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Review

Microneedles-mediated transdermal drug delivery techniques in modern medicine

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Abstract

Transdermal Drug Delivery Systems (TDDS) present a transformative alternative to traditional drug administration methods, addressing key challenges and revolutionizing the pharmaceutical industry. Despite the prevalence of traditional methods due to their ease of administration and cost-effectiveness, they face limitations such as low bioavailability, gastrointestinal side effects, patient non-adherence, and additional risks associated with invasive procedures. TDDS offer a near-painless administration route that minimizes fluctuations in systemic drug exposure and enhances treatment adherence, especially in low and middle-income countries. TDDS work by overcoming skin permeability barriers through modifications to drug properties and the development of novel formulations and technologies, such as microneedles (MNs), which create micro-channels in the skin for painless drug delivery. MNs have applications in treating various conditions, including HIV, neurological disorders, diabetes, and cancer. Here in this review we discuss different types of MNs, such as dissolvable, core–shell, and stimuli-responsive formulations and explore TDDS efficacy. Recent advancements, particularly in microneedle technology, promise to revolutionize drug delivery methods, allowing for a more patient-friendly and effective means of delivering necessary therapeutic agents.

Keywords

Transdermal drug delivery systems (TDDS), microneedles, drug delivery, molecular biology

1. Introduction

Skin takes up 1/5th of human body mass and protects against outside threats, the large coverage of 1.8 m^2 means there is an easy transfer of drugs. The human skin has 3 main layers to provide defense against outside assailants, consisting of the Epidermis, the Dermis, and the Hypodermis. The Epidermis is around 150-200 mm thick and composed of 5 layers: stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum germinativum. The first layer of the Epidermis, the stratum corneum(SC) is responsible for drug related activities, as it's the outermost

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layer that protects the rest, and needs to be penetrated to administer the drugs. The Dermis is somewhere around 3-100 mm thick, and hosts many functional tissues, supporting skin structure in addition. The Hypodermis is the last layer, containing loose connective tissue and assisting in regulating body temperature, as well as protecting the body from outside hits [1].

Transdermal drug delivery (TDD) minimizes side effects and maintains effectiveness despite the body's defenses. However, the chemical properties of drugs can affect absorption in the stratum corneum (SC), limiting the number of drugs deliverable in high amounts. To pass through the SC, drugs must have a molecular weight less than 600 Da, a Log P value between 1 and 3, a balanced and high vehicle partition coefficient, and a low melting point. TDDS have emerged as a transformative alternative to traditional methods of drug administration, offering solutions to several inherent drawbacks associated with conventional techniques. These traditional routes, which include enteral and parenteral methods, such as oral medications and injections (intramuscular, subcutaneous, or intravenous), are widely utilized due to their ease of administration, patient convenience, cost-effectiveness, and manufacturability on a large scale [2] [3]. However, these methods present significant challenges. Oral medications often suffer from low bioavailability, gastrointestinal side effects, and poor patient adherence due to high pill burden. Injections, while effective, are invasive and painful, require trained medical personnel or patient training, produce hazardous sharps waste, and increase the risk of disease transmission through needle reuse, particularly in low-resource settings [4]. TDDS, on the other hand, offer a near-painless administration route, allowing for self-administration with minimal training, minimizing fluctuations in systemic drug exposure, and improving treatment adherence. This is especially advantageous in low and middle-income countries. The market potential for TDDS is substantial and growing, with the segment of transdermal microneedles alone expected to reach about $10.8 billion by 2033 [5]. This market growth is supported by recent regulatory advancements and improvements in design and safety, facilitating easy administration and consistent therapeutic dosing over extended periods. Recent advancements in drug delivery technologies, such as microneedles and novel sensing methods, are enhancing the capabilities of transdermal systems. For instance, a paper microchip with a graphene-modified silver nano-composite electrode has been developed for the electrical sensing of microbial pathogens [6] [7].

