

Review Article

Emerging Technologies in Transdermal Drug Delivery

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A B S T R A C T

Transdermal drug delivery (TDD) represents a promising alternative to traditional oral and injectable routes, offering non-invasive, controlled, and sustained administration of therapeutic agents. The various advanced TDD techniques, including microneedles, iontophoresis, sonophoresis, and nanotechnology-based systems, which address the inherent challenges of skin permeability and drug stability. Microneedles, including coated, dissolving, and hydrogel-forming types, enhance drug delivery through minimally invasive means, improving patient compliance. Iontophoresis utilizes mild electric currents to drive charged drug molecules across the skin, while sonophoresis employs ultrasound waves to increase skin permeability through mechanisms such as cavitation and thermal effects. Nanotechnology-based systems, including liposomes, solid lipid nanoparticles, nanoemulsions, polymeric nanoparticles, dendrimers, and nanocrystals, offer versatile platforms for enhanced drug solubility, stability, and targeted delivery.

Keywords: Transdermal, Drug Delivery, Solid Lipid Nanoparticles, Microneedles

Introduction

Transdermal drug delivery systems have gained attention due to their ability to provide continuous and controlled drug release, improve bioavailability, and enhance patient compliance. However, the stratum corneum, the outermost layer of the skin, poses a significant barrier to drug penetration. Emerging technologies aim to overcome this barrier, enabling the delivery of a wider range of therapeutic agents.¹

Microneedle-Based Systems

Microneedles (MNs) represent a breakthrough in TDDS by creating microchannels in the skin to facilitate drug delivery. These microchannels bypass the stratum corneum, allowing direct access to deeper skin layers.

Types of Microneedles

- **Solid Microneedles:** Create microchannels through which drugs can be applied. Solid microneedles are a

type of microneedle used for transdermal drug delivery. These tiny, needle-like structures, typically made of solid materials like silicon, metals, or polymers, are designed to penetrate the outer layer of the skin (stratum corneum) to deliver therapeutic agents directly into the dermis or epidermis. Solid microneedles are typically less than 1 mm in length, allowing them to pierce the skin without reaching nerve endings, thereby reducing pain. They are made from materials such as silicon, stainless steel, titanium, or biocompatible polymers. Microneedles can come in various shapes (e.g., conical, pyramidal) to optimize skin penetration and drug delivery efficiency.² Solid microneedles can be used in two main ways: Poke and Patch. In this method, microneedles are used to create microchannels in the skin, and then a drug-containing patch is applied over these microchannels to allow for enhanced drug absorption. Coated Microneedles The surface of solid

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microneedles is coated with the drug. Upon insertion into the skin, the drug is deposited in the upper layers of the skin. Microneedles can deliver vaccines directly into the skin, which is rich in immune cells, potentially enhancing the immune response. They are used for the administration of medications like insulin, hormones, and pain management drugs. Microneedles are also used in dermatology for treatments such as anti-aging, scar reduction, and enhancing the delivery of cosmetic products. Due to their small size, microneedles cause less pain compared to traditional hypodermic needles. Easier and less painful administration improves patient compliance, especially for chronic conditions requiring regular injections. Direct delivery to the skin can improve the bioavailability of certain drugs. Precise fabrication is required to ensure the microneedles are strong enough to penetrate the skin without breaking. Some drugs may not be stable when coated on microneedles or may require special handling. New drug delivery systems like microneedles must undergo rigorous testing and approval processes.³

- **Coated Microneedles:** Coated microneedles represent an innovative advancement in transdermal drug delivery systems. These devices consist of tiny needles, often measuring less than a millimeter in length, which are coated with a drug formulation. Upon application to the skin, these microneedles painlessly penetrate the stratum corneum, the outermost layer of the skin, allowing the coated drug to dissolve and be absorbed into the underlying dermal tissue and eventually into the bloodstream.⁴ This method offers a minimally invasive alternative to traditional hypodermic needles, providing a significant reduction in patient discomfort and anxiety associated with needle injections. The design and material composition of coated microneedles can vary, but they are typically made from biocompatible materials such as silicon, stainless steel, or polymers. The drug coating is meticulously applied using techniques like dip-coating, spray-coating, or inkjet printing to ensure precise dosing. Once the microneedles pierce the skin, the drug coating rapidly dissolves, facilitating efficient drug delivery.⁵ This approach is particularly advantageous for delivering vaccines, peptides, proteins, and other therapeutics that are unstable or poorly absorbed when administered orally. One of the key benefits of coated microneedles is their ability to enhance patient compliance, especially among populations that are needle-phobic or have difficulty with self-administration of injectable medications. Additionally, they can provide a more controlled and sustained release of drugs, improving therapeutic outcomes. Coated microneedles also reduce the risk of needlestick injuries and cross-contamination, which are

