RESEARCH PAPER

Advances in Transdermal Drug Delivery: From Microneedles to Nanofiber Systems

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ABSTRACT

Transdermal Drug Delivery Systems have undergone a technological evolution where the ability to deliver drugs non-invasively to a target site has been expanded far beyond standard patch applications (i.e., disadvantages of low permeability and limited types of drugs). The development of Microneedles and Nanofiber based Transdermal systems have shown great promise at providing adequate means for the efficient transport of a broad assortment of products. Even large molecules such as peptides, proteins, and vaccines are being delivered transdermally via microneedles with much higher efficiencies compared to standard patch applications. Microneedles allow the creation of micro channels through the stratum corneum of the skin with minimal trauma to the surrounding skin, allowing for the rapid delivery of drugs. Nanofiber based transdermal systems are primarily fabricated by electrospinning/solvent casting techniques, which allows for a very large surface area to hold a very large number of drug molecules while providing controlled release profiles for long-term local and sustained drug delivery. Microneedle and Nanofiber systems combined to form a hybrid system greatly improve upon the limitations of both types of systems. Microneedles and Nanofibers are capable of providing both immediate and long-term therapeutic benefit, which is very desirable for chronic disease management, wound healing, and when targeting specific tissues or organs. While the technological advancements make great strides, other challenges remain (manufacturing complexities; stability; scalability; and regulatory issues), which have greatly limited the transition of these advanced systems into clinical settings. Thus, the development of these advanced systems represents a new generation of non-invasive, effectively utilized, and patient-oriented drug delivery systems that have the potential to significantly impact modern therapeutic approaches and aid in the development of personalised medicine.

Keywords: Transdermal drug delivery, microneedles, nanofibers, controlled drug release, drug delivery systems

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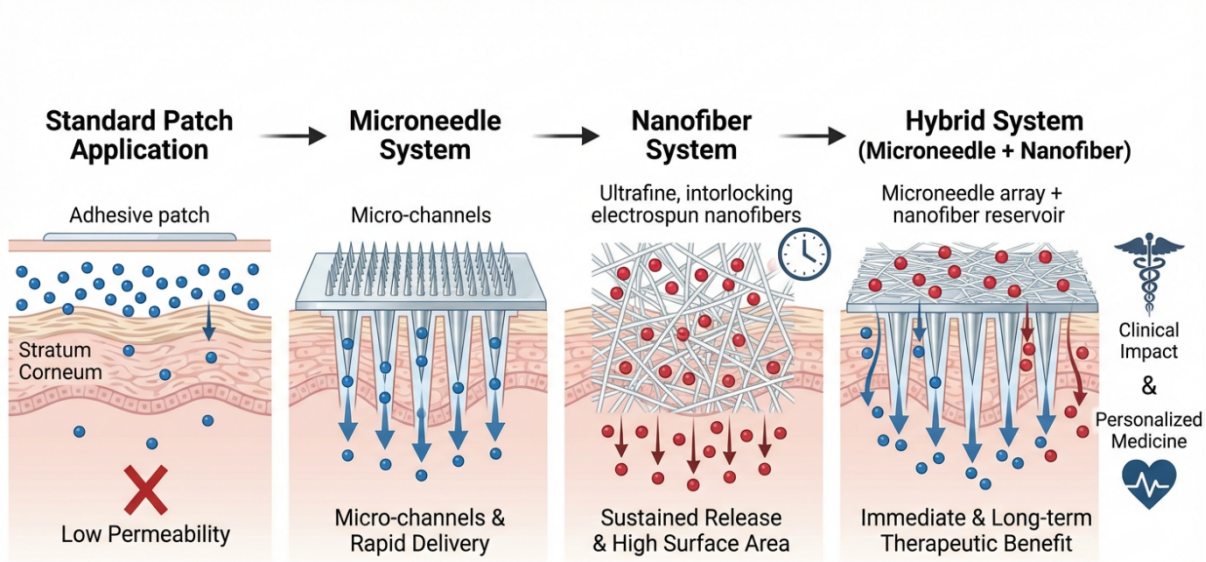

1. Introduction

Transdermal delivery systems are a promising new way to deliver medicines via the skin and have been gaining popularity as an alternative to traditional medicine delivery systems, which involve taking oral medicines or injecting. There are many benefits to using the transdermal route of administration; for example, medications delivered in this manner will not be affected by the first pass metabolism that occurs with oral medications. Patients also have better compliance when using TDDS than with injectable or oral medications because they do not require any special instructions and release the medication over a longer period of time. The advantages of using TDDS make these systems particularly appealing for long-term therapy (e.g. for patients requiring chronic treatment)[1].

Conventional TDDS are limited by the properties of skin, in particular, the stratum corneum, which is the outermost layer of skin. The stratum corneum is a very effective barrier to most medications and thus will not allow most drugs to penetrate through it, particularly large, hydrophilic drugs or those that are not therapeutically effective in the liquid state. Therefore, only a small number of medications can be administered via conventional TDDS such as transdermal patches.

Due to the limitations of traditional TDDS, there are many ongoing research efforts to develop newer technologies that can improve drug delivery through skin and to greatly increase the number of therapeutic agents that can be delivered via transdermal systems.