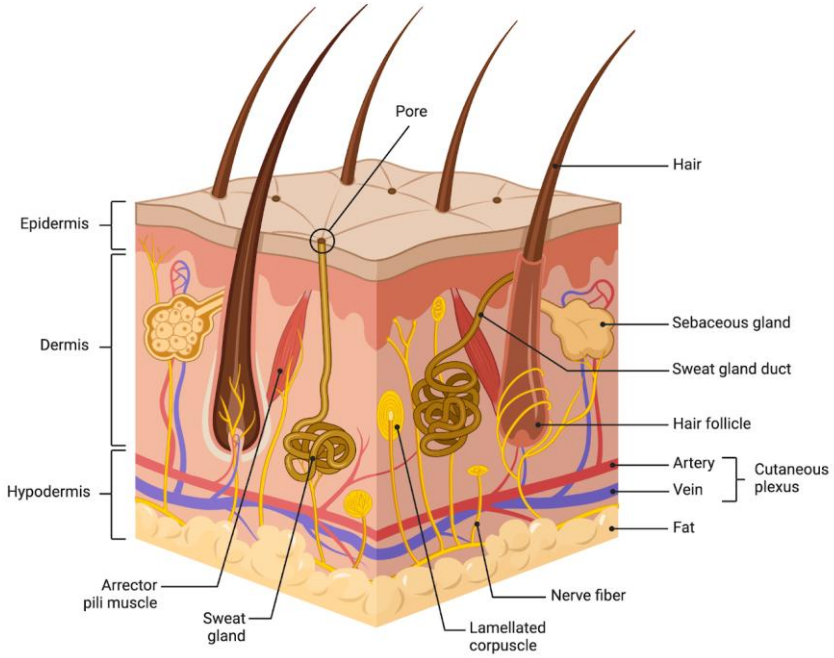

Figure 1. Anatomy of the skin. Adapted from "Anatomy of the skin", by BioRender.com (2024). Retrieved from https://app.biorender.com/biorender-templates.

There are three distinct generations of TDD that can be described; (1) first generation, included basic patches that had a limited selection of drugs meeting strict criteria, (2) second generation extended applications through iontophoresis,

chemical enhancers, or non-cavitational ultrasound, though these methods did not adequately protect deeper tissues or increase molecule distribution, (3) third generation advanced methods including electroporation, chemical enhancers, cavitational ultrasound, MNs, thermal ablation, and microdermabrasion, with MNs becoming preferred due to increased efficacy and reduced skin damage [8] [2]. MNs can be categorized into five types: solid, coated, hollow, dissolving, and hydrogel-forming. Solid MNs involve needles piercing the skin with a drug patch applied. Coated MNs poke the skin and have a patch placed over them, while hollow MNs allow drug flow from a hollow needle tip. Dissolving MNs consist of polymer needles that dissolve the drug into the body, and hydrogel-forming MNs absorb water during the process. MNs are typically made from metal, polymer, glass, or silicone, with silicone being less favored due to its inability to metabolize [9].

Despite the clear advantages of TDDS, there are challenges that need to be addressed. The stratum corneum's tightly ordered lipid structure limits medication penetration. Passive approaches as well as active techniques are being investigated to overcome this barrier [10]. However, these methods can present downsides, including skin susceptibility, unpleasant sensations, tissue injury, difficulty with multiple formulations, bleeding, etc [11].

Microneedles, in particular, have demonstrated significant potential in surpassing traditional and parenteral drug administration methods. They penetrate the outer skin layer, the stratum corneum, to release the drug into the dermal microcirculation, allowing for stable and prolonged drug release [12]. MNs are less invasive and painful than hypodermic needles, offering higher drug permeability and effectiveness, faster action onset, increased bioavailability, and superior patient compliance. Their versatility makes them viable for a wide range of applications, from vaccination and medication to cosmetic administration [13].