significant concerns in healthcare settings. Furthermore, because they can be designed for self-administration, they hold the potential to reduce healthcare costs by minimizing the need for medical personnel during drug administration.⁶

- **Dissolving Microneedles:** Dissolving microneedles are an advanced type of transdermal drug delivery system designed to overcome many of the limitations associated with traditional drug administration methods. These microneedles are composed of biodegradable and biocompatible materials that dissolve completely in the skin after delivering their therapeutic payload. Unlike coated microneedles, which leave behind a solid needle structure, dissolving microneedles break down and are absorbed by the body, eliminating the need for removal and reducing waste and the risk of needlestick injuries. The fabrication of dissolving microneedles involves embedding drugs within a matrix of dissolvable polymers such as hyaluronic acid, polyvinylpyrrolidone (PVP), or carboxymethyl cellulose.⁷ These polymers are carefully selected for their safety, compatibility with various drugs, and ability to form strong, sharp microneedle structures. Upon insertion into the skin, the microneedles rapidly dissolve, releasing the drug in a controlled manner. This process ensures that the drug is delivered directly into the dermal or subdermal layers, enhancing its bioavailability and therapeutic efficacy. One of the primary advantages of dissolving microneedles is their ability to deliver a wide range of therapeutics, including small molecules, proteins, peptides, vaccines, and even nucleic acids. This versatility makes them suitable for numerous medical applications, from routine vaccinations to the treatment of chronic conditions such as diabetes and cancer. Furthermore, the use of dissolving microneedles can significantly improve patient compliance, especially for those who are needle-phobic or require frequent dosing.⁸ The painless and easy-to-use nature of these microneedles makes them an attractive option for self-administration, potentially reducing the burden on healthcare systems. In addition to their clinical benefits, dissolving microneedles offer several practical and logistical advantages. Since they dissolve completely, there is no need for sharps disposal, which simplifies waste management and reduces the risk of environmental contamination. This attribute is particularly beneficial in resource-limited settings where proper disposal of medical waste can be challenging. Moreover, dissolving microneedles can be produced at a relatively low cost using scalable manufacturing processes, making them accessible for widespread use.⁹

- **Hydrogel-Forming Microneedles:** Hydrogel-forming microneedles are an innovative type of transdermal drug delivery system that combines the benefits of microneedle technology with the unique properties of hydrogels. These microneedles are composed of water-swollen, crosslinked polymer networks capable of absorbing significant amounts of biological fluids while maintaining their structural integrity.[10] Unlike dissolving or coated microneedles, hydrogel-forming microneedles are designed to remain intact within the skin, creating a continuous conduit for drug delivery or fluid extraction. The fabrication of hydrogel-forming microneedles involves the use of biocompatible and biodegradable polymers such as polyvinyl alcohol (PVA), methacrylated hyaluronic acid, or chitosan. These materials are engineered to form a solid yet flexible microneedle array that can penetrate the skin's stratum corneum without breaking. Upon insertion, the microneedles rapidly absorb interstitial fluid, causing them to swell and form a hydrogel matrix. This swelling action creates microscopic channels through which drugs can diffuse from a reservoir patch into the skin, allowing for sustained and controlled release of therapeutics. One of the standout features of hydrogel-forming microneedles is their ability to provide prolonged and steady drug delivery. This is particularly advantageous for medications that require consistent plasma levels over extended periods, such as hormones, pain relievers, or chronic disease treatments. Additionally, because the hydrogel matrix can be engineered to respond to specific stimuli, such as pH or temperature changes, it is possible to create responsive delivery systems that release drugs in response to physiological cues, enhancing therapeutic precision and efficacy.¹¹ Hydrogel-forming microneedles also offer significant benefits for patient compliance and convenience. They are generally painless to apply, causing minimal discomfort compared to traditional injections. This makes them suitable for self-administration, which can improve adherence to treatment regimens, especially for individuals who require regular medication. Furthermore, because the hydrogel matrix is biocompatible and biodegradable, these microneedles do not leave behind any residual material, reducing the risk of infection or irritation.[12]

