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Review Article

Microneedle-Based Transdermal Systems for Vaccines and Biologics: A Review

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ABSTRACT

Traditional vaccine and biologic delivery via intramuscular or subcutaneous injections is often limited by pain, needle-related anxiety, infection risk, and the requirement for trained healthcare personnel. Microneedle-based transdermal systems have emerged as a promising alternative, offering a minimally invasive, painless, and patient-friendly approach for administering macromolecules. These systems employ tiny projections that penetrate the stratum corneum to deliver therapeutic agents directly into the dermis, a layer abundant in immune cells and vascular networks. A variety of microneedle designs—including solid, coated, dissolving, hollow, and hydrogel-forming types—have been engineered to deliver vaccines, peptides, proteins, and nucleic acid-based biologics. Both preclinical and clinical studies have demonstrated their potential to elicit strong immune responses while enhancing patient compliance. Despite these advantages, challenges such as large-scale manufacturing, biologic stability, and regulatory approval continue to hinder widespread implementation. This review focuses on the recent advances, applications, obstacles, and future directions of microneedle-based transdermal delivery systems for vaccines and biologics.

INTRODUCTION

Vaccination remains one of the most effective public health strategies for preventing infectious diseases. Traditionally, vaccines and biologics are administered via hypodermic needles, which, despite their efficacy, have notable limitations. Pain during injection, the risk of needle-stick injuries, and the reliance on trained healthcare personnel pose challenges for large-scale immunization, especially in low-resource settings (Kim et al., 2012). Additionally, biologics such as proteins, peptides, and nucleic acids are large molecules with poor oral bioavailability, due to enzymatic degradation and limited intestinal absorption, necessitating parenteral administration (Prausnitz, 2017).

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Microneedle-based transdermal systems have emerged as a promising alternative for delivering macromolecules. These systems employ micron-sized projections that painlessly penetrate the skin's outer barrier, the stratum corneum, without reaching nerve-rich deeper layers (Ding et al., 2020). By delivering antigens directly to the dermal layer, which is rich in immune cells, microneedles are particularly well-suited for vaccination and biologic administration. This review examines the underlying principles, current applications, and future prospects of microneedle-based delivery systems for vaccines and biologics.

Types and Designs of Microneedles:

Microneedles can be classified into five primary types according to their design, fabrication material, and drug delivery mechanism. Each type offers distinct advantages and is selected based on the therapeutic agent, intended release profile, and specific clinical application.

1. Solid Microneedles:

Description: Solid, sharp projections that form microscopic pores in the stratum corneum, following a "poke and patch" approach.

Mechanism: The microneedles first create channels in the skin, after which the drug is applied via a gel or patch.

Materials: Commonly made from stainless steel, silicon, or polymers.

Applications: Used to enhance the permeability of small molecules and in preclinical vaccine studies.

Advantages/Limitations: Simple and straightforward design; however, it requires a two-step application process.

2. Coated Microneedles:

Description: Solid microneedles coated with a thin layer of drug or vaccine.

Mechanism: Follows a "coat and poke" approach, where the coating dissolves upon insertion to release the therapeutic agent.

Materials: Metals such as titanium or stainless steel, and silicon.

Applications: Delivery of vaccines including influenza, hepatitis B, and DNA-based vaccines.

Advantages/Limitations: Provides rapid drug release, but has limited drug-loading capacity.

3. Dissolving Microneedles

Description: Microneedles fabricated from water-soluble polymers that encapsulate the drug or vaccine.

Mechanism: Upon insertion into the skin, the microneedles dissolve, releasing the therapeutic agent directly into the dermal layers.

Materials: Biodegradable polymers such as polyvinylpyrrolidone (PVP), carboxymethylcellulose (CMC), or hyaluronic acid.

Applications: Delivery of vaccines, peptides, proteins, and other macromolecules.

Advantages/Limitations: Enables painless, single-step delivery with minimal waste; however, mechanical strength may be limited compared to solid microneedles.

4. Hollow Microneedles

Description: Microneedles with a hollow bore that allows direct infusion of liquid drugs or vaccines into the skin.

Mechanism: Therapeutic agents are injected through the hollow channels into the dermal or epidermal layers.

Materials: Metals (stainless steel, titanium), silicon, or polymers.

Applications: Delivery of vaccines, proteins, peptides, and other liquid biologics.

Advantages/Limitations: Allows precise dosing and continuous delivery; however, fabrication is complex and there is a risk of clogging.

5. Hydrogel-forming Microneedles

Description: Microneedles made from swellable hydrogel materials that absorb interstitial fluid to form a continuous conduit for drug delivery.

Mechanism: Upon insertion, the microneedles swell and allow the controlled diffusion of the therapeutic agent from a connected patch or reservoir into the skin.

Materials: Biocompatible polymers such as crosslinked poly(methylvinylether-co-maleic acid), polyvinyl alcohol, or polyethylene glycol derivatives.

Applications: Sustained and controlled delivery of vaccines, proteins, peptides, and other macromolecules.