TDD offers increased release time, versatility, and self-administration possibilities. Microneedles provide an optimal solution for transdermal drug delivery, penetrating the skin while avoiding nerves and capillaries, and causing minimal pain. Polymers are commonly used for MN production due to their biocompatibility and versatility, though they have some drawbacks such as hydrophilic nature, instability, and poor absorption. Effectiveness of the MNs depends on their mechanical strength, skin permeation, and release kinetics. The dimensions also affect these, being the heights, tip radius, widths, lengths, and interspacing of the polymer MNs, which are determined through stereomicroscopy, transmission electron microscopy, or scanning electron microscopy. The amount of the drug that can be administered depends on these structural properties [14]. Mechanical strength is found through a texture analyzer or a motorized force measurement test stand. Studies have found that a smaller tip diameter, smaller angle, and high ratio of height to base width most likely results in a successful drug delivery. In relation, since MNs pierce the skin to deliver drugs, their success of penetration can be measured using parafilm or porcine skin to mimic human skin. The holes left after the needles pierce the test subjects are observed using methylene blue staining, by finding the number of blue dots and dividing it by the number of microneedles to find the percentage of successful penetration. Drug encapsulation is measured through Franz diffusion, the porcine pointed upwards in the donor compartment of the diffusion cell, phosphate-buffered saline at pH 7.4 and temperature at 37 °C in the receiver compartment of the cell. The array is then applied at different set intervals, the samples taken to be evaluated [15]. The MNs are also put inside the receiver compartment, or a beaker, samples taken at set intervals to find the drug concentration. Similarly, there are multiple testing methods for MNs. One example is In vivo, which involves using animals, mostly rats or mice, and removing their fur, proceeding to use an MN patch on them to determine the variables in relation to the efficacy of the MNs. Most clinical trials of MNs involve this method and Ex vivo, or testing on real human skin. The reason both are tested is due to the structure and immune response of animals different from humans, which has been found to affect the side effects and efficiency of drugs in the past. In this review, we classify the various types of transdermal drug delivery techniques, diving into the three generations and exploring microneedles as an advantageous method of transdermal drug delivery techniques compared to other methods.

2. Methodology

2.1. Principle of Operation of TDDS

The principle of TDDS involves overcoming the skin's permeability barriers through modifications to the physicochemical properties of drugs and the development of novel formulations and physical enhancement technologies [16]. Among these innovations, microneedles (MNs) stand out for creating micro-channels in the skin that allow for drug delivery without reaching nerve endings, thus providing painless administration. MNs have applications in treating a variety of conditions, including HIV, neurological disorders,

diabetes, cardiovascular diseases, contraception, and cancer. Different types of MNs, such as dissolvable, core–shell, stimuli-responsive, and delayed/pulsatile-release formulations, along with molecularly imprinted polymers (MIPs) and 3D-printing technologies, are being explored to enhance TDDS efficacy [17]. Long-term drug delivery is particularly focused on polymeric/hydrogel MNs-based approaches [18].

2.2. Evolution and Mechanisms of Transdermal Drug Delivery Systems

TDD has gained prominence due to its controlled release time, versatility, and self-administration capability [19]. Recent advancements in drug delivery technologies, including microfluidic platforms for drug screening in complex environments, further enhance the potential of these systems in modern medicine [6]. TDD minimizes side effects and maintains effectiveness while traveling through the body, despite the numerous defense mechanisms it encounters [20] [21]. However, chemical properties of the drugs can change the absorption in the stratum corneum layer, so only a select few can be delivered using this method in high amounts [22]. The criteria is as follows: the molecular weight must be less than 600 Da, the Log p value must be between 1 and 3, the vehicle partition coefficient must be balanced and high, and there must be a low melting point [23]. MN effectiveness depends on multiple factors, namely their mechanical strength, skin permeation, and release kinetics[24]. The heights, tip radius, widths, lengths, and interspacing of the polymer MNs, the dimensions, are determined through stereomicroscopy, transmission electron microscopy, or scanning electron microscopy, and also play a role in the effectiveness of MNs These structural properties determine how much of a drug is administered [25]. A texture analyzer or a motorized force measurement test stand finds out the mechanical strength, for instance. Additionally, a smaller tip diameter, smaller angle, and high ratio of height to base width has been shown to increase chances of a successful drug delivery [26]. Relating to this, MN success at penetration can be measured with porcine skin to mimic human skin or parafilm [27] [28] [29]. The needle holes left after piercing are observed using methylene blue staining. Once the number of blue dots is found and divided by the number of microneedles, the percentage of successful penetration is derived [30]. Franz diffusion measures drug encapsulation, with the porcine pointed upwards in the diffusion cell's donor compartment, temperature at 37 °C, and phosphate-buffered saline at pH 7.4 in the cell's receiver compartment. At different set intervals, the array is then applied, samples taken to be later evaluated. To find the drug concentration, the same thing is done but with MNs in beakers in the receiver compartment [31]. This relates to how there are multiple testing methods for MNs. In vivo, which involves using animals such as rats or mice, for instance, involves removing their fur and using an MN patch on them to determine the appropriate data that is used to find the efficacy. Ex vivo is another similar method, albeit with human skin [32]. Both are tested due to the difference in structure and immune responses between humans and animals, which can allow for more clear ideas of the side effects [33].