Iontophoresis

Iontophoresis is an advanced non-invasive transdermal drug delivery technique that uses a mild electric current to enhance the penetration of drugs through the skin. This method leverages the principles of electromigration and electroosmosis to facilitate the movement of charged and neutral molecules, respectively, into the skin and underlying tissues. Iontophoresis is particularly useful for delivering a

variety of therapeutic agents, including small molecules, peptides, and even macromolecules, that otherwise have limited ability to permeate the skin's natural barrier.

Mechanism of Action

Iontophoresis operates through two primary mechanisms:

- **Electromigration:** The application of an electric field drives charged drug molecules across the skin. Positively charged molecules are repelled from the anode (positive electrode) and attracted to the cathode (negative electrode), while negatively charged molecules move in the opposite direction. This movement enhances the concentration gradient across the skin, promoting greater drug penetration.¹³
- **Electroosmosis:** When an electric current is applied, it induces the movement of water and other neutral molecules across the skin through a process called electroosmosis. This is particularly effective for the transdermal delivery of neutral or weakly charged molecules. The electric field creates a solvent flow that can carry these molecules through the skin's aqueous pathways.

Iontophoresis significantly enhances the permeability of the skin, allowing for the effective delivery of drugs that are typically difficult to administer transdermally. This includes large molecules and hydrophilic drugs that do not easily penetrate the stratum corneum. **Controlled and Targeted Delivery:** The technique allows precise control over the rate and extent of drug delivery by adjusting the electric current. This precision helps in achieving targeted therapeutic effects, reducing the risk of systemic side effects. **Non-Invasive and Painless:** Iontophoresis is a non-invasive method, causing minimal to no discomfort compared to traditional injections. This makes it particularly suitable for patients who are needle-phobic or require frequent medication administration. **Reduced Risk of Infection:** Since iontophoresis does not involve skin penetration with needles, the risk of infection is significantly lower. This enhances patient safety and comfort. **Versatility in Drug Types:** Iontophoresis can be used to deliver a wide range of therapeutic agents, including ions, peptides, proteins, and small molecules. This versatility makes it applicable in various medical fields, from dermatology to pain management and hormone replacement therapy.^[13,14]

Sonophoresis

Sonophoresis, also known as phonophoresis or ultrasound-enhanced transdermal delivery, is a non-invasive technique that utilizes ultrasound waves to enhance the permeation of drugs through the skin. By applying ultrasound at specific frequencies, sonophoresis increases the skin's permeability, allowing larger molecules and a wider range of therapeutic agents to penetrate the stratum corneum and reach systemic circulation.

Mechanism of Action

Sonophoresis enhances transdermal drug delivery through several mechanisms:

- **Cavitation:** Ultrasound waves create microscopic gas bubbles within the skin's intercellular lipid matrix. These bubbles oscillate and collapse, disrupting the lipid structure and creating temporary pathways that increase the permeability of the skin.
- **Thermal Effects:** The absorption of ultrasound energy generates heat, which can enhance the fluidity of the stratum corneum lipids and increase skin permeability. This thermal effect facilitates the diffusion of drugs into deeper layers of the skin.¹⁵
- **Mechanical Pressure:** Ultrasound waves exert mechanical pressure on the skin, which can increase the intercellular spaces and enhance the movement of drug molecules across the skin barrier.
- **Microstreaming:** The oscillation of ultrasound waves induces microstreaming, which refers to localized fluid movement around the oscillating bubbles. This can enhance the transport of drug molecules through the skin by disrupting the skin barrier and promoting drug diffusion.

