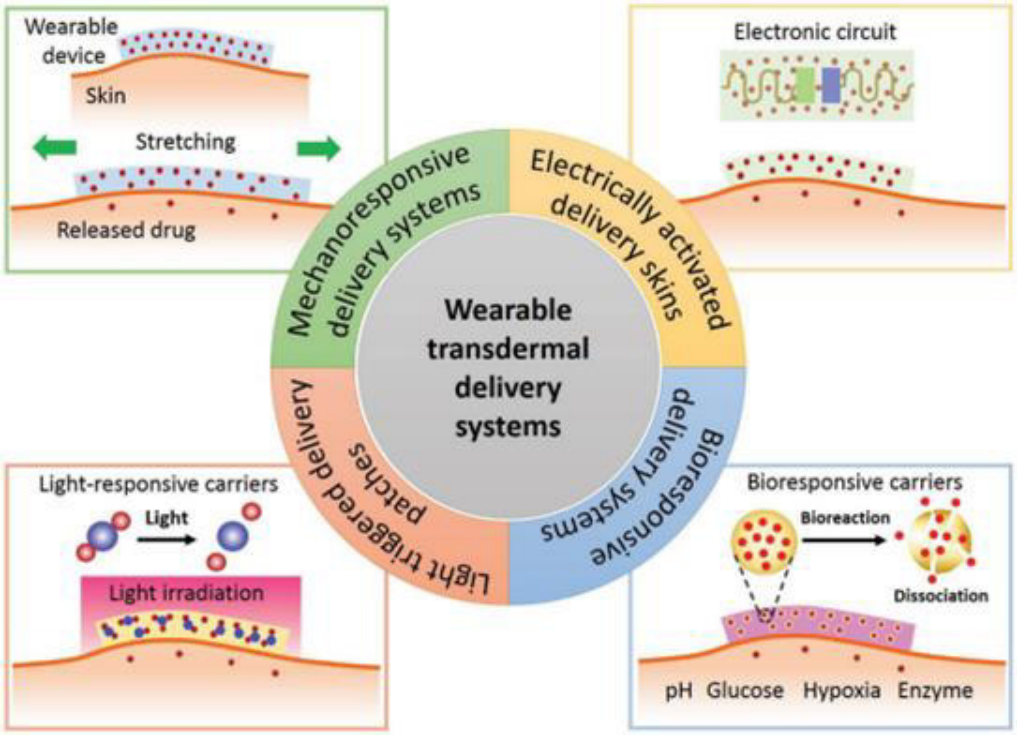


Fig.8. Categorizing wearable transdermal delivery systems. It is reproduced with permission from [164] Copyrights 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Figure 8 categorizes the wearable transdermal delivery systems into mechanoresponsive delivery systems, electrically activated drug delivery skins, light-triggered delivery patches, and bioresponsive therapeutic delivery systems.

5.1.1. Mechanoresponsive transdermal delivery systems

The mechanoresponsive carriers release the enclosed therapeutic agents by applying shear, tension, or external forces via mechanoresponsive activation.[166-167]The active carriers are linked to stretchable backing materials for medicament release in the mechanoresponsive wearable transdermal delivery systems. On applying shear to these devices, the incorporated medicament can be released through the skin by changes due to variations originating from activation of muscles, strain in tendons, drifting of organs, bones, joints, etc. [166] It has been extensively investigated whether the temperature can trigger the release of a payload from an environment-sensitive polymer.[167] The role of temperature and release of active moiety from the payload is well explained by Moghadam et al.[167] The authors showed a lag time of 5-8 minutes of active substance release from the payload hydrogels after initiation of mechanical loading.

5.1.2. Electrically activated transdermal delivery patches

Electrically activated wearable transdermal devices are considered an essential category of delivery patches due to their ease of use. These types of patches get triggered by the stimulation of electric pulses.[168-169]One can easily integrate the electrically activated delivery systems with other electronic devices such as sensors, controllers, circuit components, communication modules, and power supplies. These make the device useful for multifunctional purposes.[170] Recently, flexible electro-resistive heaters have been combined with electrically activated wearable transdermal patches for suitable applications.[171] To achieve this goal, Bagherifard et al. engineered a dermal patch that utilizes thermo-responsive drug microcarriers encapsulated within a hydrogel layer attached to a flexible heater with integrated electronic heat control circuitry. The system is capable of releasing two active molecules at a time. Wearable sensors are commonly used to monitor biophysical information. Still, flexible electronics that can assess body fluids for biochemical markers are becoming increasingly popular since body fluids contain a variety of biomarkers that could indicate health conditions. Wearable and implantable glucose sensors have the potential to monitor blood glucose levels, and the same study was conducted by Song et al.[172] by analyzing interstitial fluids from the skin. Thermo-responsive carriers usually encounter a quick structural change with a difference in their surrounding temperature, eliciting the release of the embedded therapeutic agent.[172]

