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REVIEW ARTICLE

# A Review on Microneedle-Based Transdermal Drug Delivery Systems

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**Abstract:** Microneedles are minimally invasive transdermal drug delivery systems consisting of microscopic projections that penetrate the stratum corneum to facilitate drug administration. These devices range from 25-2000 µm in length and are fabricated using various materials including metals, polymers, and biodegradable substances. The fundamental classifications encompass solid microneedles that create temporary channels, coated microneedles carrying drugs on their surface, hollow microneedles enabling direct fluid transport, and dissolving microneedles that release encapsulated drugs upon degradation. The fabrication processes involve techniques such as photolithography, micromolding, and 3D printing, with each method optimized for specific microneedle designs and materials. Therapeutic applications extend across multiple domains, particularly in treating superficial cancers through various modalities including chemotherapy, photodynamic therapy, and immunotherapy. For cancer treatment, microneedles enable localized drug delivery, reducing systemic toxicity while maintaining therapeutic efficacy. In managing inflammatory skin conditions like psoriasis and atopic dermatitis, microneedles facilitate targeted delivery of anti-inflammatory agents and biologics directly to affected areas. The technology demonstrates significant potential in wound healing, particularly for diabetic and infected wounds, by delivering growth factors and antimicrobial agents precisely to the wound bed. Additional applications include aesthetic dermatology, vaccine delivery, and diagnostic sampling. Current research focuses on developing smart materials, improving drug loading capacity, and enhancing long-term stability while maintaining cost-effectiveness and patient compliance.

**Keywords:** Microneedles; Transdermal drug delivery; Cancer therapy; Wound healing; Skin disorders.

## 1. Introduction

The practice of delivering therapeutic agents through the skin has deep historical roots, spanning several millennia across various civilizations. Ancient healing traditions recognized the skin as a viable route for administering medicinal compounds. The Greeks made particularly notable contributions by developing sophisticated topical formulations that combined therapeutic agents with natural oils and botanical extracts [1]. These early innovations laid the groundwork for modern transdermal drug delivery systems, though the scientific principles underlying skin absorption remained unknown for centuries. The late 19th century marked a pivotal moment in transdermal drug delivery when Bourget conducted groundbreaking experiments demonstrating the systematic absorption of salicylic acid through intact skin [2]. This discovery initiated a new era of scientific investigation into transdermal drug administration, prompting researchers to explore the skin's potential as a therapeutic interface systematically.

Modern drug delivery systems face numerous challenges that impact their therapeutic efficacy. Oral administration, while convenient, often results in significantly reduced bioavailability. This reduction occurs primarily due to first-pass metabolism in the liver and extensive enzymatic degradation throughout the gastrointestinal tract [3]. The limitations of oral delivery are particularly pronounced for protein-based therapeutics and other sensitive biological compounds. Injectable medications, administered through hypodermic needles, present their own set of challenges. While they bypass many of the limitations associated with oral delivery, injections frequently cause pain and anxiety in patients. These psychological barriers often lead to reduced treatment compliance. Additionally, the requirement for trained healthcare professionals to administer injections increases healthcare costs and reduces accessibility, particularly in resource-limited settings [4].

The skin's sophisticated barrier function, particularly the stratum corneum, presents significant challenges for drug delivery. This outermost layer, measuring approximately 10-15 µm in thickness, serves as a highly effective barrier against external substances. Its unique structure limits the passive diffusion of molecules, generally preventing the absorption of compounds larger than 400-500 Daltons [5]. This limitation has historically restricted the use of conventional transdermal patches to a small subset of therapeutic agents, primarily small lipophilic molecules, while excluding larger biological therapeutics such as proteins, peptides, and vaccines

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[6]. The development of microneedle technology represents a significant breakthrough in addressing these limitations. The concept was first proposed in 1976, but significant technical advances didn't occur until the late 1990s, coinciding with developments in microelectronics fabrication techniques [7]. This innovative approach creates temporary microchannels in the skin that bypass the stratum corneum barrier without stimulating deeper nerve endings, thereby enabling painless drug delivery. Microneedles effectively bridge the gap between traditional transdermal systems and injectable medications, offering the advantages of both while minimizing their respective limitations [8]. This technology has opened new possibilities in drug delivery, enabling the administration of a broader range of therapeutic agents through the transdermal route while maintaining patient comfort and compliance.