Recent advances in technology have created innovative methods of enhancing drug delivery through the skin, including microneedles and nanofiber-based systems, that have the ability to safely and effectively increase the amount of drug delivered through the skin and improve patient comfort.

Microneedles are very small needles (30-1000 µm in length) and are considered a minimally invasive delivery method because they can create temporary microchannel openings in the skin for drug delivery.Microneedles allow for effective delivery of drugs, such as macromolecules (peptide/protein/vaccines), across the stratum corneum, stated the authors. There are four classifications of microneedles that offer their own advantages for drug loading and release kinetics: solid, coated, dissolving and hollow[2].

Similarly, electrospun nanofibers provide superior surface area to volume ratios, tunable porosity, and substantial drug loading capacity as compared to conventional (non-nanofiber) delivery systems. In addition to providing sustained and controlled drug-release rates, these materials are being utilized to improve wound healing, localized therapy and transdermal delivery of drugs that are poorly soluble. Nanofibers can also be developed with "smart" delivery systems by combining them with stimulus responsive materials so that they can respond to environmental changes in pH, temperature, or moisture.

Combining the use of microneedles and nanofibers has expanded the opportunities for advancing transdermal drug delivery systems. “Hybrid”

systems utilizing microneedle arrays and drug-loaded nanofibers will provide synergistic benefits, such as enhanced penetration, regulated-release kinetics, and higher therapeutic benefits. The continued utilization of hybrid systems will have great significance for the advancement of vaccine delivery, cancer treatment, and long-term management of chronic conditions.

Alternative enhancement techniques (e.g., iontophoresis, sonophoresis, chemical permeability enhancers) are also being explored to enhance transdermal drug delivery systems but microneedles and nanofiber systems stand out because of their versatility, scalability and capability for delivering a range of drugs from a single device.

Although there have been many recent advancements in microneedles and nanofiber-based systems, several challenges in the manufacturing process remain, including: the complexity of manufacture, mechanical strength, drug stability and regulatory considerations; as well as, manufacturing at a large scale. Uniformity, reproducibility and patient safety should be strong considerations for successful clinical translation.

Recent advances in technology have created innovative methods of enhancing drug delivery through the skin, including microneedles and nanofiber-based systems. This review will detail the design, function, benefits, limitations, applications and future advancements of next-generation transdermal drug delivery systems[3].

2. Skin Structure and Barrier Function

Skin's structure and barrier action transition functionally from the epidermis through the dermis to the hypodermis. The three layers determined how the skin functions as a barrier to protect the body's underlying tissues from external temperature extremes, pollutants, and ultraviolet light. Understanding the anatomy and physiology of these three layers is important for designing transdermal drug delivery systems[4].

The skin consists of three layers: the epidermis, dermis, and subcutaneous tissue (hypodermis).

1. Epidermis: This is the outermost layer of the skin and is responsible for protecting against the external environment. The epidermis is made up of several sublayers, including:

Corneocytes (the outermost layer, consisting of dead keratinized cells embedded in lipids);

This is also the primary barrier for drug absorption into the skin.

Stratum Lucidum (found only in thick skin, located on the palms of the hands and soles of the feet).

Stratum Granulosum & Stratum Spinosum (these layers provide for cell proliferation, maturation, and differentiation).

The Stratum Corneum (outermost layer of skin) represents the most important aspect of transdermal drug delivery due to its "brick-and-mortar" construction, with corneocytes (the "bricks") surrounded by intercellular lipid (the "mortar").

2. Dermis: This layer of skin lies directly below the epidermis and consists of connective tissue, blood vessels, lymphatic vessels, and nerves. The dermis providesAfter penetration of the cutaneous tissue into systemic (blood) circulation, drug delivery can occur rapidly through diffusion across dermal (skin) layers, such as dermis and epidermis.

The hypodermis (subcutaneous tissue) is primarily made of adipose tissue. It functions to store energy as reservoir; create insulation by preventing body heat loss; and provide cushioning or protection from mechanical injury. Although the hypodermis does not function directly in the actual delivery of drugs into the body, it can affect the distribution of the drug throughout the body once the drug has already crossed through the permeation barrier into the body[5].

The primary function of skin is to be a barrier to prevent water loss and to protect the body against exposure to foreign substances (like a barrier). The most important layer of skin contributing to barrier function is the stratum corneum. Barrier characteristics include:

1. Structurally organized lipid bilayers (made up of ceramide, cholesterol, and fat)
2. Hydration/dehydration of lipid bilayers = very low hydration (dehydrated)
3. Highly compact corneocytes compose the majority of the stratum corneum

These characteristics highly restrict the number of drugs that can permeate through the stratum corneum, particularly hydrophilic (water soluble) or high molecular weight drugs.

Drug Delivery Pathways

Drugs can permeate through skin by one of the following three pathways:

1. Transcellular Pathway
   Direct passage through the corneocytes (cell surface membranes) multiple times for partitioning back and forth (dissolution) between hydrophilic and lipophilic phases

1. Intercellular Pathway
   Movement/distribution through spaces and/or lipid matrix between cells
2. Transappendageal Pathway (shunt pathway)
   Through follicles and glands

This last pathway is infrequent but can be significant for larger molecular weight or nanoparticle-sized materials. Advances in microneedle and nanofiber technology intended to enhance drug delivery via the skin will be focused on this pathway[6].