Advantages/Limitations: Enables prolonged and controlled drug release with minimal invasiveness; however, manufacturing complexity and slow drug release may be limiting factors.

Comparative Summary of Microneedle Designs

Type	Drug Loading	Release Profile	Typical Applications	Limitations
Solid	External patch/gel	Sustained (via pores)	Permeation enhancers, vaccines	Two-step process
Coated	Surface coating	Rapid (minutes)	Vaccines, DNA delivery	Limited loading
Dissolving	Encapsulated polymer	Rapid to sustained	Insulin, vaccines, mAbs	Limited strength
Hollow	Liquid in lumen	Controlled infusion	High-dose biologics	Risk of clogging
Hydrogel-forming	From external reservoir	Sustained (hours–days)	Peptides, proteins, vaccines	Requires reservoir

Each microneedle type offers specific advantages and limitations, which depend on the physicochemical properties of the biologic and the intended therapeutic outcome (Larrañeta et al., 2016).

Mechanism of Transdermal Delivery:

The human skin serves as a robust barrier, with the stratum corneum restricting the penetration of most hydrophilic and large molecules. Microneedles bypass this barrier by forming microchannels that reach the viable epidermis or dermis. This allows direct interaction with antigen-presenting cells (APCs), including Langerhans cells and dermal dendritic cells, which play a pivotal role in initiating immune responses (van der Maaden et al., 2012). Targeted delivery to these immune-rich layers enhances vaccine immunogenicity while reducing systemic exposure.

Applications in Vaccines and Biologics:

Vaccines:

- *Influenza Vaccines:* Clinical studies have shown that microneedle patches delivering influenza antigens can elicit immune

responses that are comparable or superior to those achieved with intramuscular injections (Rouphael et al., 2017).

- *COVID-19 Vaccines:* Experimental microneedle platforms have been investigated for both mRNA and protein-based COVID-19 vaccines, offering advantages such as improved thermostability and potential for self-administration.

- *Polio and Measles Vaccines:* Preclinical studies indicate promising immunogenicity with enhanced thermostability, which may help overcome storage challenges in resource-limited settings.

Biologics:

- *Insulin:* Dissolving microneedles loaded with insulin have demonstrated effective glycemic control in diabetic animal models.

- *Monoclonal Antibodies:* Early research suggests potential for both localized and systemic delivery using microneedles.

- *Nucleic Acid Therapeutics:* Microneedles have been employed for DNA- and RNA-based vaccines, enhancing gene expression and immune responses compared to traditional injection methods.

Challenges and Limitations:

While microneedle-based transdermal delivery systems have shown considerable promise in both preclinical and clinical studies, their adoption as widely used therapeutic products remains limited. The barriers to translation include challenges in formulation development, device engineering, large-scale manufacturing, regulatory approval, and user acceptance.

1. Formulation Stability:

Biologics, including proteins, peptides, and nucleic acids, are inherently unstable and susceptible to degradation under stress conditions such as heat, moisture, or mechanical pressure. During microneedle fabrication, processes like casting, drying, or coating can expose these biologics to harsh conditions, potentially compromising their structural integrity and biological activity. For instance, dissolving microneedles composed of sugars or polymers may absorb atmospheric moisture, reducing mechanical strength and diminishing drug stability. Maintaining biologic activity throughout the shelf life of microneedle products remains a significant and unresolved challenge.

2. Dose Uniformity and Loading Capacity:

Achieving accurate and consistent drug loading in microneedles remains a technical challenge. Coated microneedles can exhibit variability in coating thickness, whereas dissolving microneedles are limited in drug capacity due to size constraints. These limitations are particularly critical for biologics that require higher therapeutic doses, such as monoclonal antibodies. Inconsistent or insufficient dosing may lead to suboptimal therapeutic effects or variability in patient responses.

3. Mechanical Strength and Penetration Consistency:

Effective microneedle delivery requires adequate mechanical strength to penetrate the stratum corneum without fracturing. Microneedles composed of biodegradable polymers or sugars can be fragile, risking breakage during insertion, which may result in incomplete drug delivery or safety concerns from retained fragments in the skin. Additionally, penetration depth and

consistency can be influenced by factors such as skin thickness, elasticity, and insertion force, raising challenges for dose reproducibility across diverse patient populations.

4. Manufacturing and Scalability:

Scaling microneedle production from laboratory to industrial levels remains a major challenge. Techniques such as micromolding, laser cutting, and photolithography require specialized equipment and can be expensive when applied at large scale. Ensuring consistent quality, sterility, and performance across mass-produced batches is difficult. Additionally, incorporating biologics into microneedle systems without compromising their stability during large-scale manufacturing continues to be an area of active research.

5. Regulatory and Quality Control Challenges:

Unlike traditional injections or oral dosage forms, microneedle patches are considered combination drug-device products, which adds complexity to regulatory approval. Agencies such as the FDA and EMA have limited specific guidelines for microneedle systems, creating uncertainties in clinical trial design, quality control, and approval pathways. Furthermore, establishing long-term safety, skin tolerability, and equivalence to conventional delivery methods requires extensive data, which can further extend development timelines.