**Table 1. Current Commercial Development Status of Microneedle Products**

| Company | Product | Technology | Application | Regulatory Status |
|---|---|---|---|---|
| 3M | Microtrans | Solid | Drug delivery | FDA cleared |
| Zosano | ZP-PTH | Coated | Osteoporosis | Phase III |
| Corium | MicroCor | Dissolving | Vaccines | Phase II |
| BD Technologies | Soluvia | Hollow | Influenza vaccine | Approved (EU) |
| Vaxxas | Nanopatch | Solid | Vaccination | Clinical trials |

## 2. Transdermal Drug Delivery Systems

### 2.1. Skin Structure and Drug Penetration

The skin consists of three primary layers: epidermis, dermis, and hypodermis. The epidermis, particularly its outermost stratum corneum, functions as the main barrier against external substances [9]. This barrier comprises corneocytes arranged in a "brick and mortar" pattern, with intercellular lipids forming highly organized lamellar structures [10]. Drug molecules must navigate this complex architecture through intercellular, transcellular, or appendageal routes [11].

### 2.2. Conventional Transdermal Delivery Methods

Traditional transdermal delivery systems rely on passive diffusion through intact skin. These include:

*2.2.1. Matrix Systems*

Matrix-type patches incorporate drugs within a polymer matrix, controlling release through diffusion kinetics [12]. The release rate depends on drug solubility, partition coefficient, and matrix properties [13].

*2.2.2. Reservoir Systems*

These systems contain liquid drug reservoirs with rate-controlling membranes, offering more precise control over drug release but requiring careful design to prevent dose dumping [14].

*2.2.3. Skin Permeation Enhancement Techniques*

Various methods have been developed to improve skin permeability, including:

- Chemical enhancers that disrupt lipid organization
- Iontophoresis using electrical current
- Sonophoresis employing ultrasound waves
- Electroporation creating temporary pores through electrical pulses [15]

## 3. Microneedles

### 3.1. Principle

Microneedles function by creating microscopic channels through the stratum corneum, enabling direct access to the viable epidermis or dermis. The optimal penetration depth ranges from 50-900 μm, deep enough to bypass the primary barrier while avoiding stimulation of dermal nerve endings [16]. This approach combines the patient compliance advantages of transdermal patches with the delivery efficiency of hypodermic needles [17].

### 3.2. Classification of Microneedles

#### *3.2.1. Solid Microneedles*

Solid microneedles represent the earliest and structurally simplest category of microneedle design. These devices typically consist of arrays of sharp, solid projections fabricated from metals or polymers. The primary mechanism involves creating temporary microchannels in the skin, followed by the application of drug formulations that diffuse through these channels [18]. Silicon and stainless steel remain the predominant materials for solid microneedle fabrication due to their excellent mechanical properties and biocompatibility [19]. The 'poke and patch' approach characterizes their application method, where skin perforation precedes drug application, while the 'coat and poke' method involves drug coating directly on the microneedle surface [20].

**Table 2. Classification of Microneedles and Their Characteristics**

| Type | Material | Length Range | Mechanism | Advantages | Limitations |
|---|---|---|---|---|---|
| Solid | Silicon, Metal, Polymer | 150-700 µm | Pre-treatment followed by drug application | Simple fabrication, Strength | Two-step application |
| Coated | Stainless steel, Titanium | 200-800 µm | Drug coated on needle surface | Quick dissolution, Direct delivery | Limited drug loading |
| Dissolving | PVA, PVP, Hyaluronic acid | 400-900 µm | Complete dissolution in skin | No sharp waste, Controlled release | Storage stability concerns |
| Hollow | Silicon, Metal, Glass | 500-1500 µm | Active fluid flow through bore | Precise volume control | Complex fabrication |
| Hydrogel-forming | Cross-linked polymers | 400-1000 µm | Swelling upon skin insertion | Controlled release, Safety | Slower onset |

#### *3.2.2. Coated Microneedles*

Coated microneedles advance the basic solid design by incorporating drug formulations directly onto the microneedle surface. The coating process demands precise control over uniformity and thickness to ensure consistent drug delivery [21]. Various coating techniques have been developed, including dip coating, spray coating, and electrohydrodynamic atomization. Each method offers specific advantages in terms of coating uniformity and drug loading capacity [22]. The selection of coating materials critically influences drug stability and release kinetics, with common excipients including surfactants, viscosity enhancers, and stabilizing agents [23].

