Section A-Research paper
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A Critical Review on Novel approaches to Increase Efficiency of Trans-dermal Drug Delivery Systems by Penetration Enhancement Techniques

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Abstract: The transdermal route has received a lot of attention and has established itself as a reliable substitute to address the shortcomings of drug delivery via the oral and parenteral routes. However, the stratum corneum (SC), the skin's top layer that functions as a barrier to drug diffusion, frequently reduces the efficacy of TDDS. The drug's molecular weight, hydrophilicity, and ionic makeup can also affect how effectively it is delivered transdermally. Nano-carriers, wearable delivery devices, and combination-based strategies are just a few of the techniques that have been developed to get beyond these restrictions and enable medication penetration across the SC. Nano-carriers including dendrimers, liposomes, niosomes, and micro sponges have the potential to improve TDDS's effectiveness. Wearable delivery systems, which provide non-invasive, practical, and extended drug administration, are another new development for TDDS. The focus of interest in the study of TDDS technologies is combination-based approaches, such as ultrasound and microneedle-based systems or ultrasound and electrical-based techniques. This review enumerates all unique penetration enhancement methods that have been employed to improve the efficacy of transdermal drug delivery systems but which have not been fully covered by prior review papers. These penetration augmentation approaches were emphasised separately in the majority of review papers. But there isn't a comprehensive analysis of all the penetration augmentation methods in one piece. Therefore, the goal of this paper is to thoroughly examine and summarise in one article the most recent penetration augmentation approaches as well as any potential mechanisms of action. Our main goal is to gather pertinent reviews and research articles through the use of numerous databases in order to present a thorough overview of the topic. This review article will assist students and researchers keep current with the most recent advancements in the field of innovative

penetration enhancement strategies used to increase the efficiency of TDDS by giving a thorough overview of the existing techniques.

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

1. INTRODUCTION

Since the first scopolamine transdermal patch was approved in 1979, systemic drug administration through transdermal drug delivery has been pushed. This area has been the subject of extensive research. It has been shown to be advantageous for lowering dose frequency, achieving target delivery, and preventing hepatic first-pass metabolism. The most important and influential organ in the body is the skin. Pharmacological drugs have traditionally been delivered through the skin. Additionally, it can only be used to treat disorders that are localised. By putting medicated patches to the skin, transdermal drug delivery has many advantages over oral and hypodermic injections in terms of addressing issues with drug delivery.[1-2] However, there are several limitations with transdermal medication delivery systems. The physical makeup of the skin contributes to its ability to function as a barrier and further restricts the use of medications applied transdermally. The keratinocyte-containing stratum layers that make up the human skin's intricate system are numerous. Corneocytes, which make up the majority of the stratum corneum (SC), the skin's outermost layer, serve as the principal barrier to the penetration of drug molecules.[3] The intricate anatomy of the skin prevents medications from diffusing through it without structural modification, which reduces the efficiency of transdermal administration. Drugs with undesirable pharmacokinetic or pharmacodynamic features can include those with fast clearance and cutaneous first-pass effects. The biopharmaceutical characteristics of some medication compounds further impede TDDS's ability to work.[4] Only a select few categories of pharmacological molecules may be viable for transdermal distribution due to the aforementioned limitations and issues. So, increasing the amount of medication molecules carried through the skin is the main problem for transdermal delivery. Numerous studies demonstrate how cutting-edge flux creation techniques can support ongoing transdermal medication delivery of various therapeutic compounds. More research has been done using cutting-edge methods to boost the flow in the transdermal area. Third-generation techniques are used in some techniques, including permeation enhancers, electric devices, wearable technology, ultrasonic, and nano-carriers.[5] The use of electrical techniques (iontophoresis/electroporation), wearable transdermal devices integrated with suitable electrical device(s), ultrasonic techniques, microneedles, and electrical techniques is becoming more and more common among researchers. Wearable transdermal drug delivery methods have, however, become much more common. Over the past few years, wearable electronic devices have attracted a lot of attention. In the early stages of wearable technology, skin-mountable sensors are used. These sensors have potential uses in health nursing, human motion detection, and intelligent human-machine interface. Transdermal delivery is being explored by new developments in wearable technologies. Due to its flawless ability to integrate with the human body, ability to accurately capture physiological signals over an extended period of time, and general user-friendliness, wearable clinical devices are already being actively used. Amazing developments in material science, nanotechnology, and biotechnology also produced cutting-edge wearable medical devices for the transdermal delivery of active medication molecules. In this review, the authors first go over the fundamentals of skin structure to help readers grasp the theoretical applicability before concentrating on TDDS's improved drug administration methods. The study then continues to determine the most recent advancements, constraints, and upcoming difficulties in this area of study. [6] We categorise the present methods for enhancing medication penetration through the skin and, in particular, review recent advancements in transdermal formulations based on newly accessible technology. This review goes into further detail about how to make the skin more permeable using various physical techniques as iontophoresis, electroporation, sonophoresis, and microneedles. Additionally, it showcases the most recent developments in wearable and multipurpose therapeutic delivery devices. This study focuses on wearable systems as the most pertinent and crucial technique to highlight parallels and distinctions, despite the fact that many publications discuss any other particular approach. [7-8]

2. CHARACTERISTICS OF DRUG MOLECULES SUITABLE FOR TRANSDERMAL PATCHES

Transdermal administration of various medicinal substances has been the subject of extensive research. Transdermal administration of medicinal substances has various benefits, including simplicity of administration and avoiding issues with oral distribution, such as first-pass metabolism. However, many medications cannot be delivered transdermally since it is highly challenging to pierce the skin with ordinary patches and disturb the SC. The pharmacokinetic parameters and physicochemical characteristics of the drug molecules, which are restrictive, are the major cause of the restriction. Low molecular mass (400 Da), solubility, crystallinity, high lipophilicity (oil soluble), small needed dose (up to milligrammes), and partition coefficient Log P (octanol-water) between 1.0 and 4 were highlighted by Mitragotri et al. in their study. We have outlined both the optimal physicochemical characteristics of the possible drug molecule and the criteria that should be taken into consideration when choosing a drug candidate for transdermal drug administration. Additionally, a therapeutic molecule's pharmacokinetics features need to be thoroughly assessed. These are extremely important in assessing if it is suitable for transdermal delivery. [9-11]

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

The most suitable channel for the transport of medicines in TDDS is the intracellular pathway. The epidermis, dermis, and hypodermis are the three primary layers that make up the skin. There are five layers in the epidermis. The skin's top layer, the stratum corneum (SC), emerges from this layer (Fig. 1). The lipid membrane of the SC layer is damaged as part of the intracellular

route. Therefore, the fundamental goals of all cutting-edge methods and strategies are to either increase the drug's lipophilicity in the SC environment or change the SC structure. [12-14]