6. Cost and Accessibility:

While microneedle systems are intended to lower healthcare costs by reducing the need for trained personnel, their initial production and specialized fabrication equipment can make them more expensive than conventional injections in the short term. For large-scale vaccination programs in low- and middle-income countries, affordability and supply chain logistics remain significant challenges.

7. Patient Acceptance and Human Factors:

Although microneedles are typically painless, patient perception and acceptance can vary. Some individuals may hesitate to adopt novel delivery technologies due to unfamiliarity or concerns about their effectiveness compared to conventional injections. Furthermore, successful self-administration requires clear instructions, training, and confidence to ensure proper patch adhesion and accurate drug delivery. Improper application could result in incomplete penetration and diminished therapeutic efficacy.

8. Limited Clinical Data:

Although numerous preclinical studies and early-stage clinical trials have demonstrated promising outcomes, large-scale, long-term clinical data remain limited. Comprehensive information on immunogenicity, durability of protection, and safety across diverse populations is necessary before widespread regulatory approval and commercialization can be achieved.

Microneedle-based transdermal systems continue to face technical, regulatory, and social challenges that impede their rapid transition from research laboratories to routine clinical practice. Addressing these obstacles will require advancements in biologic stabilization, reliable manufacturing processes, standardized regulatory frameworks, cost-effective production strategies, and enhanced patient education. Collaborative efforts among academia, industry, and regulatory authorities are critical to accelerate clinical adoption and fully realize the potential of this innovative technology.

FUTURE PERSPECTIVES:

Microneedle-based transdermal systems have the potential to revolutionize vaccine and biologic delivery, but realizing their full impact depends on progress in several areas, including materials science, device engineering, formulation development, clinical application, and regulatory pathways. Key future directions include:

1. Thermostable and Long-Term Formulations:

A major challenge for vaccines and biologics is their reliance on the cold chain. Many protein- and nucleic acid-based vaccines require refrigeration, restricting global accessibility, especially in low-resource settings.

Future research is focusing on developing thermostable microneedle formulations that remain stable at ambient temperatures for extended periods, thereby lowering storage and transportation costs.

Examples include sugar-based dissolving microneedles and polymeric encapsulation methods, both of which help protect the therapeutic payload from degradation.

2. Smart and Responsive Microneedles:

Emerging microneedle designs can be engineered to respond to physiological stimuli, including pH, glucose levels, temperature, or enzymatic activity. Smart micro needles could enable on-demand drug release, for instance:

Anti-inflammatory peptides released at sites of localized inflammation. Insulin is secreted in response to increased blood glucose levels. Integration with biosensors could enable closed-loop systems, connecting real-time monitoring with automatic, responsive drug release.

3. Integration with Wearable and Digital Health Devices :

The combination of microneedle patches with wearable electronics enables continuous biomarker monitoring alongside controlled biologic delivery. Future designs may incorporate IoT-connected patches, allowing remote monitoring by healthcare providers and adherence tracking for chronic therapies. This approach holds particular promise for diabetes management, long-term vaccination, and hormone replacement therapy.

4. Expanding Therapeutic Applications:

Beyond vaccines, microneedles show potential applications in cancer immunotherapy, gene therapy, and biologic-based therapies. For example:

- Cancer vaccines delivered transdermally to activate local immune cells.
- mRNA therapies delivered directly to the skin to reduce systemic toxicity.
- Monoclonal antibody delivery via microneedles to reduce injection frequency.

5. Advanced Fabrication and 3D Printing:

Current micro needle manufacturing commonly relies on micromolding and lithography, methods that can be costly and challenging to scale.

3D printing and laser-assisted fabrication are emerging as scalable alternatives, enabling:

- Complex geometries care being developed to enhance skin penetration and optimize drug release.
- Customizable microneedle patches can be customized to suit individual patients or specific therapeutic agents.

- Rapid prototyping enables the development and testing of experimental vaccines and biologics.

6. Regulatory Harmonization and Standardization:

Regulatory approval continues to be a key barrier to the widespread clinical adoption of microneedles. Future efforts should focus on establishing global guidelines for their safety, efficacy, and quality control. Standardization will support faster clinical trials, promote global adoption of microneedle vaccines in mass immunization programs, and ensure consistency in manufacturing, drug loading, and mechanical performance.

7. Patient-Centric Design and Acceptability:

Future microneedle systems will prioritize usability, convenience, and aesthetics to improve patient compliance. Potential features include painless self-administration, minimal training requirements, and compact patch designs that still provide sufficient drug capacity for multi-dose delivery.

CONCLUSION:

Microneedle-based transdermal systems represent a transformative approach for delivering vaccines and biologics. By enabling painless administration, enhancing immunogenicity, and supporting potential self-application, they overcome many limitations associated with traditional injections. While technical, manufacturing, and regulatory challenges persist, ongoing advances in materials science, device engineering, and clinical evaluation are poised to establish microneedles as a mainstream drug delivery platform in the near future.

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