#### *3.2.3. Hollow Microneedles*

Hollow microneedles incorporate internal channels that enable fluid flow through the needle shaft. This design permits active fluid delivery and precise control over administration rates [24]. The fabrication process typically involves sophisticated microfabrication techniques including deep reactive ion etching and laser drilling. Critical design parameters include channel diameter, wall thickness, and tip geometry, all of which influence flow dynamics and mechanical strength [25]. The hollow architecture facilitates the delivery of larger volumes compared to solid or coated designs, making them particularly suitable for vaccine delivery and biological drug administration [26].

#### *3.2.4. Dissolving Microneedles*

Dissolving microneedles represent an innovative approach where the entire needle structure dissolves within the skin after insertion. These devices are fabricated from biocompatible, water-soluble polymers or sugars that encapsulate the therapeutic agent within their matrix [27]. Common materials include polyvinylpyrrolidone, hyaluronic acid, and various polysaccharides. The dissolution rate can be tailored through material selection and formulation optimization [28]. This design eliminates concerns about needle disposal and reduces the risk of needle stick injuries. The drug loading capacity depends on the polymer matrix properties and drug stability during the fabrication process [29].

#### *3.2.5. Hydrogel-Forming Microneedles*

Hydrogel-forming microneedles combine the advantages of traditional hydrogel materials with microneedle technology. Upon insertion, these needles absorb interstitial fluid, forming continuous hydrogel channels that facilitate controlled drug release [30]. The crosslinked polymer networks can be designed to respond to specific stimuli such as pH, temperature, or enzymatic activity, enabling smart drug delivery [31]. The swelling behavior and mechanical properties of these systems can be precisely controlled through polymer selection and crosslinking density [32].

## 4. Fabrication Methods

### 4.1. Materials Selection

The choice of materials for microneedle fabrication significantly influences device performance, drug stability, and manufacturing feasibility [33]. Material requirements extend beyond mechanical strength to include biocompatibility, degradation characteristics, and drug compatibility.

### 4.2. Fabrication Methods

*4.2.1. Photolithography and Etching*

Photolithography represents a fundamental microfabrication technique extensively used for silicon and metal microneedles. The process involves precise pattern transfer using photoresist materials, followed by selective etching to create the desired needle geometry [34]. Deep reactive ion etching enables the formation of high aspect ratio structures with controlled sidewall profiles. The optimization of etching parameters, including gas composition, power, and duration, determines the final microneedle morphology [35].

**Table 3. Common Fabrication Methods for Microneedles**

| Method | Materials Used | Resolution | Cost | Scale-up Potential | Key Features |
|---|---|---|---|---|---|
| Photolithography | Silicon, SU-8 | < 1 μm | High | Moderate | High precision |
| Micromolding | Polymers | 5-10 μm | Low | High | Mass production |
| 3D Printing | Photopolymers | 10-50 μm | Medium | High | Design flexibility |
| Laser Cutting | Metals, Polymers | 20-100 μm | Medium | Moderate | Rapid prototyping |
| Drawing Lithography | Thermoplastics | 50-200 μm | Low | High | Simple process |

*4.2.2. Micromolding Techniques*

Micromolding offers scalable production of polymer-based microneedles through master template replication. The process begins with master mold fabrication, typically using photolithography or precision machining [36]. Various molding approaches include injection molding, investment molding, and solvent casting. The selection of molding parameters critically influences the reproduction fidelity and mechanical properties of the final product. Temperature control during polymer filling and demolding stages ensures optimal structure preservation [37].