Sonophoresis significantly improves the permeability of the skin, allowing a broader range of drugs, including larger and more complex molecules, to be delivered transdermally. This expands the potential for transdermal drug delivery to include a wider variety of therapeutic agents. [16] Similar to other non-invasive methods, sonophoresis is painless and does not cause the discomfort associated with needle-based drug delivery. This makes it more acceptable to patients and improves compliance, especially for those who require frequent administration of medication. Sonophoresis allows for controlled and localized drug delivery by adjusting the ultrasound parameters, such as frequency, intensity, and duration. This precision enhances therapeutic outcomes by ensuring that the drug is delivered to the desired site in optimal concentrations. Sonophoresis can be used to deliver a wide range of therapeutic agents, including hydrophilic and hydrophobic drugs, peptides, proteins, and even nanoparticles. This versatility makes it a valuable tool for various medical applications, from pain management to hormone replacement therapy. By enhancing localized drug delivery, sonophoresis can reduce the required systemic dose and minimize the risk of systemic side effects. This targeted approach can improve the safety profile of drugs, particularly those with narrow therapeutic windows. [17,18]

Nanotechnology-Based Systems

Nanotechnology-based systems represent a significant advancement in the field of transdermal drug delivery. These systems utilize nanoparticles to enhance the

delivery of drugs through the skin, overcoming many of the limitations associated with traditional transdermal methods. Nanoparticles, due to their small size and unique properties, can improve drug stability, bioavailability, and targeted delivery, making them highly effective for a wide range of therapeutic applications.

Types of Nanoparticles Used in Transdermal Delivery

- **Liposomes:** These are spherical vesicles composed of lipid bilayers, which can encapsulate both hydrophilic and hydrophobic drugs. Liposomes enhance drug absorption through the skin by merging with the skin's lipid layers, facilitating the delivery of their payload.
- **Solid Lipid Nanoparticles (SLNs):** These are composed of solid lipids and can carry lipophilic drugs. SLNs provide controlled release and enhance the stability of the encapsulated drug, protecting it from degradation.^{4,5,6}
- **Nanoemulsions:** These are fine oil-in-water or water-in-oil emulsions with droplet sizes in the nanometer range. Nanoemulsions increase drug solubility and penetration through the skin, improving bioavailability.
- **Polymeric Nanoparticles:** These are made from biodegradable polymers like PLGA (poly(lactic-co-glycolic acid)). They can be engineered to release drugs in a controlled manner and can be functionalized for targeted delivery.
- **Dendrimers:** These are highly branched, tree-like structures with numerous surface functional groups. Dendrimers can enhance drug solubility and facilitate targeted delivery through skin penetration enhancers.¹⁹
- **Nanocrystals:** These are pure drug particles with sizes in the nanometer range. Nanocrystals increase the surface area of the drug, enhancing its dissolution rate and permeability through the skin.

Nanoparticles can penetrate the stratum corneum more effectively than larger particles. Their small size and surface properties allow them to navigate through the skin's lipid matrix, improving drug delivery to deeper layers. Nanoparticles can be engineered to release drugs in a controlled manner over an extended period. This sustained release profile ensures consistent therapeutic levels of the drug, reducing the frequency of administration. Nanoparticles can protect drugs from degradation by encapsulating them, thereby improving their stability. [20] They also enhance the solubility of poorly water-soluble drugs, increasing their bioavailability. Nanoparticles can be functionalized with ligands that target specific cells or tissues, ensuring that the drug is delivered precisely to the desired site. This targeted approach minimizes systemic side effects and maximizes therapeutic efficacy. Nanoparticles can encapsulate a wide range of therapeutic agents, including small molecules, peptides, proteins,

and nucleic acids. This versatility makes them suitable for various medical applications, from pain management to cancer therapy. By enhancing localized drug delivery and reducing systemic exposure, nanoparticles minimize the risk of side effects commonly associated with traditional drug delivery methods.²¹

Advantages

- **Improved Patient Compliance**

Minimally invasive and painless transdermal drug delivery systems, such as microneedles, significantly enhance patient compliance. Traditional drug delivery methods like hypodermic injections often cause discomfort, pain, and anxiety, particularly in needle-phobic individuals. These negative experiences can lead to poor adherence to prescribed treatments, especially those requiring frequent administration. Transdermal systems, being virtually painless and easy to use, make the process more acceptable and less intimidating, encouraging patients to follow their treatment regimens consistently, thereby improving therapeutic outcomes.