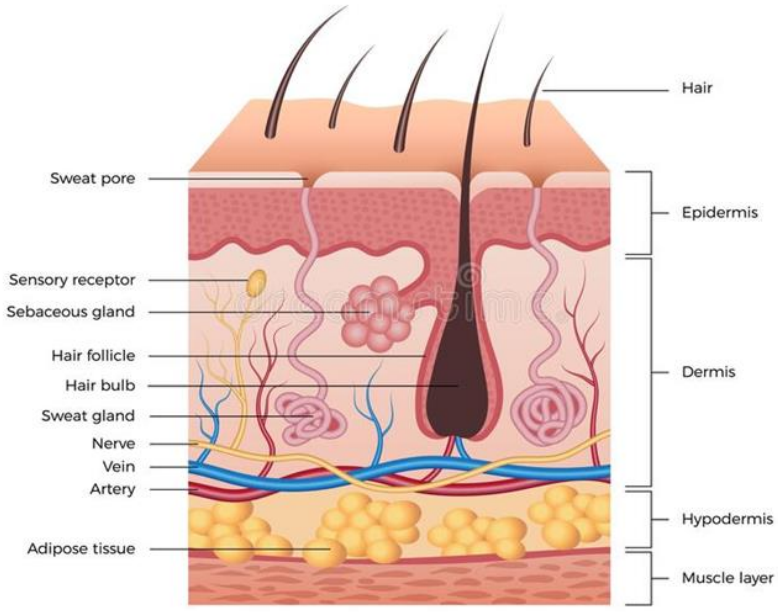

Fig.1.Schematic representation of the layers of skin[18].

The various layers of the skin are shown in Fig. 1. The epidermis, dermis, and hypodermis are the three primary layers that make up the skin. The basal layer, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum are the five layers that make up the epidermis. The outermost layer is called the stratum corneum. The disruption of the SC layer is the foundation for the majority of sophisticated TDDS approaches.

3.1 Techniques to improve the permeability of the skin

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

Numerous investigations on the application of ultrasound-based systems in TDDS have been conducted for many years. But it is important to be clear about the precise delivery action and transit mechanism. It is thought that the sonophoretic process is primarily how the ultrasound-based system functions. Third-generation energy-driven methodology includes the sonophoresis technology. The main mechanism by which the sonophoretic system functions is the generation of microjets from the acoustic cavities (Fig. 2). This microjet creates tiny channels, enables the movement of molecules, and ultimately aids in increasing skin permeability.19 Low-frequency sonophoresis (LFS) is the subject of the current review. It focuses primarily on the perspective, fundamental principles, and appropriate illustrations, noting the LFS approach's efficacy in delivering medicinal compounds transdermally. [15]

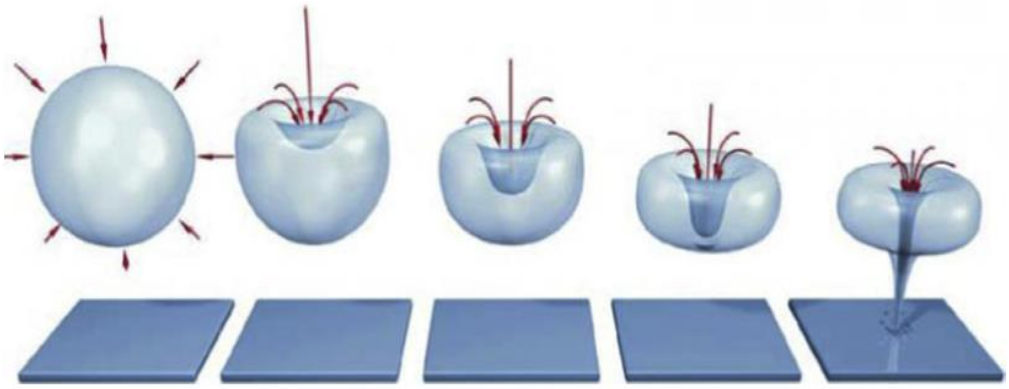

Fig.2. A micro-jet is produced when the cavitation collapse mechanism occurs close to the skin's surface. reproduced with their consent.

2014 Elsevier BV Copyrights. In Figure 2, the sonophoresis mechanism has been briefly illustrated. The main mechanism by which the sonophoresis system functions is the generation of microjets by cavitation collapse near the skin surface. Ultrasound (US) is used by LFS to permeabilize the SC. Ultrasound is a high longitudinal frequency sound wave with frequencies more than 20 kHz, which corresponds to the upper limit of human hearing.20 Low frequency (100 kHz), therapeutic (0.7 to 3 MHz), and high frequency (> 3 MHz) ultrasounds are typically separated into these three frequency categories. The main mechanism relies on the induction of transitory cavitation in the coupling medium, which permits cavitation bubbles. Park et al. [19], who summarised the cavitation mechanism, bubble formation, inertial cavitation, and the role of shear in cavitation generation and transmission, provided a clear explanation of the cavitation theory. Due to the intense local pressure, the bubbles become unstable and slowly deflate, creating a streamlined liquid jet that aids in penetrating the SC. Strong and inversely associated with ultrasonic frequency is the permeabilization efficiency of LFS. The spatial distribution of acoustic cavitation bubbles at various ultrasonic frequencies was highlighted in a study by Ashok et al. The skin is often treated with LFS and a chemical penetration enhancer (CPE). According to a study by Tezel et al., doing CPE alongside LFS had a positive synergistic effect. The study found that as compared to surfactants with nonionic head groups, those with anionic and cationic head groups had a substantial synergistic effect on boosting skin conductivity in ultrasound. Following LFS treatment, the skin develops "localised transport regions" (LTRs) and "non-localized transport regions" (non-LTRs), two distinct regions. The permeability of the two transport areas varies. The areas of the skin where there has been a significant amount of fluidization as a result of high CPE concentrations are known as the LTR regions. Due to nearby cavitation generation, the skin surface physically tears, aggravating CPE penetration into the skin in those areas. The creation of the cavity close to the skin surface is the key factor influencing the permeability capacity of both regions. Non-LTRs have lower CPE content and permeability than LTRs because fewer cavitation events occur in them. Joseph K. et al. talked about the functions of CPE, specifically sulforhodamine B (SRB), a fluorescent hydrophilic permeant, and Rhodamine B hexyl ester (RBHE), a luminous hydrophobic permeant. According to the study's findings, the coupling medium must contain a chemical enhancer during ultrasonic treatment in order to achieve two significant levels of increased SRB and RBHE penetration in US-treated skin compared to US-untreated skin. Utilising a variety of medicinal substances, numerous research on ultrasound-mediated transdermal transport have been conducted. Due to the high prevalence, high expense, and challenging nature of treating diabetes, several have investigated the potential to give transdermal insulin. Feiszthuber et al. discussed the viability of transdermal transportation of insulin in skin agar models and pig skin in one of the recent studies linked to insulin. [16-18]