5.1.3. Light-responsive skin patches

Light induction mainly activates the light-responsive transdermal patches as a primary source. The main advantages of light-responsive systems are their fast, quick, and well-controlled release.[173] The mechanism of drug release from these systems mainly involves different photolytic reactions like photo-triggered surface charge conversion, photoisomerization, photocleavage reaction, and light-to-heat mechanism.[173-175]According to Bagherifard et al., the main sources of light-to-heat components that are used in light-responsive devices are mainly light-absorbing materials such as gold, graphene, CNTs, magnetite nanoparticles (MNPs), and lanthanum hexaboride (LaB6).[171] However, some current studies by Mura et al. reveal that near-infrared (NIR) light-activated skin patches can be used in cancer chemotherapy.[176]

5.1.4. Bioresponsive materials for wearable transdermal delivery

Physical parameters are always of paramount consideration for some specific disease conditions. Conversely, any changes in

physiological parameters often indicate essential signals of particular diseases. In this context, the progress of bioresponsive drug materials is necessary for targeted therapeutic delivery. Till now, researchers have identified many materials that can recognize variations in the physical or chemical changes upon their contact with different biological triggers such as pH, enzymes, hormones, glucose, nucleic acids, etc.[177-179] Similarly, researchers using microneedle-based drug delivery systems utilize soluble, biocompatible, and swellable polymeric materials. In a recent development in bioresponsive materials for microneedle-based drug delivery systems, Iqubal et al. concluded that microneedle-based drug delivery systems have evolved as an emerging technology in the bioresponsive wearable transdermal delivery category.[180] In a recent development, Ping et al. [178] concluded that metal-phenolic networks (MPNs) could load, deliver, and release anticancer drugs in pH-responsive capsules.

5.2. Current challenges associated with wearable TDDS

Wearable transdermal delivery systems combined with multifunctional electronic devices have shown encouraging results in real-time sensing and transdermal delivery of different therapeutic substances. Table 8 summarizes the wearable systems' operation mechanism, benefits, and therapeutic substance delivered.

Table 8. Summary of wearable transdermal delivery systems with example [164]

Triggering input	Benefits	Administrated therapeutics
Stretch	Simple release mechanism	Doxorubicin hydrochloride
	Sustained release	Ciprofloxacin
	Pulsatile release	Insulin
Stretch	Release of both hydrophilic and hydrophobic drugs	Cisplatin
	Sustained release	SN-38
	Simple release mechanism	
Electric power	On-demand drug release	Dextran
		Metformin
Electric power	On-demand drug release	Metformin
	Multistage delivery	Chlorpropamide
Voltage	Low-voltage electroporation	DNA and siRNA
Current	Low-voltage delivery	Doxorubicin
	High penetration depth	Dexamethasone
DC voltage	Low-voltage release	Doxorubicin
	Pulsatile release profile	
NIR light	Switchable release	Doxorubicin
	Remote drug release	Ondansetron
Visible light	Remote triggering	Dexamethasone
	Sustained release	
Biodegradation and swelling	Sustained release	Ovalbumin
		Bovine serum albumin
Enzymatic reaction	Feedback-controlled release	Insulin
	Pulsatile release	
Enzymatic reaction	Sustained release	aPD-1
Thrombin	Feedback-controlled release	Heparin
	Pulsatile release	

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Table 8 briefly summarizes the performance summary of wearable transdermal delivery systems with the mechanism triggering the effect and the potential molecule delivered.

However, several problems related to design complications, device assimilation, and safety concerns hinder the practical implications of wearable transdermal drug delivery systems. Several researchers highlighted some of the major drawbacks of wearable devices. However, in this review, we highlighted some of the most common negative aspects of this system reported by Lou et al. [181]., Lee et al. [182], Lewy et al. [183], and Tang et al.[184]

1. Even though much research is done to enhance the SC layer's permeability, administering high doses remains challenging.[181]
2. It is challenging to accomplish both efficient delivery and a high degree of safety. The majority of wearable TDDS have restricted therapeutic loading ability.[182]
3. Due to recent advancements in wearable medical systems and the attachment of different other devices, there is an increase in their costs which is only economical for some.[183]
4. Consistent attachment with human skin is important for the noiseless, precise, and accurate evaluation of biomarkers and effective transdermal delivery.[184]

6. COMMERCIALIZATION OF TDDS TECHNOLOGY

Scopolamine is the first transdermal patch permitted in 1979 to treat motion sickness. It is a sustained release delivery, advised for three days' regimen. [5,185] Since today, the TDDS emerged as a potential drug delivery system due to its

advantages. Different technologies and deliverable devices for the transdermal delivery of drugs have been commercialized and are accessible to patients in the global market. The research towards TDDS technology has reached a great height, and the US Food and Drug Administration (FDA) has approved several molecules for topical use (Table 9). However, the driving force that restricted its global presence and commercialization compared to other drug delivery systems and technology is the market size, sales drivers, competition, risks, and opportunity window in the global market.