Factors Affecting Drug Permeation through the Skin

The transdermal drug delivery process is influenced by a variety of factors as follows:

- Drug Physicochemical Properties (i.e. molecular weight <500 Da; log P (lipophilicity) between 1 and 3; solubility and ionization)
- Skin Characteristics (i.e. hydration; thickness of stratum corneum; age; disease)
- Formulation Characteristics (i.e. presence of permeation enhancers and formulation vehicle for drug)

Limitations of Conventional Transdermal Delivery Methods:

Because of the significant barrier function created by the stratum corneum, conventional transdermal drugs are limited by:

- The delivery of small hydrophobic drugs; and no or very limited ability to permeate through the stratum corneum for macromolecules (i.e. proteins, peptides, vaccines).
- The delayed onset of drug delivery; peripheral pharmacokinetic variation (i.e. extent of absorption).
- Innovative transdermal drug delivery systems focused on the use of microneedle devices or nanofiber systems will eliminate the barrier created by the stratum corneum.

The various structures of the layers of skin related to the barrier function of the stratum corneum will contribute to the success of transdermal drug delivery systems. As important as the overall protection of the body is, these same structures can impede drug perm-selection. To advance to the next level of drug delivery through the skin, new drug delivery systems are required that bypass the barrier functions, as well as understanding how these structures and their functions affect the design of future transdermal devices[7].

3. Conventional vs Advanced Transdermal Drug Delivery Systems

Conventional transdermal delivery systems (TDDS) include all TDDS that do not have any modified drug delivery characteristics or use any advanced techniques to deliver the drug through the skin (through a device), usually in the form of transdermal patches, which deliver drugs to the systemic circulation over an extended period of time at a controlled rate. Some examples of successful use of conventional TDDS include: nitroglycerin (angina), fentanyl (pain), nicotine (smoking cessation), and hormonal replacement (estrogens).

Type of Conventional Transdermal Delivery Systems Include:

- Reservoir Systems: drug is held in a liquid reservoir separated from the adhesive by rate-controlling membrane.
- Matrix Systems: drug is dispersed in the polymer matrix.
- Drug-in-Adhesive Systems: drug mixed with adhesive.

Most conventional TDDS deliver drugs via passive diffusion across the stratum corneum, following Fick's laws. While conventional TDDS provide sustained release, increased patient compliance, and no first-pass elimination, such as nitroglycerin, fentanyl, nicotine, and hormonal replacement, the use of these TDDS are limited to very specific drugs with specific physicochemical characteristics.Limitations of Traditional Systems

While traditional systems have been effective for many years for the purpose of providing clinical results, they do present a number of challenges:

1. Barrier of Skin: The maximum absorption of a drug into the systemic circulation via the skin typically requires a drug which has a low molecular weight (i.e., < 500 Da) and moderate solubility.
2. Drug Loading Limitations: The delivery of large doses of medication is very difficult.
3. Delay in Onset of Action: The time between the administration of a drug and the occurrence of therapeutic effects is usually longer than expected due to the passive nature of diffusion.
4. Reaction/Sensitization to Adhesives and Other Excipients: The majority of patients will have an adverse reaction to at least one type of adhesive or excipient.

5. Ineffective Delivery of Biologics: Biologics such as peptides, proteins, vaccines and nucleic acids cannot be delivered effectively.

These shortcomings have led to the development of innovative transdermal delivery systems that will increase the permeability of the skin and the availability of numerous different therapeutics[8].

Advantages of Innovative Transdermal Delivery Systems

Innovative transdermal delivery systems provide a number of benefits when compared to conventional systems:

- Increased skin permeability: Ability to deliver large molecules and hydrophilic drugs.
- Controlled and directed drug delivery: Provide better treatment outcomes.
- Decreased risk for systemic toxicity: Delivery of drug to site of action.
- Versatile: Various types of drugs have been delivered using TDDS.
- Minimally invasive: Particularly microneedles.

Disadvantages of Innovative Transdermal Delivery Systems

There are still many challenges associated with innovative systems:

- Complex manufacturing process.
- More expensive to manufacture than traditional systems.
- Safety and regulatory issues.
- Limited stability/storage.

Due to the effectiveness of conventional TDDS over the last several decades, there have been additional options available for clinicians to deliver medication non-invasively. The limitations of conventional systems have led to the advancement of innovative systems. Innovative TDDS using microneedles, nanofibers, etc. will be the future of transdermal delivery methods due to the increased skin permeability and increased variety of drugs available leading to improved therapeutic effects[8].

4. Microneedle-Based Drug Delivery Systems

Microneedles, the newest advancement in transdermal drug delivery systems, are a minimally invasive way to create channels through the stratum corneum, which is the major barrier preventing the penetration of drugs into the skin. Microneedles are very small projections that range from 25 to 1000 mm long, and they are designed to penetrate the outer layer of the skin without reaching the nerve endings in the skin. This enables drug administration painlessly or almost painlessly, and creates temporary microchannels, which enable increased penetration of drugs through the skin.

Microneedle technology is based on the principle of bypassing the stratum corneum, which is the main reason why transdermal drug delivery is difficult. When a microneedle is inserted into the skin, it disrupts the well-ordered lipid structure of the stratum corneum, which allows the drug to diffuse through the drug into the viable epidermis and dermis of the skin, where the drug can then enter into the systemic circulation through the capillary network[9].

