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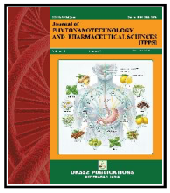

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Microneedles: A novel approach in transdermal drug delivery system

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Abstract

The transdermal route of drug administration has gradually assumed an important place alongside not only oral but also conventional parenteral methods, as it offers many benefits over them, such as better patient compliance, controlled and continuous drug release, and fewer systemic side effects. Among the several methods of transdermal delivery, microneedles (MNs) are the most innovative ones, providing a way for very small needles to penetrate the skin barrier without drawing blood and at the same time allowing the delivery of a wide range of therapeutic agents, from vaccines, insulin, analgesics, anticancer drugs, to biologics. Recent studies have confirmed that MN systems are effective in treating diseases such as diabetes mellitus, chronic pain, skin cancers, and infectious diseases; thereby revealing their clinical potential. The present article is a review of microneedle systems and is a comprehensive study concerning their classification, mechanisms of action, fabrication methodologies, and applications in the pharmaceutical and biomedical fields. Moreover, it discusses the limitations of current MN technologies, such as drug loading capacity, mechanical strength, and regulatory challenges, and outlines prospects, including smart, stimuli-responsive, and 3D-printed microneedle systems. This reference is a comprehensive one for undergraduate and postgraduate students, researchers, and professionals who are working on the design, validation, and clinical application of micro needle-based transdermal drug delivery systems.

1. Introduction

The microneedle idea was suggested for the first time in the 1970s; however, it only became practical after the microfabrication and materials science breakthroughs in the late 1990s. Since that time, the microneedle technology has developed very quickly, adopting innovative designs and materials like metals, silicon, polymers, and biodegradable compounds. Such devices have been realised as an effective way for vaccine, insulin, hormones, and even nanoparticle delivery. Microneedles are basically a hybrid system of transdermal and injectable systems with minimal invasive process, easy to use, targeting areas for drug delivery locally or systemically with better absorption and bioavailability. Microneedles find their application in the fields of cosmetics, biosensing, and even diagnostics, which is a reflection of their enormous usability.

Skin is the body's main line of defence against the external world, and the outermost layer of skin (stratum corneum) is the main barrier to drug penetration through the skin (Prausnitz and Lanzer, 2008). In the case of traditional drug delivery, *i.e.,* oral and parenteral methods, several drawbacks like low bioavailability, gastrointestinal destruction, first-pass metabolism, pain, and patient non-compliance happen to be among the hurdles (Henry *et al.,* 1998). Transdermal drug delivery systems (TDDS) have gradually taken over the traditional methods due to their advantages of controlled, sustained release of therapeutic agents, and at the same time avoiding gastrointestinal and hepatic metabolism (Bao *et al.,* 2022).

Among multiple technologies used in the field of transdermal drug delivery systems, microneedles (MNs) have been a subject of great interest because they can penetrate the stratum corneum and enhance drug permeation without causing pain and at the same time they do not affect the nerve-rich deeper dermis area (Donnelly *et al*., 2012). MNs are defined as needle-sized projections which range from a few hundred to a thousand micrometres in length (100-1000 µm). They create very small holes or pores in the skin that allow polar or macromolecular drugs to overcome the skin barrier very efficiently. The use of MNs includes a wide range of therapeutic areas such as diabetes management through insulin delivery, vaccinations against infectious diseases, pain management through analgesics delivery and skin cancer treatments through targeted chemotherapy (Kim *et al.,* 2012; Larrañeta *et al.,* 2016).

Innovations in microneedle design and production processes have paved the way for the creation of dissolving, hollow, coated and hydrogel-forming MNs, each one tailored for particular drug types and clinical applications. Additionally, the unification with nanocarriers, stimuli-responsive polymers, and 3D printing technologies has not only improved their effectiveness but also broadened their application in the delivery of small molecules, proteins, nucleotides, and vaccines (Nguyen and Banga, 2025). To be the case, their potential is inescapable, but there are still some issues to be faced, including low drug loading capacity, fragility, possibly irritating skin, and regulatory issues for getting through clinical trials. These microchannels act as direct pathways facilitating the passage of drug molecules from the microneedle system into the underlying skin tissues.

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The objective of this review is to offer a thorough and meticulous evaluation of the microneedle-based transdermal drug delivery system. The evaluation will cover the classification, mechanisms of action, fabrication methods, clinical applications, limitations, and future prospects. The article intends to be a reference for all researchers and professionals who are working on the design and fabrication of microneedles for therapeutic purposes by putting together the existing knowledge and the latest innovations.