Table 9. Marketed transdermal drug delivery product [63,186]

Product name	Drug	Manufacturer	Indication
Androderm	Testosterone	TheraTech/GlaxoSmithKline	Hypogonadism (males)
Alor	Estradiol	TheraTech/Proctor and Gamble	Postmenstrual syndrome
BuTrans	Buprenorphine	Purdue Pharma LP	Analgesic
Climaderm	Estradiol	Ethical Holdings/Wyeth-Ayerest	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals/Berlex Labs	Postmenstrual syndrome
Catapres-TTS	Clonidine	Alza/BoehingerIngelheim	Hypertension
CombiPatch	Estradiol/ Norethindrone	Noven, Inc./Aventis	Hormone replacement therapy
Duragesic	Fentanyl	Alza/Janssen Pharmaceuticals	Moderate/severe pain
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Daytrana	Ethylphenidate	Novena	ADHD
Emsam	Selegiline	Somerset Pharmaceuticals, Inc.	Depressive disorder
Estraderm	Estradiol	Alza/Novartis	Postmenstrual syndrome
Fematrix	Estrogen	Ethical Holdings/Solvay Healthcare	Postmenstrual syndrome
FemPatch	Estradiol	Parke-Davis	Postmenstrual syndrome
Habitrol	Nicotine	Novartis	Smoking cessation
Lidoderm	Lidocaine	Endo Pharmaceuticals Inc.	Anesthetics
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Nitro-Dur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Nicoderm	Nicotine	Alza/ GlaxoSmithKline	Smoking cessation
Nuvelle TS	Estrogen/ Progesterone	Ethical Holdings/Schering	Hormone replacement therapy
Neupro	Rotigotine	Veronique UCB	Parkinson's disease
Ortho-Evra	Norelgestromin/ estradiol	Ortho-McNeil Pharmaceuticals	Birth control
Oxytrol	Oxybutynin	Actavis Pharma, Inc.	Anti-muscarinic agent
ProStep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation
RivastigmineTS	Rivastigmine	Sandoz	Dementia
Sancuso®	Granisetron	Kyowa Kirin International Plc	Nausea, vomiting
Testoderm TTP	Testosterone	Alza	Hypogonadism in males
Transderm-Scop®	Scopolamine	Alza/Novartis	Motion sickness
Transderm-Nitro	Nitroglycerine	Alza/Novartis	Angina Pectoris

Table 9 contains FDA-approved transdermal patches (listed on the US FDA site).

7. CONCLUSION

This paper introduces an outline to assess and discuss the various techniques or methods for enhancing the administration of medicament by TDDS. Different techniques like chemical penetration enhancers, electric fields, and ultrasound have been widely utilized to improve drug transport by TDDS. Various techniques, including microneedle systems, have been studied to overcome the stratum corneum barrier and enable drug delivery through the skin. The structural geometry and different categories of microneedles, such as coated and dissolving, demonstrate a novel and aspiring technology to reinforce skin permeability. Microneedling technology has progressed significantly and is now suitable for large-scale production, making microneedle-based drug delivery systems a potential emerging technology in the pharmaceutical and cosmeceutical market. Our review summarized the concept of wearable transdermal therapeutic delivery and the recent advances in the progress of wearable systems for transdermal therapeutic delivery.

On the other hand, among the different strategies available for TDD, nanoparticles have attracted the most attention and have undergone the most development. Nanoparticles such as flexible liposomes, niosomes, dendrimers, microsponges, and others penetrate the skin by squeezing through intercellular spaces within the nanoparticles. Subsequently, nanoformulations, such as S/O dispersion, have been effectively used for TDDS. The purpose and goal of this review are to comprehensively review and summarize the recently used penetration enhancement techniques along with the possible mechanism of action. We have captured all the state-of-the-art technologies and elaborately discussed the probable mechanism of action. In conclusion, we opined that the rapid development of penetration enhancement technologies

facilitates the breakthrough of the SC barrier, expanding the application of transdermal delivery in different complex therapeutic applications such as chemotherapy, gene therapy, immunotherapy, phototherapy, and vaccine delivery. This review article can be used as a baseline for the researchers working on the TDDS technology. However, we recommended that despite these advancements, many issues still need to be addressed. The detailed and fundamental studies associated with penetration mechanisms at the molecular levels and uncovering the penetration difference between physiological and pathological skin should be thoroughly performed. Meanwhile, the researchers should further investigate the tumor microenvironment and cellular barriers related to skin tissues to enhance the delivery efficiency and drug retention time.

8. AUTHORS CONTRIBUTION STATEMENT

Dr. Abikesh Prasada Kumar Mahapatra has conceptualized the article and conceived the idea. Dr. Neelkant Prasad and Dr. Niranjan Panda have contributed to literature search followed by its critical review. Dr. Abhiram Rout and Basudev Paul have compiled the article and also contributed towards design of the review article. All authors have read and approved the final version of the manuscript.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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