There are several types of microneedles, and can be classified according to their structure, composition, and mechanism of drug delivery. Each type of microneedle has unique advantages and disadvantages for different therapeutic applications, and for different types of drugs.

The most common use of solid microneedles is to create microchannels in the skin, and subsequently apply the drug formulation to the skin with a patch or a gel. The solid microneedle method of drug delivery is often referred to as the 'poke and patch' or 'poke and apply' method and increases drug permeability by creating micro-channels without loading the drug into the microneedles.

Coated microneedles are made by coating the surface of the microneedles with the drug formulation. The drug dissolves when the microneedle is inserted into the skin and is immediately released. This method is particularly advantageous for vaccines and for drugs that require a high degree of precision in dosage.Microneedles are made from biodegradable materials that contain drugs in their matrix that dissolve completely when inserted into the skin and release the drug over time in a controlled manner. This reduces sharp waste disposal, creating a safer environment for patients receiving the microneedle delivery.

Hollow microneedles can be used like standard needles; however, they can deliver a liquid drug formulation transcutaneously or through to the target site with precise control of the drug dosage and rate of delivery.

Microneedles can be made from many different materials including metals, silicon, ceramics and polymers. The earliest microneedles were typically made of silicon or metals such as stainless steel because of their strength and ease of fabrication. However, due to concerns regarding their

brittleness, high costs and low biocompatibility, there is now increased interest in the use of polymer based microneedles.

Dissolvable microneedles typically employ biodegradable materials such as polylactic acid (PLA), polyglycolic acid (PGA), polyvinylpyrrolidone (PVP) and hyaluronic acid. These materials provide many advantageous properties, such as biocompatibility, controlled degradation and ease of drug incorporation[10].

In general, drug delivery utilizing microneedles is carried out by creating microchannels in the skin and allowing for drug diffusion or direct deposition into the epidermis or dermis. After the microneedles penetrate the skin, there are several potential pathways for the drug to enter the body depending on the type of microneedleThere exist Three varieties of Microneedles: dissolve, hollow, and either coated or solid. When using dissolve microneedles, the drug will be released through the dissolution of the polymer matrix after it has absorbed interstitial fluid from the body. With the hollow types of microneedles, the liquid medication is injected into the skin directly through the hollow tip. Coated (or solid) microneedles will have the drug released when the coating has dissolved during administration by the microneedle entry into the skin; thus creating microchannels that enhance permeability.

Many different variables need to be considered when determining the efficacy of the drug delivery system including; length, density, insertion force used to deliver the needle, as well as the method of drug manufacture. Optimal parameters for each of these variables can result in consistent efficacy and reliability of drug delivery.

Additionally, due to their ability to target antigen-presenting cells for vaccine delivery and subsequently produce an immune response, microneedles have become an attractive option for mass vaccination programs, due to ease of use and ability to be administered without trained professional.

Microneedles also have been used in the management of chronic illnesses such as diabetes and other hormonal therapies with sustained and controlled release of the medication which increases the patients' compliance in their outpatient success[11].

Current research supports the potential for microneedles to facilitate effective transdermal delivery of biologics (i.e. proteins, peptides, and deoxyribonucleic acid) that are often difficult or impossible to deliver using traditional methods. Additionally, microneedles are being researched for potential treatments of common dermatological conditions such as acne, scarring, and skin rejuvenation.

Microneedles offer several advantages to the patient when compared to conventional drug delivery methods including minimal invasiveness, painless administration, better patient compliance, and the ability to deliver a wide range of medications with macromolecular size. Microneedling also lowers the risk of needle-stick injuries and can in many instances eliminate the need for traditional intramuscular injections.

Although there are many benefits associated with microneedling, there are also several disadvantages associated with microneedle delivery systems including complications during manufacturing, uncertainty of penetration depth into the skin, risk of irritation at the site of needle insertion, and limitations associated with large volume drug delivery[12].

Additionally, microneedles must be thoroughly evaluated for mechanical properties such as stability and strength for successful use when delivering drugs in this manner.

In conclusion, microneedle delivery systems represent an emerging and promising technology that could help overcome some of the limitations posed by current transdermal drug delivery methods, through delivery systems that are effective and painless for a wide variety of medications including biologics and vaccines. Continuous improvements in material development, manufacturing techniques, and overall system design are critical to the successful clinical applications of this technology[13].

5. Nanofiber-Based Transdermal Drug Delivery Systems

Nanofiber-based therapeutic systems offer a unique and novel platform for drug delivery via the skin (via transdermal systems). They are typically made from „nanofibers," which are drawn out using an electrospinning process. Nanofibers have a very large surface area compared to their volume (i.e., Surface Area-to-Volume Ratio), and a very high capacity for the incorporation of drugs, making them ideal for an extended release of drugs.

Nanofibers imitate the extracellular matrix (ECM) of biological tissues by providing a structural/functional environment to support cellular

attachment, growth, and tissue regeneration. As such, nanofibers are well suited for applications including transdermal drug delivery and tissue engineering, as well as in wound healing[14].