3.1.2. Microneedles (MNs)

Currently, intradermal injections are used to solve the problems with transdermal administration. But because of drawbacks including needle injuries, needle anxiety, the requirement for specially trained workers, and higher delivery costs, intradermal injections lost some of their appeal. One of the best kinds of conventional intradermal injection is the microneedle drug delivery device. Small compounds and diverse macromolecules can be delivered using microneedles, according to research. Additionally, they distribute micro- and nanoparticles and cosmeceuticals Du G et al. examined the use of varied microneedles via the transdermal system for diagnostic applications, patient observation, and enhanced immunisation. Microneedle research has made significant strides in the transdermal drug delivery field and has established their use in various ophthalmic, oral, and diagnostic fields. Microneedles were used in intestines and cosmetics, according to investigations by Prausnitz et al. and Jung et al. Due of its widespread use, the commercialization of this technology has received a lot of attention. In Fig. 3, we have distinguished between the conventional injection system and the microneedles for the reader's benefit. A microneedling device uses a needle that is only the size of a human hair to puncture the skin's outermost epidermal layer. This procedure is painless and leaves no wounds or infections behind. Nagrakar et al. highlighted that the microneedles primarily penetrate the outermost dermal layer by diffusion process in a recent assessment of advancements in microneedle technology. They also presented the potential mechanism of penetration. The therapeutic chemicals enter the dermal layer, which is heavily permeated with blood vessels, based on their diffusion mechanism. An significant consideration is the microneedle's length, which can be adjusted to ensure epidermal penetration without harming blood vessels or nerve fibers. Since the channels are larger than the typical therapeutic agents, the microneedle delivery method does not exhibit any limits based on their molecular size. Alderman et al. and Park et al. built microneedles (MNs) in their study using a wide range of microfabrication techniques. Microneedles can range in height from 50 to 900 meters and have a surface area of 2000 millimeters square. [19-20]

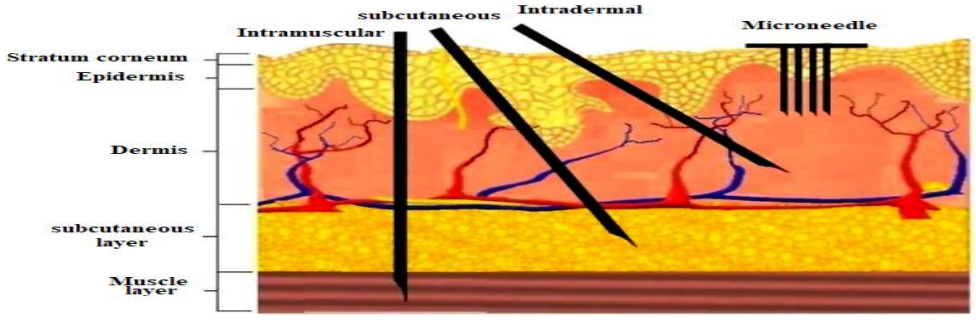

Fig.3. Comparison of microneedles with an old-fashioned injection delivery method.

The administration of conventional injection systems, such as intradermal, subcutaneous, and intramuscular injection systems, differs from those of microneedle injection systems, as shown in Fig. 3. The MN's length is measured in microns, and the tip protrudes just enough to enter the SC. Because the needles are the right size, they do not penetrate the skin very deeply and do not damage the nerves, making them painless. MNs come in four different forms: solid, hollow, coated, and dissolving. Gupta et al. investigated the use of hollow microneedles for minimally invasive insulin administration in type 1 diabetic individuals. After using a topical cream, solid one has been commonly used as a preparation for the skin. A bigger medication is directly injected into the skin by the hollow MN. The application of coated MNs was proven by Zhu et al. The medication is coated onto the surface of solid MNs in coated MNs. The needle is a dissolvable material containing the drug in the dissolving MNs. Dissolving microneedles for transdermal medication administration were created by Lee et al. by carefully drawing maltose step-by-step. The use of microneedles in medicine is hampered by two basic factors. Scaling up production is the first, and the delivery of a constrained quantity of drug material and the scope of services for a variety of molecules are the second. In order to increase the delivery of MNs, several new tactics have been devised in response to the earlier issue, which has drawn a lot of attention. The capability to carry drugs and the capacity to penetrate the skin, however, are shared by all MNs. In recent years, the use of dissolving MNs has significantly risen. Dissolution period is a crucial factor to take into account when dissolving MNs. A longer disintegration period can increase the biohazard impact whereas a shorter dissolution time can provide less medicines through the patches. According to Boks MA et al., making water-soluble biocompatible polymeric MNs is a modern technique that addresses both difficulties. The distinctive design of the water-soluble patches disappears in 5 minutes. As a result, there is no need to disconnect the device, and it guarantees the necessary time for dissolving while minimizing biological risks to the skin. These microneedle patches' exceptionally flexible backings mean that they require minimal insertion forces, which eventually improves the MNs' capacity for penetration. The user can deliver a multitude of medication compounds because to the advancements in MNs technology. Using MN technology in TDDS, researchers delivered various metabolites, medicinal compounds, and vaccinations successfully. For the benefit of the reader's understanding, Table 1 provides a summary of the goods created using various microneedles. [21-24]

Table 1. A list of goods created with several kinds of microneedles

Product	Type of MN
Insulin	Hollow
Influenza vaccine	Coated
A combination vaccine against anthrax, botulism, plague	Hollow
Doxorubicin	PVA micro mold
Lidocaine	Solid microneedle with PEG matrix
Calcein	Silicon MN
Soluvia (Influenza vaccine)	Metal
Micron jet (Influenza vaccine)	Silicon
Macromolecules, such as BSA and insulin	Metal
Diclofenac, Ibuprofen, ketoprofen and paracetamol	MN roller devices
Desmopressin	Coated
Caffeine, lidocaine, metronidazole	Dissolving

The various microneedle-based TDDS are listed in Table 2 along with the kinds of MNs used in each device.