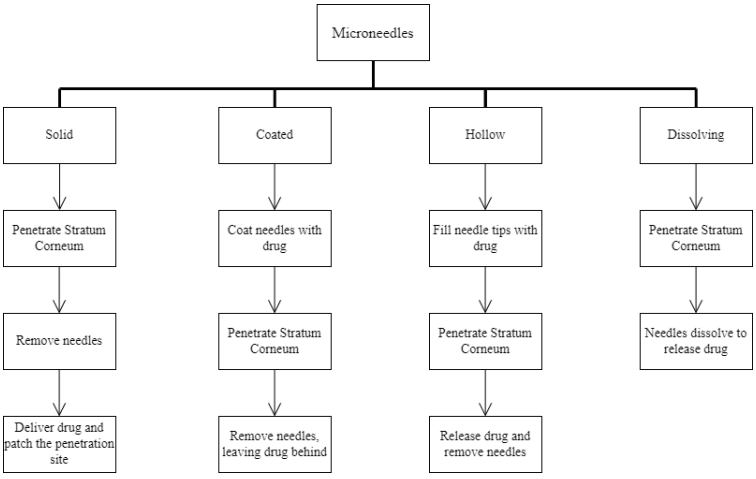

Figure 2. *Classification of microneedles*

2.3. Generations of TDDS

Transdermal Drug Delivery has seen many stages of improvement, resulting in different generations. The first, second, and third generations all excelled at different things

and improved upon the former's weaknesses. Each generation of transdermal drug delivery systems represents progression in the range and effectiveness of drugs that can be delivered through the use of TDD. Transitioning from simpler, passive systems to more advanced methods able to deliver complex macromolecules illustrates the continued interest and innovation in this field, aiming to enhance therapeutic outcomes and patient compliance.

The first generation mainly targets small, lipophilic, and low-dose drugs that are able to naturally permeate the skin, being effective due to their utilization of the inherent properties of certain drugs that can passively cross the skin's outermost layer, the stratum corneum, without any enhancement techniques. However, this generation is limited by the restriction of the delivery of larger or more complex molecules, which is the skin's natural barrier function [34]. This makes first-generation TDDS ideal for the drugs that are able to passively penetrate the skin, allowing for wide clinical usage due to their simplicity and non-invasiveness. Common applications include patches for nicotine replacement therapy, hormone replacement, and pain relief, which have become standard treatments for their respective conditions [35].

The second generation of transdermal delivery systems aimed to enhance skin permeability in order to expand the range of drugs that can utilize TDDS. Chemical enhancers, iontophoresis, and non cavitational ultrasound are some examples of improvement techniques used to temporarily disrupt the stratum corneum. This allows for larger molecules and a broader range of drugs to penetrate the skin, increasing the range of administrable drugs. One notable example is iontophoretic systems, which utilize electrical currents to increase the penetration rates of drugs, thus facilitating more efficient delivery. However, the second generation utilizes chemical enhancers and other excipients to increase skin permeability,which can lead to skin irritation and sensitization at the application site. Additionally, they often require external devices to be effective, which can be costly and limit the practicality of the system. These risks necessitate careful control of the duration and intensity of current use to minimize adverse effects.

The third generation of transdermal drug delivery focuses on delivering macromolecules, such as proteins and vaccines, which are significantly more complex and larger than those targeted by previous generations, by overcoming the stratum corneum. Through employing innovative techniques like microneedles, thermal ablation, and electroporation to create microchannels or disrupt the barrier, this generation enables enhanced delivery of larger therapeutic agents [36] [35]. These more advanced methods also allow for the transdermal administration of substances such as insulin and vaccines, leading to new possibilities for treatment options. Even though it is still in development, third-generation systems display great promise for expanding the scope of transdermal drug delivery through allowing the administration of a wider variety of therapeutic agents. However, due to incorporation of advanced technologies such as microneedles and electroporation, there is added complexity and cost compared to earlier generations, making systems less accessible and more expensive to produce and implement, one issue that is still being worked towards fixing [37].