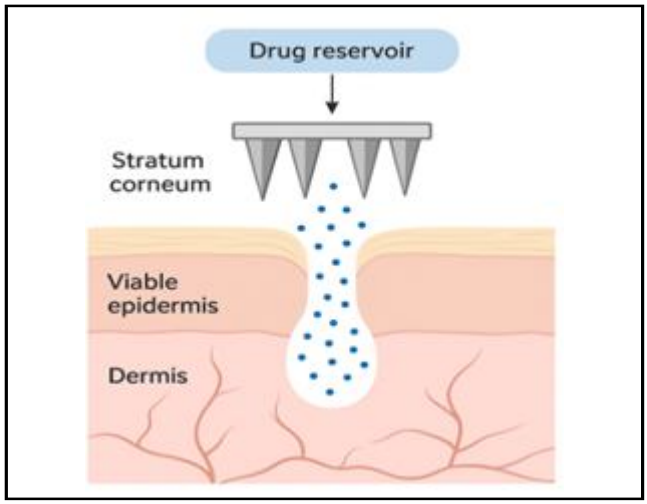

Figure 1: Microneedle-based drug discovery.

2. Types of microneedles

Microneedles (MNs) are categorised by their composition, structure, and method of drug delivery. Different types are designed to optimise drug loading, release kinetics, mechanical strength and patient comfort (Donnelly *et al.*, 2012; Prausnitz and Lanzer, 2008). The main types are summarised below:

i. Solid microneedles
ii. Hollow microneedles
iii. Coated microneedles
iv. Dissolving microneedles
v. Hydrogel-forming microneedles
vi. Porous microneedles
vii. Smart/stimuli-responsive microneedles
viii. Hybrid microneedles (combinations for improved performance)

2.1 Solid microneedles

Solid microneedle (MNs) technology has been predominantly employed to facilitate drug delivery by establishing microchannels on the skin. The patient's skin is first pricked, and then the area is primed for drug application (poke-and-patch). The needles are usually made from a solid material, including metal and polymer, and despite being very strong and simple to operate, they still require a double-step process consisting of skin pre-treatment and drug delivery (Henry *et al.,* 1998).

Mechanism: The application of the Solid MNs requires a poke-and-patch approach. The insertion of the needles into the cutaneous layer results in the temporary opening of small channels that avoid the nerve endings in the dermis and thus cause minimal pain. After the MNs are removed, a drug formulation (gel, cream, and patch) is applied to the treated area. The drug molecule diffuses through the microchannels into the epidermis and dermis, where it may then be either absorbed into circulation or exert its effect locally (Henry *et al.,* 1998; Parhi, 2023). Diffusion rate is influenced by skin hydration, microchannel width, and drug physicochemical characteristics.

2.2 Hollow microneedles

The hollow MNs resemble small hypodermic needles and can deposit liquid formulations into the dermis. They provide excellent control overdose and release profiles, but are less mechanically robust and need to be fabricated with more attention (Larrañeta *et al.,* 2016; Oliveira *et al*., 2024).

Mechanism: Hollow MNs work by employing a mechanism analogous to that of tiny syringes for direct application of liquid treatments to either the epidermis or dermis. This approach is reflective of precise dosing, rapid onset of action and the efficient administration even of large macromolecules like insulin, vaccines or monoclonal antibodies. The formulation travels through the lumen of the needle with either pressure or capillary action and spreads into the surrounding tissue. There is a direct correlation between the efficacy rate and needle thickness, depth of penetration, and duration of flow (Larrañeta *et al.,* 2016; Guillot *et al.,* 2020).

2.3 Coated microneedles

The drug formulation for coated MNs is applied directly onto the surface of the needles. The coating dissolves, and the drug gets released quickly as soon as the insertion is made. These are limited to the application of low-dose vaccines and potent therapeutics with the benefit of single-step administration (Wang *et al.,* 2023).

Mechanism: The use of coated MNs in drug delivery involves the instant dissolution of the coating layer that is spread over the needle. The coating, when inserted, engages with the interstitial fluid and gradually dissolves over the period of seconds to minutes, thus liberating the active ingredient into the skin. The total quantity of drug permeating the skin is mainly influenced by the thickness of the coating, its solubility, and the depth of the insertion. This technique is especially applicable for strong low-dose pharmaceuticals and vaccines, providing a one-step delivery system (Wang *et al.,* 2023; Lee *et al.,* 2020).

2.4 Dissolving microneedles

Dissolving MNs are mainly composed of biodegradable polymers, in which the drug is loaded. The dissolving of needles results in the release of the active ingredient without the generation of sharp wastes. The applications are immense in vaccine delivery, insulin administration, and cosmetic procedures (Donnelly *et al.*, 2012; Nguyen and Banga, 2025).

Mechanism: Dissolving MNs are fabricated from biodegradable polymers loaded with a drug. Upon insertion, needles undergo absorption of interstitial fluid, swelling, and dissolve gradually to slowly release the drug. Thus, this process of controlled or sustained release reduces sharp waste and can provide accurate delivery for sensitive biomolecules such as peptides, proteins, and vaccines. The actual rate of drug release from dissolution of MNs will be determined

by polymer composition and molecular weight, along with environmental conditions of the environment (Donnelly *et al.*, 2012; Nguyen and Banga, 2025).