3.1.3. Electrical techniques

Iontophoresis and electroporation are the two key techniques for electrically aided TDD. Iontophoresis uses a high-voltage electric gradient to use electrostatic forces to push charged permeants into the skin. In an iontophoresis system, the usual current-voltage ranges from 0.1 to 1.0 mA/cm^2. The sole drawback to this approach is the reported low electric fluxes in the uncharged species, which limited its applicability. The electro-osmotic flow and its role in iontophoretic administration were examined by Herr NR et al. The research demonstrated that the observed ejections are caused by a combination of electro-osmotic and iontophoretic forces. The outcomes also showed that the ejection % owing to electroosmotic flow may be predicted using capillary electrophoresis (CE). Electricity is also used in electroporation to damage cellular membranes. A normal electrical pulse lasting 10 s to 10 ms powers this system. Using skin electroporation, Denet et al. presented a transdermal topical administration device. The study emphasised that the development of an electric pulse causes cell membranes to become disrupted and creates aqueous pores in the lipid bilayer of the SC. The delivery is controlled via passive diffusion through the pores, which is mostly caused by the brief pulse duration (usually milliseconds), which does provide the device a shove.60However, the application of longer and shorter pulses, as well as the duration of the pulse, played a key part in the transport of the active material via TDDS. Through experimentation, Zorec et al. demonstrated that the longer LV pulses considerably boost future passive transfer of calcein through dermatomed pig skin, corroborating their initial hypothesis. In contrast, minimal passive transdermal transport of calcein is produced by brief HV pulses alone. Iontophoresis, when compared to electroporation, has a little impact on the cutaneous

architecture due to the brief application of a low gradient electric current. After a protracted treatment method, resistive heating causes a sizable morphological alteration to be visible. Electroporation is within the third generation of techniques, but iontophoresis falls under the second generation due to its special effect. These two approaches working together, though, provide better drug delivery. Proteins can be delivered using the transdermal iontophoretic process of iontophoresis technology. Transdermal iontophoretic system-based ribonuclease administration was demonstrated by Dubey et al. The work also showed that it is possible to transfer a functional protein, ribonuclease A (RNAse; 13.6 kDa), non-invasively across the skin via transdermal iontophoresis. There are many issues with the therapeutic usability of electrical procedures, notwithstanding how simple they are to use. The major issue is how electrical techniques are used and whether they have a positive outcome when applied to charged molecules. Compared to electroporation, the application of iontophoresis can swiftly change the electrical resistance of the SC.[60] The study of electroporation for TDDS has been tempered by all of these problems. Currently, it plays a crucial part in the study of vaccinations. Research is currently being done on its application to achieve intracellular uptake of DNA-based vaccinations by skin-resident dendritic cells. In their study, Denet AR et al. focused on the electrical delivery of DNA-based vaccinations. Examples of three commercially available products based on iontophoresis delivery methods include Phoresor®, Lidosite®, and E-trans®. However, the FDA has currently removed Phoresor® and Lidosite® from the market. Table 2 lists the many transdermal patches that are commercially available and modulate skin structure by disturbing the stratum corneum (SC) using various methods. [25-28]

Table 2. Marketed products of ultrasound, microneedles, and electric-based transdermal drug delivery system

TDDS method	Brand Name	Manufacturer	Product
Ultrasound	SonodermTM	Imrax	Insulin
Microneedles	Intranet	Weston medial	Vaccine
Micro projection	Macroflux	Alza Corporate	Vaccines, therapeutic proteins
Iontophoresis	E-Trans	Alza Corporate	Fentanyl
Ultrasound	Sonoprop®	Sontra Medical Corporation	Peptides and other large molecules
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

3.1.4. Combination methods or penetration-enhancing procedures that have a synergistic impact

Recent study also prioritised combining skin permeabilizing methods. The use of microneedles, ultrasound, ultrasonic pretreatment followed by iontophoresis, or a combination of microneedles and electric techniques was highlighted by the majority of studies. This review also discusses the synergistic effects of the TDD method's combining approaches. We therefore set aside a piece of this essay to discuss this concept. Two key elements of integrating multiple transdermal medication delivery techniques were the focus of our review. As more research on these techniques is being done, we mainly focused on the operational process of the combination strategy (Table 3). [29-31]

Table 3. A summary of product developed based on a combination method approach for TDD

Microneedling and sonophoresis combined in a transdermal delivery method				
Drugs used	**Types of needle**	**Frequency of ultrasonic wave**	**Skin model**	**Conclusion drawn**
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.
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.
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.
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.
Methotrexate	Solid tetrahedron	Current density 0.4 mA cm2 applied for 60 min	Male hairless rats	The study concluded that in vivo, there is a 25-fold increase in methotrexate delivery with a 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.
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.

3.1.4.1. Microneedles combined with electrical driving forces

It is easy to combine MNs with electrical procedures (such as electroporation or iontophoresis). Through the aqueous pores the MNs form, the electrical driving forces' current is carried into the skin. Usually, MNs are used to prepare the skin before the target drug is applied via immediate iontophoresis for 4-6 hours. Using modulated iontophoresis and microneedles to administer ropinirole hydrochloride via the skin, Singh and Banga were successful.69 The ability to regulate drug flux through control of the applied current and a reduction in the time it takes for drug molecules to penetrate the skin are two advantages of this combined delivery method. Compared to other methods, this one produces the greatest outcomes for tiny molecules the quickest. The SC layer should be slightly disturbed in the combination process since it is crucial for delivering tiny compounds. In the end, the technique's sequential structure and awkwardness limit its application. However, the drug's molecule's lipophilicity can alter how it travels over the skin after incorporation. The study by Pawar et al. which reported a connection between the lipophilicity of the chemical and electrically assisted transdermal drug administration over the integrated skin, and the aforementioned result were both accurate. [32-35]

3.1.4.2. Microneedles combined with ultrasound for transdermal drug delivery

There are numerous scientific studies on the simultaneous application of MNs and ultrasonic for medication administration, however this is the main focus of attention. In this technique, the SC layer of the skin is punctured by microneedles, and the ultrasonic system is employed to penetrate and permeate the medicine into the skin. Both systems have previously been consolidated through efforts. An MN device with a 20 kHz piezoelectric crystal was developed by Singh and Banga's research team in order for each MN to transmit ultrasound into the skin. This method's use is made simpler by the instantaneous application of treatments and their incorporation into a single device. In a different investigation by Chen B et al., combined administration of calcein and bovine serum albumin resulted in superior transdermal transport of both substances. Another option is to combine ultrasound cavitation with solid MNs. Solid MNs can aid in improving permeability by generating obvious holes. Applying high-intensity ultrasound to the MN's pretreated base can significantly increase permeability. Large molecules can be delivered more effectively using this setup, which is also a better setup for a long-term transdermal drug delivery system. [36-38]