Reference	Delivery Method	Active Ingredient	Advantages	Disadvantages	Clinical Applications
[38]	Iontophoresis	Acetylsalicylic acid, Acidulated phosphate fluoride, Aciclovir, Aciclovir prodrugs, Amikacin, Amikacin sulphate, 5-Aminolevulinic acid, Amoxicillin, Cefuroxime, Celecoxib, Ciprofloxacin, Ciprofloxacin hydrochloride, Cupral, Curcumin,Dexamethasone, Diclofenac,	This method is safe to use overall, exhibits high transdermal efficiency, and has a simple application process.	Side effects such as redness, skin irritation, and even burns can be caused by direct currents. Additionally, only potent molecules can be delivered by this method.	Iontophoresis can be used in local anesthetics, steroids, opioids, non-steroidal anti-inflammatory drugs, antibacterial drugs, antifungal drugs, antiviral drugs, anticancer drugs, fluorides, and vitamins.

		Diclofenac sodium, Ibuprofen, Indemethacin, Fentanyl hydrochloride, 5-Fluorouracil			
[39]	Microemulsions	dioctyl sodium sulfosuccinate, tricyclic amines	They improve drug solubilization and bioavailability, both huge challenges in TDDS. Their low interfacial tension and large interfacial area promote drug absorption and release. Additionally, they exhibit low toxicity levels and cost-effectiveness.	The formulation is complex and the optimization of said formulation is both costly and takes a lot of time. The surfactants and co surfactants have the potential to be toxic, as even with minimization patients can still experience adverse effects.	Cutaneous drug delivery, therapeutic uses, skin delivery of drugs
[40] [41]	Microneedles	Silicon, metal, polymer, sugar, lipids	Microneedles are an effective method for transdermal drug delivery because this method allows for bypassing vital organs like the liver, thus avoiding first-pass metabolism. They additionally offer a pain-free alternative to intravenous injections, and are user-friendly since medical personnel are not required for administration. MNs are user-friendly, requiring no trained personnel, which reduces the risk of infection transmission.	Their extended application time, needing multiple patches in an area, and requirements for mechanical strength and biocompatibility all pose as disadvantages, along with skin irritation, redness, pain, swelling, and infection at the application site.	Can be used to treat a wide range of conditions from pain management to mental disorders, or diseases like diabetes and such, along with skin problems.
[40]	Patches	Silicon, metal, polymer, sugar, lipids	This method allows for bypassing the digestive system, continuous dosing, less invasion, and avoidance of first-pass metabolism.	They do however have limited types of medication, may cause skin irritation, limited dosing options,	Can be used to treat a wide range of conditions from pain management to mental disorders, or diseases like diabetes and such.

				and inconsistent absorption.	
[42] [43]	Ultrasound-based systems	Frequency	Enhanced skin permeability, non-invasive, controlled delivery, and versatility	Thermal effects, cavitation damage, and delayed bioeffects	Currently used in some clinics for skin care.

Table 1. *Comparison of Transdermal Drug Delivery Methods and Technologies*

2.4. Pain Perception and Patient Experience with Microneedles

The development of microneedles has led to them being engineered to overcome traditional limitations of most TDDS, enabling the delivery of larger molecules such as proteins and vaccines, claimed to be mostly painless and effective. Transdermal drug patches, despite promising a convenient and painless alternative to hypodermic needles, have been limited due to the stratum corneum. Only a limited number of small, lipophilic drugs can currently be delivered through transdermal patches. In contrast, microneedles enable the transdermal delivery of larger and hydrophilic compounds [40]. These tiny needles, which can penetrate the stratum corneum without reaching pain receptors in the deeper layers, offer a method to deliver a wide range of drugs, including insulin and vaccines for diseases like influenza and hepatitis B [44]. Patients themselves have been asked and tested for their perceptions of the pain caused by MNs.

The expectation of painless delivery is a vital part in their design, allowing for penetration of the skin's surface layers without activating deeper pain receptors. However, patient perceptions of pain associated with microneedles have not been extensively studied yet. The few studies that have been conducted suggest that microneedles can indeed be less painful. One study, through inserting 400 microneedles of 150 μm length, found that MNs were perceived as painless compared to the insertion of a 2-mm deep 26-gauge hypodermic needle [45]. Similarly, scraping the skin with microneedles measuring 50-200 μm was reported as painless [46]. However, in spite of these findings, the variation in pain perception among individuals leads to the need for a more detailed examination of how microneedles affect pain. Larger MNs that allow for increased delivery, for example, might be expected to cause more pain [45]. Understanding the relationship between microneedle design and pain perception is vital for developing microneedles that maximize drug delivery efficiency while minimizing discomfort.