- **Reduced Risk of Infection**

The minimally invasive nature of transdermal drug delivery systems reduces the risk of infection compared to traditional injection methods. Hypodermic needles penetrate deep into tissues, creating a potential pathway for pathogens to enter the body. In contrast, microneedles and other transdermal devices typically penetrate only the outermost layers of the skin, minimizing the entry points for bacteria and viruses. This shallow penetration significantly lowers the likelihood of infections, enhancing patient safety and reducing the burden on healthcare systems to manage injection-related complications.^{11,14,17}

- **Enhanced Safety and Convenience**

Transdermal drug delivery systems offer substantial safety and convenience benefits. Patients can often self-administer these treatments at home without the need for professional assistance, reducing the frequency of hospital visits and associated healthcare costs. This independence is particularly beneficial for managing chronic conditions, as it allows patients to maintain their treatment schedules without interruption. Additionally, the reduced need for skilled healthcare professionals to administer these treatments alleviates the demand on medical resources, freeing up healthcare workers to focus on more critical tasks.²²

- **Steady and Controlled Drug Release**

One of the key advantages of transdermal drug delivery systems is their ability to provide steady and controlled drug release. Unlike traditional oral medications, which can lead to fluctuations in drug levels in the bloodstream, transdermal systems offer a sustained release of medication over an extended period. This consistent delivery

can enhance the therapeutic efficacy of drugs, reduce the frequency of dosing, and minimize side effects associated with peak concentrations of medication. It is particularly advantageous for medications that require precise plasma levels for optimal effectiveness, such as hormones and pain relievers.

- **Non-Invasive Monitoring and Diagnostic Potential**

Transdermal drug delivery systems, particularly hydrogel-forming microneedles, also hold potential for non-invasive monitoring and diagnostics. These systems can be designed to absorb interstitial fluid, allowing for the continuous monitoring of biomarkers. This capability enables real-time health monitoring and early detection of diseases, facilitating timely interventions. The dual functionality of drug delivery and diagnostics makes these systems versatile tools in modern healthcare, contributing to more personalized and responsive treatment strategies.^{9,10}

- **Reduced Environmental Impact**

Minimally invasive transdermal systems, especially those made from biodegradable materials, contribute to reduced environmental impact. Traditional needles and syringes generate significant medical waste that requires careful disposal to avoid environmental contamination. In contrast, microneedles and other transdermal devices made from biodegradable polymers dissolve or degrade within the body or in the environment, minimizing medical waste and simplifying disposal processes. This eco-friendly aspect is particularly important in resource-limited settings where waste management infrastructure may be lacking.

- **Broader Range of Therapeutic Applications**

Minimally invasive and painless transdermal drug delivery systems are versatile and can be used for a wide range of therapeutic applications. They are suitable for delivering small molecules, peptides, proteins, vaccines, and even nucleic acids. This versatility makes them applicable for various medical needs, from routine vaccinations to the treatment of chronic diseases like diabetes and cancer. The ability to deliver a broad spectrum of therapeutics enhances the applicability of transdermal systems, making them a valuable addition to the pharmaceutical and medical device arsenal.²³

Challenges

Limited Drug Permeability

One of the primary challenges of transdermal drug delivery is the limited permeability of the skin. The stratum corneum, the outermost layer of the skin, serves as a formidable barrier that protects the body from external substances. While this barrier function is crucial for preventing infections and dehydration, it also restricts the types and sizes of molecules

that can be effectively delivered through the skin. Large, hydrophilic, or highly charged molecules often struggle to penetrate the stratum corneum, limiting the range of drugs that can be administered transdermally.¹⁴ Overcoming this barrier requires innovative formulations and delivery mechanisms, such as microneedles, iontophoresis, or the use of permeation enhancers, which can complicate the development process.