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

The specialised compounds known as chemical penetration enhancers (CPEs) disrupt the lipid bilayer in the subcutaneous layer. The second generation of transdermal delivery devices mostly includes the CPEs. Combinations have had more success with transdermal formulations than chemical boosters alone, which have had a limited amount of success. The logical combinations of penetration enhancers are severely constrained by the lack of mechanical knowledge regarding how each chemical enhancer interacts with the stratum corneum. High-throughput screening of transdermal formulations can directly address this bottleneck and may result in the discovery of a novel combination of penetration enhancers. The CPE mixtures, on the other hand, belong to the third generation of transdermal delivery systems. Chemical penetration enhancers (CPEs), as opposed to the physically improved delivery methods outlined above, guarantee benefits such simplicity of use and design flexibility. A number of classes of penetration enhancers, including surfactants, fatty acids/esters, terpenes, and solvents, have been developed in recent research that have a stronger emphasis on (CPEs). A few number of chemical enhancers, however, have been found to improve drug transport most effectively. Pure fatty acids, alcohols or surfactants with significant polar groups, and H-bond acceptor solvents make up the majority of the CPEs. The potential mechanism of improved drug penetration via CPEs was discussed by Pathan et al. in 76. The improved penetrating activity of CPEs is caused by the breaking of the hydrogen bonds between the ceramides,

according to thorough mechanistic studies. It swiftly penetrates the thick lipid layer, lowering resistance to the vital skin barrier. The drug formulation contains a lot of water, which further improves penetration into the cell. Amino acids cause inflammation of the cells within corneocytes. It primarily disturbs the lipid plane and increases the amount of water present in the intercellular space. However, because of accompanying side effects including an unpleasant and burning sensation in the skin, individuals occasionally experience discomfort. [39-41]

4. MODIFICATION OF THE DRUG FORMULATION USING NANO-CARRIERS

In TDDS, the physicochemical characteristics of the drug material (i.e., the prodrugs method) or the drug formulation employing nano-carriers can be changed to increase the penetration capability of pharmacological substances through the skin. The prodrug method modifies the physicochemical properties of the drug material by synthesising an active ingredient with an adduct or a new salt form to achieve the desired modified physicochemical qualities. However, a novel scientific method known as nano-carriers creates various formulations of the pharmacologically active chemical with the appropriate quality characteristics. Because nano-carriers have such a wide range of applications in the medical and pharmaceutical fields, we have focused more on them in this review. Liquid crystals, solid lipid nanoparticles, and nanoemulsion are only a few examples of the lipophilic nanoparticles that are used in the pharmaceutical and cosmetic sectors for drug delivery. The use of nanoparticles in gels, creams, lotions, and solutions is possible. Escobar-Chavez et al. have covered the utilisation of the nanoparticles in great detail. These systems' mechanisms of action entail disrupting the tight junctions, the stratum corneum, and the structure of the cell membrane in order to hasten drug penetration. The potential for the NPs to enhance medication penetration through the skin is enormous. Both hydrophilic and hydrophobic medicines can be used with NPs. By limiting the deterioration of the skin microflora, ensuring site-specific targeting that covers a significant amount of the skin region, and enabling controlled release distribution, the advantages associated with nano-transporters boost medication stability. The nanoparticles' most noticeable characteristics are that they are non-invasive and helpful for formulations with controlled release. [42-45]

4.1. Liposome and its derivative

Phospholipids with a hydrophilic head and a hydrophobic tail make up liposomes (Fig. 4). Both hydrophilic and hydrophobic medicines can be transported inside the aqueous phase and membrane bilayer of liposomes and their analogues, respectively. Cationic liposomes exhibit greater penetration due to the interplay between their positive charge and the skin's negative charge. Small peptides that have been functionalized may help enhance cellular absorption and penetration into the epidermal layers if they are attached to the liposome's surface. Using edge activators will help liposomes penetrate more effectively. Edge activators help improve the elasticity, fluidity, and deformability of liposomes by forming a chain of surfactants. These distinctive qualities of liposomes allow them to easily diffuse through the skin and restrict themselves via the intracellular space. Edge activators are included in the vesicular arrangement of transfer some, a derivative of liposome including new vesicles. A liposomal-based transdermal patch is used to target diverse compounds via the cutaneous route because of the liposomes' appealing features (Table 4). [46-48]

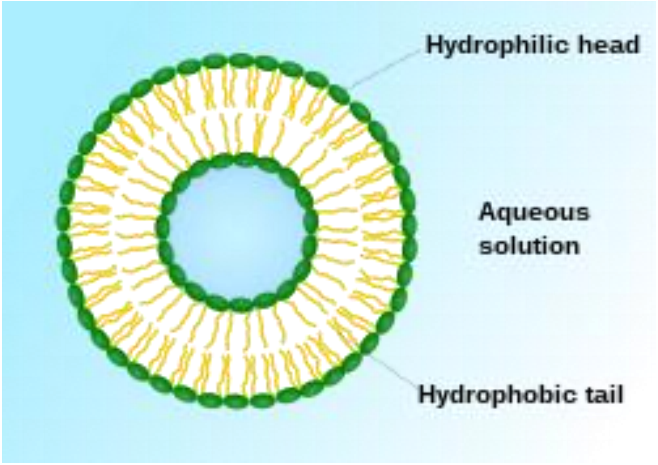

Fig.4. Liposome structure with aqueous solution, hydrophobic tail, and hydrophilic head.

A liposome with a self-assembled structure of amphiphilic lipid molecules with a hydrophilic head and a hydrophobic tail was structurally represented in Figure 4 and contained an aqueous solution inside the cavity the structure created. It briefly outlines the process by which phospholipids in an aqueous solution create liposomes. The drug's physicochemical and distinctive features can have an impact on the transdermal penetration of the liposome, among other things. Drugs can nevertheless be successfully transported over the skin by liposomal vesicles thanks to the formulation of liposomal vesicles and the choice of appropriate polymers. For the successful transdermal administration of antibiotics, NSAIDs, sex hormones, and anticancer compounds, researchers frequently use liposomes as a carrier for transdermal drug delivery systems. We have listed a few of the active compounds as well as the liposome vesicle composition in Table 4 to highlight the liposomal TDDS success stories. [49-51]

Table.4. Studies of active ingredients based on liposomes as a carrier for transdermal drug delivery system

Active Ingredient	Therapeutic category	Polymers used	Study outcome
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.
Melatonin	Neurohormone responsible for sleep	Soya phosphatidylcholine	Improved transdermal application of melatonin with enhanced transdermal flux, higher entrapment efficiency, and low skin irritant potential
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.
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.
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.
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.
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.