There are many different methods to manufacture nanofibers; however, electrospinning is the predominant method. Electrospinning uses a high voltage electric field to pull a liquid (i.e. a polymer solution) or a molten polymer (i.e. a molten polymer) to form fine fibers. The equipment utilized to electrospin nanofibers includes a syringe filled with a polymer solution, a high-voltage power source, and a collection plate.

There have been several novel arrangements of electrospinning created to increase its overall functionality. Coaxial arrangements have been designed for producing a core-shell structure. Emulsion electrospinning for encapsulating sensitive drugs is also common. There have been several multi-jet electrospinning arrangements that can produce nanofibers industrially in large volumes[15].

There have been other electrospinning methods that are being investigated as well, such as phase separation, self-assembly, and melt blowing; however, none has achieved the same level of popularity as electrospinning due to the relative simplicity and flexibility of electrospinning.

Natural vs. Synthetic Polymers Used in Nanofibers

Nanofibers can be fabricated using a variety of materials, including numerous types of natural and synthetic polymers. Natural polymers such as collagen, gelatin, chitosan and alginate are known for their high levels of biocompatibility and biodegradability. Synthetic polymers such as polycaprolactone (PCL), polyvinyl alcohol (PVA), polylactic acid (PLA) and poly(lactic-co-glycolic acid) (PLGA) have greater mechanical strength and will degrade at controlled rates[16].

In order to take advantage of both natural and synthetic polymers, it is common for manufacturers to blend the two types of polymers, producing nanofibers with properties that are well matched for mechanical strength, biocompatibility and drug delivery.

Drug Loading and Release Mechanisms

Drugs can be incorporated into nanofibers through a number of techniques, including blending with the polymer solution, adsorbing to the surface of the nanofiber, and encapsulating in the core of a core-shell arrangement. The various methods will affect drug distribution, stability and release kinetics.

The release of drugs from a nanofiber may occur through a combination of drug diffusion from the nanofiber, degradation of the polymer, and drug desorption from the nanofiber surface. Due to the high surface area of the nanofibers, the initial drug delivery will typically be rapid in comparison to the later phase absorbed by the body; i.e. the initial drug delivery will occur through a mechanism called burst release and the secondary drug delivery willThe release profile can be changed by changing parameters (i.e., fiber diameter, polymer composition, method of fabrication)[17].

Advanced nanofiber systems that are stimuli-responsive can also be developed for drug delivery at a future date by using external stimuli (such as pH, temperature, or humidity) to control when to administer a drug.

There is currently an extensive amount of research being conducted to determine the use of nanofibers in transdermal drug delivery, due to their ability to form an intimate contact with the skin and provide a sustained release of the drug. This type of therapy will especially benefit patients requiring localized treatment, such as those with a wound requiring a direct delivery of antimicrobials, growth factors, and anti-inflammatory medications[18].

Other therapeutic agents that can be delivered via transdermal systems using nanofibers include analgesics, anti-inflammatories, and anticancer agents. Nanofibers can also improve the solubility and bioavailability of poorly water-soluble drugs.

Additionally, nanofiber mats can be used with other technologies, such as microneedles, to develop hybrid systems that can assist in delivering the drug through the skin and improve the efficacy of drug delivery.

There are several advantages and disadvantages to a nanofiber-based drug delivery system. The most notable advantages include: high loading capacity for the drug, control and sustained drug release; adaptability of the design to the specific needs of individual patients; and good biocompatibility. In addition, nanofibers provide a very efficient mechanism for drug delivery to the skin and are expected to significantly enhance the therapeutic outcome for patients[19].

However, for widespread clinical use, several obstacles must be overcome before nanofibers can become more popular. Large-scale production of

nanofibers, variability in the morphology of the fibers produced, and the stability of the drug within the nanofiber must be thoroughly studied. Moreover, if a nanofiber were to provide an inappropriate burst release, there may be issues with its clinical usefulness, and therefore, its design would require specific optimization.

Due to their unique structural aspects, nanofibers afford a novel, versatile, and efficient option over traditional transdermal drug delivery products for clinical applications. As research continues and fabrication techniques improve through advancements in materials science, nanofibers should find many new applications. Continued research and development will address the existing limitations and provide for their clinical eventuality[14].

6. Microneedle–Nanofiber Hybrid Systems

A Hybrid System Overview

The microneedle and nanofiber systems present a new generation of transdermal drug delivery methods that utilize the advantages of both types of systems to address their respective limitations. Microneedles allow for efficient penetration into the skin through the stratum corneum and nanofibers provide an effective drug delivery platform due to their high capacity for drug loading and control release. Using these two systems in combination will improve healing rates (i.e. medicine) and the availability of drugs to patients via transdermal routes.

Hybrid systems are designed to deliver medication to patients in two steps: creating channels in the skin with the microneedle and then sustaining drug release through nanofiber matrices (coated to the microneedles or in patch form). This two-step approach allows for both rapid drug delivery (immediate drug effect) and prolonged drug delivery (timely regulation of drug delivery effect)[9].

Design and Manufacturing Methods of Hybrid Microneedle-Nanofiber Systems

Hybrid microneedle-nanofiber systems may be manufactured utilizing a wide variety of methods based on the target application (i.e., medical) and the characteristics of the drug itself. A very common method includes the coating of microneedle arrays with electrospun nanofibers containing drug solutions. In this application, the microneedles will penetrate the skin to deliver the drug. The nanofibers will dissolve or degrade upon contact with moisture and deliver the drug into the skin.