To figure out the details of the relationship between microneedle design and patient pain perception, an additional comprehensive study was conducted. Through varying the dimensions of microneedles - including length, thickness, tip angle, width, and the number of microneedles in an array - to compare their effects on pain with that of a traditional hypodermic needle, a better set of data on patient views on MNs can be created [45]. Participants rated their pain through a visual analogue scale, providing quantitative data on pain levels in association with different microneedle configurations.The study revealed that microneedles, regardless of their dimensions, caused significantly less pain than a 26-gauge hypodermic needle. For example, microneedles with an extremely short length of 480 μm induced only 5% of the pain reported for hypodermic needles, even the longest microneedles tested, being 1450 μm long, causing significantly less pain. This reduction in pain is due to the microneedles' ability to penetrate the skin's surface without reaching the deeper layers where more pain receptors lie [46]. The study also noted that microneedle insertion resulted in minimal skin irritation, which typically resolved within 24 hours. Furthermore, no significant relationship between microneedle thickness or width and pain levels was found, possibly meaning that factors such as the force of insertion and penetration depth might play a more crucial role in determining pain [47]. These findings support the hypothesis that microneedles can offer a pain-reduced alternative to hypodermic needles, potentially improving patient comfort and compliance.

3. Discussion

While TDDS have proven to exhibit many advantages over traditional routes, there are still many aspects that must be improved upon. The safety of the drugs must be considered, as many experience adverse effects in relation to TDDS. Conditions such as skin atrophy, phototoxicity, and cytotoxicity are noted as common, even in the circumstances that systemic side effects have had measures taken to minimize them. An example of this is NLC, which is considered a safe carrier, yet still has surfactant, albeit a small

amount, that can be harmful. Even microneedles, a rising technology in the industry, causes small skin lesions that can transmit bacteria and cause inflammation. Finally, Ethanol, even with its easy production and high encapsulation rate, has shown to irritate the skin when given at higher concentrations, as multiple unintended side effects can result from higher doses aimed at maximizing drug effectiveness. Additionally, some drugs, when specifically used in TDDS, can exert systemic effects through transdermal absorption. For these reasons, careful control must be maintained over dose and frequency, especially for damaged skin, in order to reduce absorption toxicity; reliable techniques meant to verify the dependability of devices that aid drug penetration into the skin are still lacking. Another major limitation in relation to TDD is the high cost and unresolved difficulties that hinder progression from laboratory design to industrial manufacturing. For instance, as industrial settings are more complex to maintain than laboratory environments, they require careful management of temperature, aseptic operation, humidity, and other conditions in order to create a sanitary environment that does not breed infection. Additionally, repeatability between batches must be ensured so there are no inconsistent pharmacological effects. In general, TDDS creations are much more challenging to produce than oral or injectable tools used for drug delivery. One main example of this is a microneedle patch, which bears complex structures and increasing development costs that make it difficult to maintain high-quality standards. To add on, TDD technology is more sensitive to pharmacokinetic and thermodynamic effects, meaning appropriate environmental parameters, such as light, temperature, and humidity, must be maintained during production, packaging, storage, and use to prevent medication degradation and ensure efficacy. The unpredictable nature of bioequivalence testing procedures, a method for evaluating key pharmacokinetic characteristics of reference formulations for generic drugs, hinders TDDS development. Since the FDA and EMA have not provided precise guidelines, there is significantly less interest in studying TDDS bioavailability, as current methods for determining it are not standardized due to diverse targets, unique delivery methods, and differences between animal and human skins [8]. The application of microneedle technology extends beyond drug delivery, as demonstrated in recent studies on conductive hydrogel microneedle-based assays for real-time, enzyme-less glucose sensing and pH measurement in live animals, further highlighting the versatility and potential of these systems in healthcare and biomedical engineering [14].

The emerging field of TDDS presents several challenges for optimization. A primary obstacle is the stratum corneum's dense cellular architecture and hydrophobic nature, which impede efficient drug penetration. Some factors that affect drug absorption into the skin include its physiology and chemical characteristics. The thickness of the stratum corneum along with lipid contents in different skin layers affect absorption rates, while the quantity of capillary blood vessels in certain skin parts can influence absorption into circulation [48] [49]. Drugs require sufficient solubility in oil and water in order for absorption into the SC, with the optimal log partition coefficient range being 1.0-3.0 [50]. Additionally, the molecular size of the drug should be less than 600 Da in order for optimal absorption [51].