The success of liposomes as transdermal drug delivery system carriers is seen in Table 4. It successfully delivers the various active components when liposomes are used as a transdermal medication delivery system carrier. For the reader's convenience, the table also provides the various polymers employed to create the liposome vesicles and the research result.

4.2. Niosomes

Niosomes have undergone extensive research for transdermal drug delivery over the past few years and provide good carriers for medications intended for cutaneous targets. The inherent qualities of niosomes make them particularly desirable among all topical medication delivery systems. Niosome formulations were separated from others by special qualities such superior skin permeability, prolonged drug release over a predetermined period of time, and manipulation of systemic drug absorption through

the skin. Rita et al. have provided a thorough explanation of the niosomal drug delivery process for transdermal targeting. Non-ionic surfactant molecules with a hydrophilic head and a lipophilic tail make up the majority of the niosome (Fig. 5). Drug compounds that are lipophilic and hydrophilic can both fit inside the interior structure. By ingesting hydrophilic/aqueous or hydrophobic/lipid components, the niosomes containing the pharmaceutical ingredient adhere to the skin's surface. It might also be brought on by the binding of particular ligands or receptors on the skin's surface. The skin cell membranes and the niosomal content of the cells are fused together at the same time by the niosomes. Finally, endocytosis takes place, and the niosome vesicle is absorbed by lysozymes in the cytoplasm. Additionally, the niosomal membrane is damaged, which facilitates the release of the pharmacological ingredient that has been contained inside the medium. Niosomes have been successfully used in the cosmetics sector. The discovery of niosomal surfactant vesicles was made in an L'Oreal cosmetic application. Numerous pharmacological substances, such as NSAIDs, antihypertensive, antispasmodic, flavonoids, antioxidants, anticancer, antibacterial, and other medications, can be delivered using niosomal carriers. Table 5 provides a summary of research results for transdermal niosomal drug delivery systems from recent years. [52-54]

Table 5. For transdermal drug delivery systems, an illustration of drug molecules distributed as niosomal carriers

Active Ingredient	Therapeutic Category	Polymers used	Study outcome
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.
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.
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.
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.
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.
Clomipramine	Antidepressant	Cholesterol and tween (20,60), and span (20,60)	Clomipramine was found to have improved bioavailability and patient compliance
Enoxacin	Antibiotic	Dimyristoyil-phosphatidylcholine (DMPC), soybean phosphatidylcholine, egg	A topical niosomal formulation of enoxacin was developed with a less toxic effect and enhanced skin

		phosphatidylcholine, cholesterol (CH), diacetyl phosphate (DCP), and span(40 and 60)	permeation properties.
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
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.
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

For transdermal drug delivery systems, an example of drug compounds supplied via niosomal carriers is shown in Table 5. For ease of comprehension, the various polymers used to create the niosomal vesicles and the research conclusion were provided.

4.3. Dendrimers

The permeability of dendrimers can be increased, speeding up the transit of lipophilic medicines through the skin. Dendrimers typically consist of three components: a core, branched dendrons (an internal part), and terminal groups (Fig. 6A and 6B). Typically, one of two synthetic pathways—divergent or convergent—is used to prepare dendrimers. On the skin's surface at physiological pH, negatively charged drug molecules can be transported by cationic dendrimers. For instance, peptidic dendrimers aid to disturb the structure of the skin and serve as a chemical penetration booster. Depending on the kind, dendrimers have a different mode of action. For instance, a polymeric dendrimer called polyamidoamine (PAMAM) squeezes lipid from the stratum corneum during extended contact with the skin, leading to the formation of minute holes in the skin's surface that interact with the phospholipid openings. Singh et al. provide a thorough explanation of the structure, method of manufacture, restrictions, and applications of dendrimers. The key benefit of the dendrimers system is that it causes very little skin discomfort from TDDS. Dendrimers can improve skin penetration and deposition. NSAIDs, vitamins, antifungals, and other pharmaceutical substances can all be delivered via dendrimer carriers. The reader is provided with a summary of research results from recent years on transdermal dendrimers drug delivery systems. Numerous medications have been demonstrated to work better when combined with dendrimers, including indomethacin, ketoprofen, diflunisal, diclofenac sodium, 5-fluoro uracil, 8-methoxy psoralene, tamsulosin, riboflavin, and dithranol. [55-58]

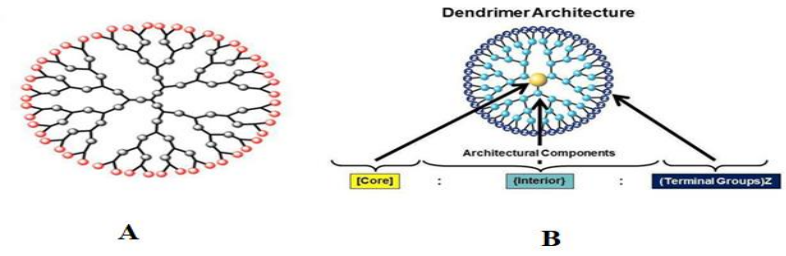

Fig. 5. (A) Basic structure of dendrimers (B) Architectural components of dendrimers

The schematic representation of dendrimers' fundamental structure is shown in Figure 5. After that, a graphic presentation of dendrimers' structural elements is shown.