An additional method includes positioning the drug-loaded nanofibers over or under the microneedle arrays. The microneedle arrays first will create the microchannel and then the nanofibers will facilitate the diffusion of drug through the microchannel.Thus, it enhances the ability of the drugs to load more and release over a longer time frame in a controlled manner[20].

The development of coaxial electrospinning and other advanced techniques for fabrication of core-shell nanofibers make it possible to encapsulate sensitive drugs, and to control release kinetics accurately.

In many instances, biodegradable polymers or polylactic acid (PLA) are used to provide a safe means of drug delivery without requiring that they be removed following application.

Mechanistic Approach to Drug Delivery

Hybrid drug delivery systems are based on two mechanisms: (1) the mechanical disruption of the stratum corneum and (2) controlled diffusion.

When microneedles penetrate the stratum corneum of the skin, they create microholes or microchannels that lead to a reduction in skin barrier resistance by almost 100 times the initial skin barrier that was in place. Consequently, drugs that had previously been blocked from entering the skin can now enter the epidermis, while still having access to the dermis[21].

After penetration into the skin via the use of microneedles, the nanofiber component of the hybrid system enables the release of the drug by virtue of one or more mechanisms, including diffusion, polymer degradation, or the use of stimuli-responsive release mechanisms. Microchannels, which were created by the use of microneedles to penetrate the stratum corneum, serve as an additional means to increase drug permeation across the skin, leading to an increase in bioavailability of the drug and a faster onset of action[22].

The dual mechanisms by which these systems allow for both an immediate release of drug through direct delivery to the microchannels, as well as slow or sustained release of the drug due to controlled degradation of the nanofibers, make these hybrid systems especially useful for chronic therapy and localized treatment.

Therapeutic Applications of Hybrid Systems

Hybrid microneedle-nanofiber systems have demonstrated significant promise in a variety of therapeutic applications. For example, these systems can be used to effectively provide vaccine antigens

to immune cells in the skin, leading to enhanced immunogenicity and a reduction in the number of doses required.

In addition, hybrid systems can be used to provide effective means of local delivery of growth factors, anti-inflammatory drugs, and antimicrobial agents directly to a wound site, thereby enhancing the healing process and reducing the risk of infection. The nanofiber component of the hybrid system also provides a structural scaffold for the regeneration of skin tissue.

Other possible applications for hybrid microneedle-nanofiber systems include the delivery of anticancer drugs, hormones, biologics, etc. Because of their ability to deliver macromolecules and to achieve sustained release of drug, hybrid systems are expected to have considerable therapeutic potential in advanced therapeutic applications[23].

Advantages and Limitations

The most significant advantage of the use of hybrid microneedle-nanofiber systems is that they allow for enhanced penetration supplemented by controlled release of drug. Combining enhanced penetration with controlled drug release yields improvements in drug bioavailability, resulting in a decreased frequency of dose administration and increased patient compliance. Due to their minimally invasive method of drug delivery, microneedle-nanofiber hybrid systems can be self-administered without pain to the patient[24].

While hybrid systems have many advantages, they present several obstacles. Key obstacles include complexity of fabrication, scalability of production, and cost. Uniformity of microneedles and consistent properties of nanofibers are critical to ensure reliable functionality of the drug delivery system. Additionally, the long-term stability of drug-loaded nanofibers and regulatory issues will need to be addressed before hybrid systems can be made available for clinical use[25].

Hybrid microneedle-nanofiber systems represent a significant advancement in transdermal drug delivery and offer the possibility of means of transdermally delivering drug to the system in an efficient manner. The synergetic effects of combining the beneficial characteristics of microneedles with the benefits of nanofibers will allow hybrid systems to successfully address the limitations experienced with current transdermal drug delivery methodologies, and provide a new hope for the successful transdermal delivery of a wide variety of therapeutic agents. Ongoing research and continued technological development will further refine and optimize hybrid systems, and accelerate the clinical application of hybrid systems for transdermal delivery[26].

7. Future Perspectives

The redefined future of transdermal drug delivery is entering a new era through a new direction for research or development, called transformation within drug delivery and utilizing next-generation doses through new-inclusive methods[27]. The use of smart and/or functionalized polymers (microneedle technology), smart substances (nanofibers), and functional hybrid microsystems (smart devices), integrated with transdermal drug delivery systems, will allow for incremental growth globally. This combines advances made in research on biopharmaceuticals (biologics) and nanotechnology (nanobiotechnology) with advancements in medical devices, patient adherence/improved therapeutic outcomes, and personalized healthcare[28].

Some of the most significant potential developments are creating smart and responsive transdermal drug delivery systems or devices[29]. Smart and responsive systems can modify a drug's release and/or absorption based upon a physiological event (physiological signal) occurring in the body; physiological signals can include pH, temperature, glucose levels, and/or inflammatory markers. Currently, researchers are investigating the use of microneedles that respond to glucose as an adjunct to insulin therapy (e.g., diabetic)[30]. Utilizing a glucose-responsive microneedle for insulin delivery could provide for self-regulated glucose and insulin levels; self-regulating glucose/insulin without often having to rely on regular insulin injections would allow for better diabetes management[31].