*4.2.3. Drawing and Thermal Forming*

Drawing lithography enables the fabrication of high-aspect-ratio microneedles through controlled polymer drawing and solidification. The process involves heating thermoplastic materials above their glass transition temperature, followed by precise elongation and cooling [38]. This method offers advantages in producing sharp tip geometries and complex three-dimensional structures. Process parameters including drawing speed, temperature profile, and cooling rate determine the final needle morphology [39].

**Table 4. Characterization Parameters for Microneedles**

| Parameter | Method | Acceptance Criteria | Significance |
|---|---|---|---|
| Mechanical Strength | Force measurement | >0.058 N/needle | Skin penetration capability |
| Sterility | USP <71> | No growth | Safety |
| Drug Content | HPLC/UV | 90-110% | Dosing accuracy |
| Dissolution Rate | Franz cell | >80% in 30 min | Drug release |
| Penetration Depth | OCT/Histology | >50% of length | Delivery efficiency |

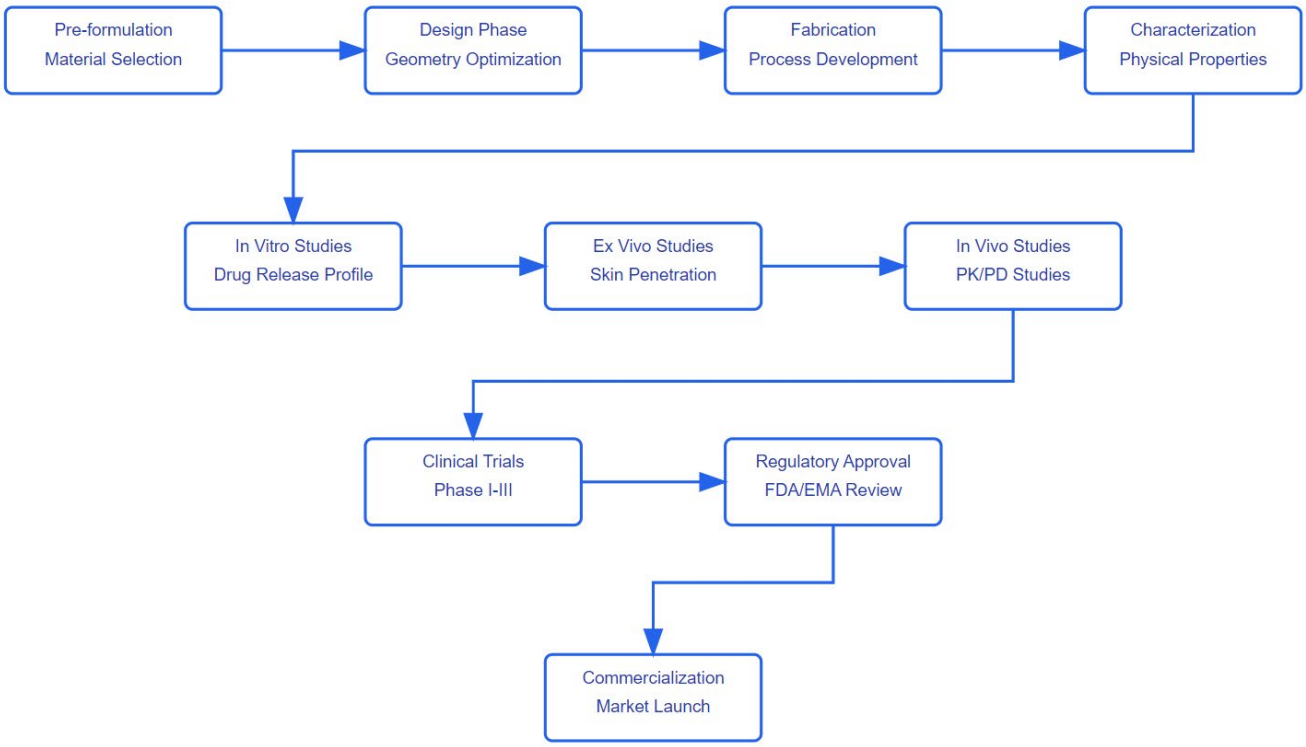


**Figure 1. Process for Microneedle Development**

## 5. Therapeutic Applications

### 5.1. Cancer Treatment

Microneedle-mediated chemotherapy delivery represents a significant advancement in localized cancer treatment. The approach enables direct delivery of cytotoxic agents to tumor sites while minimizing systemic exposure [40]. Advanced designs incorporate pH-responsive elements that enhance drug release in the acidic tumor microenvironment. Studies demonstrate improved therapeutic efficacy with reduced side effects compared to conventional systemic administration [41]. Drug loading strategies include both direct incorporation into dissolving matrices and surface modification of solid microneedles with drug-loaded nanocarriers [42].

The integration of photodynamic therapy with microneedle technology enhances the delivery of photosensitizers to target tissues. Specialized microneedle designs facilitate both photosensitizer delivery and light transmission [43]. The approach enables precise control over treatment depth and photosensitizer distribution. Clinical studies report improved outcomes in treating superficial skin cancers through enhanced photosensitizer penetration and activated oxygen species generation [44].

Microneedle platforms for cancer immunotherapy focus on delivering immune modulators and checkpoint inhibitors directly to the tumor microenvironment [45]. The approach leverages the skin's rich immune cell population to enhance antitumor responses. Sophisticated designs incorporate multiple immunotherapeutic agents within single arrays, enabling synchronized delivery of combination therapies [46]. The technology demonstrates particular promise in melanoma treatment, where local immune activation correlates with improved systemic responses [47].

### 5.2. Inflammatory Skin Conditions

*5.2.1. Psoriasis*