4.4. Solid-in-oil dispersion

Solid-in-oil (S/O) dispersion, which originated as a unique technique for administering active chemicals through the skin, is another well-liked nanosystem for TDD. An oil-based dispersion known as solid-in-oil dispersion transports hydrophilic molecules in the form of solid powder. Kitaoka et al. created the hydrophilic carrier in powder form by lyophilizing the water and cyclohexane from the water-in-oil (W/O) emulsion. The produced dispersion was combined with another oil-based carrier and used to prepare a drug-surfactant combination. The diameter of an oil-based carrier is important, and ideally, a diameter less than 500 nm significantly increases skin penetration. Isopropyl myristate (IPM) is the best choice for creating the S/O dispersion because it interacts with the skin's lipid layers in a way that is biologically friendly. An use in immuno therapy that is given through the skin is one possible example of solid-in-oil dispersion (Table 6). A hydrophilic drug's oil-based solid-in-oil (S/O) nanodispersion was studied by Hirakawa et al. in order to better understand how it could increase the penetration of proteins into the skin. To accomplish this goal, various model proteins were used as model molecules, including 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). A solid-in-oil nanosystem was successfully used by researchers to synthesise a number of pharmacological chemicals for transdermal medication delivery systems. Aceclofenac, ketoprofen, celecoxib, indomethacin, caffeine, triptolide, methotrexate, nifedipine, lidocaine and prilocaine, amlodipine, diclofenac sodium, and paclitaxel are among the drug compounds for which the application was effectively applied. [59-62]

Table 6. Research using solid-in-oil (S/O) dispersions as a TDDS carrier for protein, peptides, and antigens

Active substance	Description of study
Insulin	Developed transcutaneous delivery of fluorescein-isothiocyanate labeled insulin (6 kDa) using the Yucatan micro pig skin.
Peptide	Researchers prepared novel transcutaneous patches for a peptide (7crpR) solid-in-oil (S/O) nanodispersion delivery using the pollinosis model of mice.
Ovalbumin	Researchers achieved transcutaneous ovalbumin immunization using a solid-in-oil (S/O) nanodispersion, excluding any skin adjuvant.
Ovalbumin	Researchers studied cancer immunity in mice by vaccinating them with S/O nanodispersion of ovalbumin.

The active ingredients given using solid-in-oil (S/O) dispersions as a carrier of TDDS for delivering protein, peptides, and antigens are shown in Table 6.

4.5. Microsponge for TDD

Microsponges, a novel drug delivery technology that may overcome the limitations of nano and micro formulations, are a viable alternative for TDD. Microsponges, in particular, reduce skin itch, allergic response, and greasiness, improving patient compliance. Microporous beads representing spherical particles with diameters ranging from 5 to 300 mm make up the structural foundation of microsponges. The spherical particles can efficiently transport low-dose drug molecules and have a tendency to group together into smaller spheres.

The fundamental perspective of the microsponge is depicted in Figure 7 with microporous beads standing in for spherical particles. Additionally, it provides a clear picture of how groups of smaller spheres are formed using spherical particles. Microsponges are becoming more and more common among all transdermal medication delivery methods due to the benefits they offer. Microsponges provide advantages over conventional transdermal drug delivery systems, such as enhanced drug stability, sustained drug release, and little detectable side effects. Additionally increasing drug retention on the skin's surface and inside the epidermis are microsponge drug delivery devices. Kadhim et al. recently created a flurbiprofen microscope technology and tested it for drug release and anti-inflammatory efficacy. In this method, the medication was blended twice. Polyvinyl alcohol (PVA) and Eudragit E100 were applied with various flurbiprofen dosages in phases I and II, respectively. Drug delivery devices called microsponges are cutting-edge pharmaceutical technologies that trap

different drug molecules. For several active chemicals as flurbiprofen, benzoyl peroxide, hydroxyzine hydrochloride, oxybenzone, mupirocin, fluconazole, ketoconazole, eberconazole, diclofenac sodium, and naproxen, research on microsponge delivery on skin diseases has increased significantly. Similar to this, other studies investigated the transdermal delivery of drugs like meloxicam and fluconazole using a microsponge system. [63-68]

4.6. Challenges of nano-carriers-based TDD

The use of nano-carriers in transdermal medication delivery has a number of advantages. Despite these advantages, there are serious concerns regarding how well this approach delivers drugs to the skin. The difficulties that liposomes provide are toxicity potential as a result of medication leaking into the bloodstream as a result of vesicle bursting. Due to concerns with skin compatibility, drug loading capacity, and long-term stability, the same kinds of challenges can be found with other nano-carrier systems as well. The toxicity of surfactants is the issue with oil in the dispersion system. Similar to microsponges, their limited application is due to their difficult synthetic process. The buildup of nano-carriers close to glands and hair follicles has also caused considerable concern for the use of practically all nano-carriers. This limits the steady flow of medication ingredients from the epidermis to the delivery site and prevents consistent drug delivery. Numerous researchers emphasized the negative aspects of nanocarrier-based TDD. Kurmi et al. also covered a variety of drawbacks. The scaling up of the technology from a smaller scale to a bigger scale and the high manufacturing costs as a result of cutting-edge technology and equipment are two main drawbacks of nanocarrier-based TDD. [69-73]

5. WEARABLE TRANSDERMAL DELIVERY SYSTEMS

Due to its capacity to seamlessly assimilate with the human body, distribute medications as intended, and record physiological signals of body parameters for extended periods of time, wearable and skin-attachable medical devices are being pursued. Amjadi et al. provided examples of how wearable medical equipment are used in various settings. Remarkable advancements in medical research, pharmaceuticals, biotechnology, and nanotechnology have aided in the development of several wearable medical systems for the transdermal delivery of medications and the real-time monitoring of human activity. In order to increase patient compliance and happiness, wearable transdermal drug delivery systems transport the pharmacologically active chemicals mountable to a flexible and elastic supporting material, such as elastomers or hydrogels, for percutaneous delivery of therapeutic medicines. These specialized delivery systems are most helpful for chronic monitoring illness conditions and severe disease situations (cancer, diabetes). [74-78]

5.1. Categorization of wearable transdermal delivery systems

Mechanoresponsive transdermal delivery systems, electrically activated transdermal delivery patches, light-responsive skin patches, and bioresponsive materials for wearable transdermal delivery are the four different types of wearable transdermal delivery systems.

5.1.1. Mechanoresponsive transdermal delivery systems

By using shear, tension, or external pressures through mechanoresponsive activation, the mechanoresponsive carriers release the therapeutic chemicals that are contained within them. In the mechanoresponsive wearable transdermal delivery systems, the active carriers are connected to elastic supporting materials to facilitate medication release. When shear is applied to these devices, fluctuations resulting from muscle activation, tendon strain, organ, bone, and joint drift, among other causes, might cause the medication to be delivered through the skin. The question of whether a temperature-sensitive polymer can release a payload into the environment has been thoroughly researched. Moghadam et al. provide a clear explanation of how temperature affects the release of the active moiety from the payload. The authors demonstrated a lag time of 5-8 minutes between the start of mechanical loading and the release of the active chemical from the payload hydrogels. [79-82]