Wearable electronics, biosensors, and transdermal delivery systems are an emerging trend. These hybrid platforms allow continuous real-time monitoring of physiological events and distribution of drug-based therapy according to the individual's needs; this enables closed-loop drug delivery. These systems have the potential for transforming chronic disease management by tracking personalized therapies for chronic diseases.

3D printing and additive manufacturing are also predicted to impact the future of transdermal drug delivery; researchers believe that new technologies will enable greater precision and accuracy in manufacturing microneedle arrays and nanofiber structures, and that these technologies will enable

the production of customized transdermal drug delivery systems tailored to the individual patient's requirements regarding microneedles and/or nanofibers to optimize the patient's personalized therapy.

The application of nanotechnology, alongside the development of new multifunctional materials, will continue to reinforce and improve the capabilities of transdermal drug delivery systems. For example, nanofibers can be modified with multifunctional nanoparticles (e.g., delivery bioactive materials, growth factors, and/or antimicrobial agents), thus combining the various therapeutic values into a single hybrid material. Similar to these examples, the use of biodegradable and dynamic polymers for microneedles, will enable more effective and secure delivery of medications than currently exist[32].

Development of hybrid systems, microneedle-nanofiber composites, will also gain continued momentum. The use of hybrid systems will have an incredible synergistic effect on the function of the microneedle and nanofiber devices by improving their penetration ability, controlling their rate of drug release, and improving therapeutic benefits to the patient.

As previously mentioned, however, before all of these new developments can be realized, certain challenges must be resolved. Such challenges include: achieving scalability in manufacturing, ensuring product stability throughout the product's commercial viability, obtaining regulatory approval of all new devices/products, and proving long-term safety and efficacy. Therefore, the establishment of fabrication standards and quality-control standards are essential for transdermal drug delivery to succeed in commercializing their systems[33].

The convergence of nanotechnology, biotechnology, and digital health technologies will have the largest impact on the future of transdermal drug delivery. With continued research and technological advancement, next-generation transdermal drug delivery systems (microneedles and nanofiber-based delivery systems) will be essential for developing more effective therapeutics and for enhancing drug delivery efficiencies while providing patient-centric, non-invasive, and personalized healthcare[34].

8. Conclusion

The mechanisms for transdermal delivery of pharmaceutical agents have changed from traditional passive patches to complex engineered devices capable of overcoming the formidable barrier of the stratum corneum. Currently, microneedle systems and nanofiber-based systems appear to be the most promising transdermal drug delivery systems, providing enhanced drug permeation, controlled/release of drug products, and increased patient compliance. Providing drugs through a minimally invasive technique, microneedles create temporary micro-channels in the skin for the rapid delivery of diverse drugs including macromolecules (proteins) and vaccines. Likewise, nanofiber-based systems have a high capacity for drug loading and provide tunable release rates from the nanofiber matrix, thereby making them an excellent choice for sustained/locally delivered drug products.

By utilizing both microneedle and nanofiber systems in a hybrid microneedle-nanofiber system, a significant increase in the effectiveness of drug delivery will occur relative to the benefits of rapid drug delivery via microneedles and sustained release of drug from nanofibers. Such hybrid systems have wide-ranging applications for treating and managing chronic disease, as well as wound healing and vaccination.

Despite these advances, several challenges remain as barriers to the translation of these technologies to clinical practice including; product scalability, formulation stability, manufacturing complexity, and regulatory approval. Collaborating and conducting work in the area of interdisciplinary research (participating in multiple types of disciplines) and leveraging technological advancement will be essential to overcome these obstacles.

In summary, advanced transdermal drug delivery systems provide a disruptive approach to the delivery of pharmaceutical products, and will ultimately enable the development of non-invasive, more efficient, and enhanced patient-centered therapies that advance precision medicine.

Ethical Approval and Consent to Participate

This article is a review study and does not involve any human participants or animals. Therefore, ethical approval and informed consent were not required for this work.

Consent for Publication

Not applicable.

Availability of Data and Materials

All data and information presented in this review are derived from previously published studies and publicly available sources. No new datasets were generated or analyzed during the current study.

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Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this paper.

Author Contributions

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Compliance with Ethical Standards

This manuscript complies with all applicable ethical standards for research and publication

References:

1. Brown, M.B., et al., *Dermal and transdermal drug delivery systems: current and future prospects.* Drug delivery, 2006. **13**(3): p. 175-187.
2. Hiwrale, A., et al., *Nanofibers: A current era in drug delivery system.* Heliyon, 2023. **9**(9).
3. Kamble, P., et al., *Nanofiber based drug delivery systems for skin: A promising therapeutic approach.* Journal of Drug Delivery Science and Technology, 2017. **41**: p. 124-133.
4. Wickett, R.R. and M.O. Visscher, *Structure and function of the epidermal barrier.* American journal of infection control, 2006. **34**(10): p. S98-S110.
5. Sbarbati, A., et al., *Subcutaneous adipose tissue classification.* European journal of histochemistry: EJH, 2010. **54**(4): p. e48.
6. Bachmann, M.F. and G.T. Jennings, *Vaccine delivery: a matter of size, geometry, kinetics and molecular patterns.* Nature Reviews Immunology, 2010. **10**(11): p. 787-796.
7. Elias, P.M., *Structure and function of the stratum corneum permeability barrier.* Drug Development Research, 1988. **13**(2-3): p. 97-105.
8. Gendelberg, N.R., *Diffusivity of drug actives in transdermal drug delivery (TDD).* 2016.
9. Waghule, T., et al., *Microneedles: A smart approach and increasing potential for transdermal drug delivery system.* Biomedicine & pharmacotherapy, 2019. **109**: p. 1249-1258.
10. Prausnitz, M.R., *Microneedles for transdermal drug delivery.* Advanced drug delivery reviews, 2004. **56**(5): p. 581-587.
11. Jiang, S., et al., *Experimental study of needle–tissue interaction forces: effect of needle geometries, insertion methods and tissue characteristics.* Journal of biomechanics, 2014. **47**(13): p. 3344-3353.
12. Reinke, A., et al., *The advantages of microneedle patches compared to conventional needle-based drug delivery and biopsy devices in medicine.* Biomedical Engineering Advances, 2024. **8**: p. 100127.
13. Mdanda, S., et al., *Recent advances in microneedle platforms for transdermal drug delivery technologies.* Polymers, 2021. **13**(15): p. 2405.
14. Kumar, L., et al., *Nanofiber as a novel vehicle for transdermal delivery of therapeutic agents: challenges and opportunities.* Future Journal of Pharmaceutical Sciences, 2021. **7**(1): p. 175.
15. Alghoraibi, I. and S. Alomari, *Different methods for nanofiber design and fabrication.* Handbook of nanofibers, 2018. **1**: p. 46.
16. Keshvardoostchokami, M., et al., *Electrospun nanofibers of natural and synthetic polymers as artificial extracellular matrix for tissue engineering.* Nanomaterials, 2020. **11**(1): p. 21.
17. Monfared, M., et al., *Emerging frontiers in drug release control by core–shell nanofibers: A review.* Drug metabolism reviews, 2019. **51**(4): p. 589-611.
18. Mirhaj, M., et al., *Emerging treatment strategies in wound care.* International Wound Journal, 2022. **19**(7): p. 1934-1954.
19. Alfadhel, M., *Nanofiber-based drug delivery systems: a review on its applications, challenges, and envisioning future perspectives.* Current drug delivery, 2026. **23**(1): p. 44-55.
20. Tarbox, T.N., et al., *An update on coating/manufacturing techniques of microneedles.* Drug delivery and translational research, 2018. **8**(6): p. 1828-1843.

21. Gomaa, Y.A., et al., *Effects of microneedle length, density, insertion time and multiple applications on human skin barrier function: assessments by transepidermal water loss.* Toxicology in Vitro, 2010. **24**(7): p. 1971-1978.
22. Gowda, B.J., et al., *Stimuli-responsive microneedles as a transdermal drug delivery system: a demand-supply strategy.* Biomacromolecules, 2022. **23**(4): p. 1519-1544.
23. Pachuau, L., *Recent developments in novel drug delivery systems for wound healing.* Expert opinion on drug delivery, 2015. **12**(12): p. 1895-1909.
24. Swaminathan, J., *Electrospinning nanofiber insert for anterior ocular drug delivery for cataract treatment: A thesis submitted in partial fulfilment of the requirements for the Degree of Doctor of Philosophy at Lincoln University*. 2023, Lincoln University.
25. Khan, A., et al., *Comprehensive review of hybrid energy systems: challenges, applications, and optimization strategies.* Energies, 2025. **18**(10): p. 2612.
26. Modi, D. and B.G. Prajapati, *Processed Excipients for Transdermal Drug Delivery*, in *Processed Excipients in Advanced Drug Delivery*. 2025, Apple Academic Press. p. 287-318.
27. Alkilani, A.Z., et al., *Beneath the skin: a review of current trends and future prospects of transdermal drug delivery systems.* Pharmaceutics, 2022. **14**(6): p. 1152.
28. Wang, Y., et al., *Advances in microneedle technology for skin wound healing: integrating nanomaterials and intelligent drug delivery systems.* Nanoscale, 2025. **17**(32): p. 18505-18533.
29. Liu, D., et al., *The smart drug delivery system and its clinical potential.* Theranostics, 2016. **6**(9): p. 1306.
30. Traitel, T., R. Goldbart, and J. Kost, *Smart polymers for responsive drug-delivery systems.* Journal of Biomaterials Science, Polymer Edition, 2008. **19**(6): p. 755-767.
31. Mo, R., et al., *Emerging micro-and nanotechnology based synthetic approaches for insulin delivery.* Chemical society reviews, 2014. **43**(10): p. 3595-3629.
32. Rabiei, M., et al., *Nanomaterial and advanced technologies in transdermal drug delivery.* Journal of drug targeting, 2020. **28**(4): p. 356-367.
33. Al-Jawadi, S., P. Capasso, and M. Sharma, *The road to market implantable drug delivery systems: a review on US FDA's regulatory framework and quality control requirements.* Pharmaceutical development and technology, 2018. **23**(10): p. 953-963.
34. Panahi, O., *The future of medicine: converging technologies and human health.* Journal of Bio-Med and Clinical Research. RPC Publishers, 2025. **2**(1).