With these factors in mind, there are some enhancement techniques that can improve TDDS and their efficacy, one being Drug-vehicle interaction. A prodrug approach is utilized, with inactive moiety linked to the drug enhancing hydrophobicity, which allows for better penetration of the stratum corneum, the parent drug metabolizing into the active post-absorption [52]. A few examples of this are morphine, carbamate, and naltrexone [53] [54] [55]. Another method of drug-vehicle interaction is ion pairing, in which a neutral paired compound is formed by adding opposite ion species, enhancing permeation, allowing the drug to release post-SC partition, some examples including risedronate, berberine, and nicotine [56] [57] [58] [59]. A second technique to improve TDDS is vesicles. Liposomes, for instance, are artificial vesicles made of phospholipid and cholesterol and can encapsulate hydrophilic and hydrophobic drugs such as vitamin c, ketoprofen, and baicalein [60] [61] [62]. Ethosomes contain phospholipid and either ethanol or isopropyl alcohol to enhance drug permeability, examples being green tea extract and valsartan [63]. Transfersomes, on the other hand, are ultra-deformable liposomes with phospholipid and edge activator to penetrate deeper skin layers, like raloxifene and cilnidipine[64]. Finally, phytosomes are lipid-based nanovesicles for hydrophilic phytoconstituents meant to increase bioavailability of natural compounds, like centella asiatica and curcumin[65].

To enhance TDDS efficacy, chemical permeation enhancers are employed, including sulfoxides, azone, surfactants, and fatty acids. These compounds facilitate drug penetration through the stratum corneum by temporarily altering its structure and permeability. Sulfoxides interact with the lipid domains of the SC, some drug examples being hydrocortisone and testosterone [52] [66]. Azone disrupts the SC's lipid packing, ketoprofen being one that does so [52]. Surfactants

disrupt both lipid and protein domains of the SC, examples being lorazepam and foscarnet [68,69]. Finally, fatty acids modify the SC's lipid domains, a couple of drugs that do this being flurbiprofen and propranolol [70] [71].

3. Conclusion

The growing acceptance of MN devices by patients has led to more market entrants, which in turn reduces costs and accelerates market growth. MN clinical trials to date have primarily focused on evaluating the ability of these devices to penetrate the skin barrier and enhance delivery. Recent findings suggest that silicon, a common material used in these devices, may lack biocompatibility and may not dissolve or disintegrate effectively after administration. It has also been found that current production methods are not ideal for MN manufacturing. Batch production processes can limit the quality of the final product because the hygroscopic nature of the polymers used may compromise their structural integrity, potentially affecting their overall performance. MNs are powerful and useful tech to deliver chemical molecules to much larger biotherapeutics. Delivery through MNs don't produce the same side effects as oral or parenteral pathways, and can be administered without professional help. Developing polymer MNs successfully is determined by the type of polymer, biocompatibility, design, and mechanical strength of the MN in question, utilizing both animal and human test cases to properly test the effectiveness and side effects. For MNs to be more widely established in the market, more clinical testing is required to gauge the side effects and the standards to judge what a clinically safe MN is.

TDDS are rapidly advancing as the medical field begins to focus more and more on them and their potential to reshape drug delivery. Significant improvement can be made over the next 5-10 years, and may lead to it becoming more mainstream. More novel biocompatible materials that are capable of targeting and controlling drug release are likely to be developed, along with the creation of smart polymers and hydrogels capable of responding to environmental stimuli for precise delivery [72]. Nanotechnology is also likely to be more integrated through advancement of nanocarriers such as nanoparticles, liposomes, and nanofibers in order to enhance drug permeability and stability. Nanostructured transdermal patches for improved drug absorption may also be designed [2]. Microneedles, which are already gaining popularity, will be more refined for even more painless and efficient delivery, along with developing and using more biodegradable materials for reducing waste [2]. Additionally, considering the variety of TDD techniques, it is not far-fetched to suggest that multiple enhancement techniques can be integrated, such as microneedles with chemical enhancers [5]. The range of drugs delivered will be expanded too, as the development of techniques to deliver larger molecules and such transdermally will have advanced, as will the delivery of vaccines and immunotherapies[73].

Author Contributions

A.S. formal analysis, methodology, validation, writing – original draft, reviewing & editing. K.D., S.V., conceptualization, writing - review & editing.

Conflicts of Interest

The authors declare no competing financial interests or conflicts of interest.

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