5.1.2. Electrically activated transdermal delivery patches

Due to their simplicity of use, electrically actuated wearable transdermal devices are regarded as an essential class of delivery patches. The activation of electric pulses activates these kinds of patches. The electrically activated delivery systems are simple to connect with other electronic gadgets like sensors, controllers, circuit elements, communication modules, and power supply. These enable the item to be utilised for multiple purposes. Recently, electrically actuated wearable transdermal patches have been paired with flexible electro-

resistive heaters for appropriate applications. Bagherifard et al. created a dermal patch with thermo-responsive drug microcarriers embedded in a hydrogel layer coupled to a flexible heater with built-in electronic heat control circuitry to do this. Two active molecules can be released by the mechanism at once. It is common practice to monitor biophysical data with wearable sensors. Nevertheless, flexible electronics that can detect biochemical markers in body fluids are gaining popularity since body fluids contain a number of biomarkers that could signify medical issues. The possibility of monitoring blood glucose levels with wearable and implantable glucose sensors exists, and Song et al. carried out the same work by examining interstitial fluids from the skin. The implanted therapeutic agent usually releases when thermo-responsive carriers experience a fast structural change and a change in the temperature of their environment. [83-87]

5.1.3. Light-responsive skin patches

The light-responsive transdermal patches are primarily activated by light induction. The primary benefits of light-responsive systems are their quick, regulated, and swift release. Different photolytic events, such as photo-triggered surface charge conversion, photoisomerization, photocleavage reaction, and light-to-heat mechanism, play a major role in the mechanism of drug release from these systems. According to Bagherifard et al., light-absorbing materials like gold, graphene, CNTs, magnetite nanoparticles (MNPs), and lanthanum hexaboride (LaB6) are the primary sources of light-to-heat components that are employed in light-responsive systems. Near-infrared (NIR) light-activated skin patches can be employed in cancer chemotherapy, according to several recent investigations by Mura et al. [88-91]

5.1.4. Bioresponsive materials for wearable transdermal delivery

For some particular medical situations, physical characteristics are always of utmost importance. On the other hand, any alterations in physiological parameters frequently reveal vital signs of certain disorders. For the delivery of targeted therapeutics in this environment, bioresponsive drug materials must advance. Researchers have so far discovered a wide variety of substances that, when in touch with various biological triggers like pH, enzymes, hormones, glucose, nucleic acids, etc., can recognize variances in the physical or chemical changes. The same goes for researchers who use soluble, biocompatible, and expandable polymeric materials in their microneedle-based drug delivery devices. Iqubal et al. came to the conclusion that microneedle-based drug delivery systems have developed as an emergent technology in the bioresponsive wearable transdermal delivery category in a recent study on bioresponsive materials for such systems. In a recent breakthrough, Ping et al. came to the conclusion that pH-responsive capsules may be loaded with, delivered to, and released anticancer medicines via metal-phenolic networks (MPNs). [92-93]

5.2. Current challenges associated with wearable TDDS

Real-time sensing and transdermal distribution of various medicinal compounds have demonstrated positive results when wearable transdermal delivery systems and multifunctional electronic devices are combined. Table 8 provides a summary of the medicinal ingredient provided, wearable system advantages, and operational mechanism.

Table 7. Summary of wearable transdermal delivery systems with example

Triggering input	Benefits	Administrated therapeutics
Stretch	Release of both hydrophilic and hydrophobic drugs	Cisplatin
	Sustained release	SN-38
	Simple release mechanism	
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	

Wearable transdermal drug delivery systems have many potential applications, but they are constrained by a number of issues related to design challenges, device integration, and safety issues. Several academics emphasised some of the significant disadvantages of wearable technology. But in this study, we focused on a few of the most prevalent drawbacks of this system that Lou et al., Lee et al., Lewy et al., and Tang et al. reported.

6. COMMERCIALIZATION OF TDDS TECHNOLOGY

The first transdermal patch approved in 1979 to treat motion sickness is scopolamine. It is a sustained release administration and a three-day regimen is recommended. 5, Due to its benefits, the TDDS has become a possible drug delivery method as of late. For the transdermal administration of medications, a variety of technologies and deliverable devices have been commercialised and are available to patients on the international market. The US Food and Drug Administration (FDA) has approved numerous compounds for topical application as a result of extensive study into TDDS technology (Table 8). However, compared to other drug delivery methods and technology, the market size, sales drivers, rivalry, risks, and window of opportunity in the international market were the main factors limiting its global presence and commercialization. [94-96]

Table 8. Marketed transdermal drug delivery product

Product name	Drug	Manufacturer	Indication
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
Habitrol	Nicotine	Novartis	Smoking cessation
Lidoderm	Lidocaine	Endo Pharmaceuticals Inc.	Anesthetics
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Nitro-Dur	Nitroglycerin	Key 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

ProStep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation
RivastigmineTS	Rivastigmine	Sandoz	Dementia
Testoderm TTP	Testosterone	Alza	Hypogonadism in males

7. CONCLUSION

This paper presents a framework for evaluating and debating the various strategies or approaches for improving medication administration through TDDS. To boost drug transport via TDDS, a variety of approaches including chemical penetration enhancers, electric fields, and ultrasound have been widely used. To get past the stratum corneum barrier and permit medication administration via the skin, a number of methods, including microneedle systems, have been investigated. The structural geometry and many types of microneedles, including coated and dissolving ones, show a cutting-edge and emerging technology to improve skin permeability. Microneedle-based drug delivery systems are a potential new technology in the pharmaceutical and cosmeceutical business. Microneedling technology has advanced dramatically and is now suited for mass manufacturing. Our review provided a concise summary of the wearable transdermal medicinal delivery approach as well as recent developments in wearable system development. On the other hand, nanoparticles have received the greatest attention and have undergone the most development of the many TDD techniques. Flexible liposomes, niosomes, dendrimers, microsponges, and other types of nanoparticles can squeeze through intercellular spaces to enter the skin. Nanoformulations, such S/O dispersion, have since been successfully applied to TDDS. This review's objective is to thoroughly examine and summarise the most recent penetration augmentation techniques and their potential mechanisms of action. We have included every cutting-edge technology and thoroughly covered the most likely mode of action. It was concluded that the expansion of transdermal delivery in various complex therapeutic applications, such as chemotherapy, gene therapy, immunotherapy, phototherapy, and vaccine delivery, is made possible by the rapid development of penetration enhancement technologies. The review article mentioned here can serve as a starting point for scientists studying TDDS technology. But despite these improvements, we advised that there are still a lot of problems that need to be solved. It is important to conduct complete, in-depth investigations on the fundamentals of molecular penetration mechanisms and the differences in penetration between healthy and diseased skin. To improve drug delivery effectiveness and retention time, researchers should look more closely at the cellular barriers in skin tissues and the tumor microenvironment.

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