Variable Skin Conditions

The effectiveness of transdermal drug delivery systems can be influenced by the condition of the patient's skin, which can vary significantly among individuals and over time. Factors such as age, skin hydration, thickness, integrity, and the presence of conditions like psoriasis or eczema can affect drug absorption. These variables make it challenging to achieve consistent and predictable drug delivery across different patient populations. Formulations must be robust enough to perform effectively under varying skin conditions, necessitating extensive testing and optimization.¹⁰

Limited Drug Load Capacity

Transdermal systems are often limited by the amount of drug they can carry and deliver. The skin's limited permeability means that only small quantities of drug can be effectively absorbed over a given period. This constraint makes it difficult to use transdermal delivery for drugs that require high doses or have low potency. Achieving therapeutic levels can be challenging, particularly for treatments requiring sustained high concentrations of the active ingredient. Advanced formulation techniques and materials science are required to maximize drug loading and release rates while maintaining the stability and efficacy of the drug.²¹

Stability of Drug Formulations

Ensuring the stability of drug formulations within transdermal systems is another significant challenge. Drugs must remain stable and effective throughout the shelf life of the product and during the application period on the skin. Factors such as temperature, humidity, and exposure to light can affect the stability of the drug and the delivery system. Additionally, the interactions between the drug and the materials used in the transdermal patch or microneedles must be carefully managed to prevent degradation or loss of efficacy. This requires meticulous formulation development and rigorous testing to ensure long-term stability.²⁴

Skin Irritation and Sensitization

Prolonged or repeated use of transdermal drug delivery systems can sometimes lead to skin irritation or sensitization. Adhesives used in patches, permeation enhancers, or the active drug itself can cause adverse skin reactions, ranging from mild redness and itching to more severe dermatitis.

Managing these side effects is crucial for maintaining patient comfort and compliance. Developers must carefully select and test materials to minimize the risk of irritation and ensure the safety of the delivery system over extended use.

Technological and Manufacturing Challenges

The production of transdermal drug delivery systems, especially those involving advanced technologies like microneedles, requires sophisticated manufacturing processes. Ensuring the precision and consistency of microneedle arrays, maintaining sterility, and scaling up production can be complex and costly. The integration of drug formulation into these systems without compromising their structural integrity or delivery efficiency adds another layer of complexity. Manufacturers must invest in specialized equipment and adhere to stringent quality control measures to produce effective and reliable transdermal products.^{4,5}

Regulatory and Approval Hurdles

Gaining regulatory approval for transdermal drug delivery systems can be challenging due to the need for comprehensive safety and efficacy data. Regulatory agencies, such as the FDA and EMA, require rigorous testing to demonstrate that the delivery system can consistently achieve the desired therapeutic outcomes without causing harm to patients. This includes extensive clinical trials to assess the system's performance across different populations and conditions. Navigating the regulatory landscape requires significant time, resources, and expertise, which can be a barrier for smaller companies or novel technologies.

Cost and Accessibility

The development and production of advanced transdermal drug delivery systems can be expensive, potentially limiting their accessibility to patients. The high costs associated with research, development, manufacturing, and regulatory compliance can translate to higher prices for the end products. This cost factor can make transdermal systems less accessible to patients in lower-income regions or those without comprehensive healthcare coverage. Efforts to reduce production costs and improve the affordability of these systems are crucial for ensuring their widespread adoption and impact.¹⁰

Complex Pharmacokinetics

The pharmacokinetics of drugs delivered through the skin can be complex and unpredictable. Factors such as the drug's molecular weight, solubility, and interaction with the skin layers can affect its absorption, distribution, metabolism, and excretion. Additionally, the variability in skin conditions among patients adds another layer of complexity to predicting drug behavior. Achieving consistent and controlled pharmacokinetics requires thorough understanding and precise control over the formulation

and delivery mechanisms, which can be challenging and resource-intensive.¹¹

Conclusion

Emerging technologies in transdermal drug delivery are revolutionizing the way drugs are administered, offering non-invasive, controlled, and efficient alternatives to traditional methods. Microneedles, iontophoresis, sonophoresis, and nanotechnology-based systems each present unique advantages and challenges. Continued innovation and research in this field will likely lead to significant advancements in healthcare, improving the quality of life for patients worldwide.

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