Microneedle-based approaches for psoriasis treatment focus on delivering anti-inflammatory agents and immunomodulators directly to affected skin layers. Advanced formulations incorporate methotrexate, corticosteroids, and biological agents within dissolving microneedle matrices [48]. The technology enables precise targeting of the epidermis-dermis junction, where psoriatic inflammation predominantly occurs. Studies demonstrate enhanced drug penetration and improved clinical outcomes compared to conventional topical treatments [49]. Novel designs incorporating pH-responsive elements facilitate selective drug release in inflammatory microenvironments, optimizing therapeutic efficacy while minimizing systemic exposure [50].

*5.2.2. Atopic Dermatitis*

Microneedle systems for atopic dermatitis deliver both anti-inflammatory agents and skin barrier restoration compounds. The approach addresses both immune dysregulation and barrier dysfunction characteristic of the condition [51]. Specialized formulations combine corticosteroids with moisturizing agents in single microneedle arrays. Clinical evaluations demonstrate reduced disease severity scores and improved barrier function parameters following microneedle-based interventions [52]. Recent innovations include microneedles loaded with probiotics and antimicrobial peptides to modulate skin microbiota [53].

### 5.3. Wound Healing

Microneedle technology offers unique advantages in treating diabetic wounds through controlled delivery of growth factors and therapeutic proteins. The design enables bypass of compromised vasculature characteristic of diabetic wounds [54]. Advanced systems incorporate multiple growth factors with controlled release profiles to optimize healing progression. Studies report accelerated wound closure and enhanced granulation tissue formation compared to conventional treatments [55]. Integration of glucose-responsive elements enables smart delivery systems that respond to local metabolic conditions [56].

Antimicrobial microneedle systems provide targeted delivery of antibiotics directly to infection sites. The approach enables higher local drug concentrations while minimizing systemic exposure [57]. Novel designs incorporate biofilm-disrupting agents alongside conventional antibiotics. Research demonstrates enhanced efficacy against antibiotic-resistant strains through improved drug penetration into biofilm structures [58]. Recent developments include microneedles with integrated infection detection capabilities through pH or enzyme-responsive elements [59].

### 5.4. Diagnosis

Microneedle platforms increasingly serve dual therapeutic and diagnostic functions. Advanced designs enable interstitial fluid sampling for continuous monitoring of biomarkers [60]. Integration of electrochemical sensors allows real-time detection of glucose, proteins, and metabolites. The technology demonstrates particular promise in diabetes management through combined glucose monitoring and insulin delivery [61]. Novel approaches incorporate multiplexed sensing capabilities for simultaneous detection of multiple analytes [62].

### 5.5. Vaccines

Microneedle-based vaccination represents a significant advancement in immunization technology. The approach targets skin-resident immune cells, potentially enhancing immune responses compared to traditional intramuscular delivery [63]. Specialized designs enable stable vaccine incorporation and controlled release profiles. Clinical studies demonstrate comparable or superior immunogenicity with reduced antigen doses compared to conventional vaccination methods [64]. Recent developments focus on thermostable formulations for improved vaccine stability and cold chain independence [65].

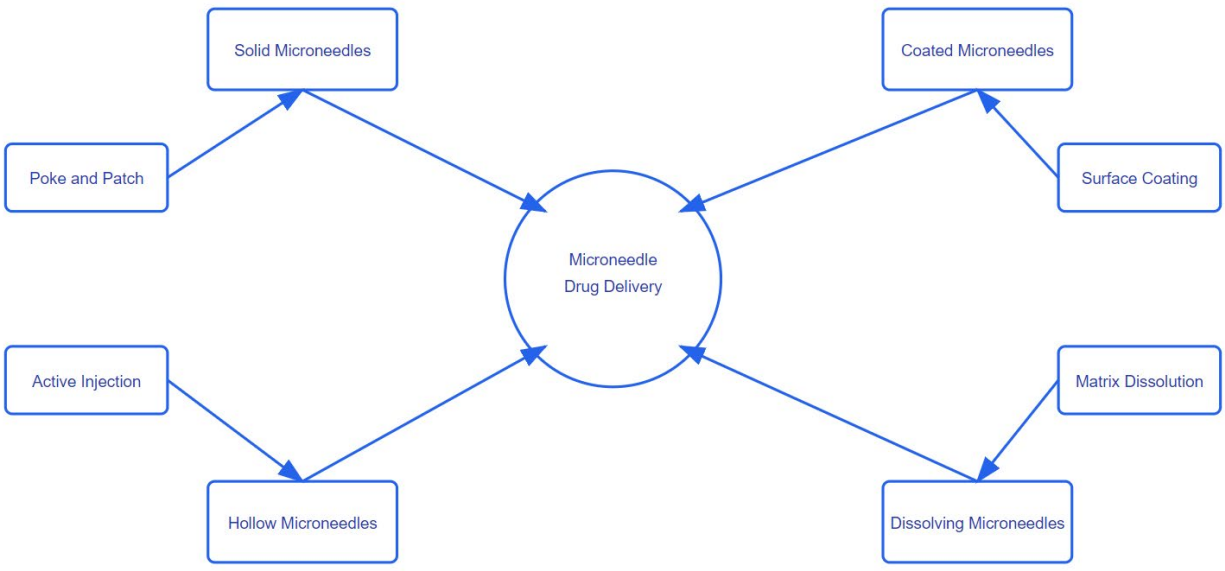


**Figure 2. Mechanisms of Microneedle Drug Delivery**

## 6. Conclusion

The success of microneedle technology in cancer treatment, inflammatory conditions, and wound healing has established its potential as a transformative platform in healthcare delivery. The ability to provide targeted, controlled release of therapeutic agents while maintaining patient comfort and compliance positions microneedles as a promising alternative to traditional delivery methods. However, several challenges remain to be addressed for widespread clinical adoption. Manufacturing scalability, long-term stability, and regulatory compliance continue to require attention. The optimization of production processes to ensure consistent quality while maintaining cost-effectiveness remains crucial. The addition of stimuli-responsive materials and advanced sensing capabilities will enable more precise control over drug delivery based on physiological conditions. Development of self-regulating systems that can adjust therapeutic delivery in response to biological markers represents a promising direction for personalized medicine. Advances in 3D printing and automated production techniques will improve manufacturing efficiency and reduce costs. The application of microneedle technology is expected to expand into new therapeutic areas, including gene therapy, cell delivery, and regenerative medicine. Continued clinical validation across different therapeutic applications will strengthen the evidence base for microneedle technology. Long-term safety and efficacy data will support broader acceptance in clinical practice.

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