2.5 Hydrogel-forming microneedles

Hydrogel microneedles swell when inserted into interstitial fluid, opening up hydrogel channels in which drugs can diffuse from an attached patch. The primary advantages of hydrogel microneedles include sustained and controlled release with minimal skin irritation.

Mechanism: The mechanism of action involves the swelling process and facilitates diffusion. When the hydrogel matrix takes up interstitial fluid, it acts like a continuous pathway between the drug reservoir and the skin. The drugs penetrate in passively, or by osmotic gradients, into the microchannel. The drugs can be administered continuously over some hours up to several days without irritation being caused by the soft, hydrated polymer matrix (Larrañeta *et al.,* 2016; Long *et al.,* 2023).

2.6 Porous microneedles

Porous microneedles contain a structure with many interconnected holes that can absorb or release liquids. This design increases drug loading and release. They make it very effective for the delivery of biologics and macromolecules in a much more controlled manner (Bao *et al.,* 2022).

Mechanism: The pores of interconnected microneedles can be filled either with liquid drugs or allow the liquid to be absorbed from an attached reservoir. The drug molecules flow into the skin by capillary action or diffusion through the pores, thus offering high loading capacity and controlled release. This method is of particular use for macromolecules and vaccines, where in general, microneedles have demonstrated very low delivery efficiency.

2.7 Smart/stimuli-responsive microneedles

These MNs change their state of activity according to external factors such as pH, temperature, and glucose levels of their surroundings. For example, the MNs sensitive to glucose can release insulin on a sliding scale when hyperglycaemia is encountered and hence provide a self-regulating drug delivery system (Guillot *et al*., 2020).

Mechanism: The smart MNs are prepared such that they will respond to various external factors such as pH, temperature, and glucose concentration. Taking the example of diabetes, glucose-responsive MNs contain substances such as polymers or nanoparticles that will automatically release insulin in case of a rise in glucose, and hence the system will be self-regulating. In addition, other smart MNs are capable of releasing drugs in response to light, heat, or enzymatic activity, thus achieving targeted, controlled and on-demand drug delivery.

2.8 Hybrid microneedles

Hybrid MNs represent a combination of at least two or more types, such as hollow-dissolving or coated-dissolving MNs, all of which together may confer the benefits of each type, including instant release combined with long-lasting delivery or strong mechanical strength combined with controlled drug release. According to Nguyen and Banga (2025), hybrid MNs work on the principle of several mechanisms combined-for example, a coated-dissolving or hollow-dissolving design-and then take the advantages of each type. For example, such a hybrid MN can first give a burst dose through the coating and then provide prolonged release from the dissolving polymer matrix. This contributes to efficient delivery of the therapeutic agent with better kinetics and an improved clinical outcome.

3. Drug transport pathways

MNs utilise two primary pathways for drug transport:

- Transcellular and intercellular diffusion through the epidermis and dermis.
- Interstitial fluid-mediated diffusion into microcapillaries for systemic circulation.

4. Clinical relevance

Mechanistic optimization is essential for the effectiveness of the treatment.

For example, the delivery of insulin through dissolving microneedles gives fast control of glucose, while the hydrogel MNs offer analgesic delivery for a longer period. Coated MNs for vaccine administration have shown a better immune response and an increase in patient compliance in comparison to traditional injections.

Table1: Summary of microneedle types

Type	Material	Drug delivery mechanism	Advantages	Limitations
Solid	Metal, silicon, polymer	Poke-and-patch	Simple, robust	Two-step, limited dosage control
Hollow	Metal, silicon, polymer	Liquid injection	Precise dosing, fast delivery	Fragile, complex fabrication
Coated	Metal, polymer	Surface dissolution	Single-step, good for potent drugs	Low drug load, coating uniformity
Dissolving	Biodegradable polymers	Needle dissolves	Safe, no sharps, controlled release	Limited mechanical strength
Hydrogel-forming	Hydrogel polymers	Swelling + diffusion	Sustained release, minimal irritation	Slower onset, material stability
Porous	Polymer, silicon	Pores absorb/release	High loading, controlled kinetics	Fragile, fabrication challenges
Smart/stimuli responsive	Polymers, composites therapeutics	Stimulus-triggered release	Self-regulating, advanced	Complex design, cost
Hybrid	Combination materials	Combined mechanisms	Optimised performance, dual benefits	Fabrication complexity, cost

5. Fabrication and manufacturing methods of microneedles

The manufacturing process of Microneedles is a critical determinant of their mechanical strength, drug loading, and delivery efficiency to a great extent. Various materials such as metals, silicon, polymers, and ceramics are used for the production of MNs, the choice being dependent on the type of MN, the drug to be delivered, and the clinical application (McCrudden *et al.,* 2014; Donnelly *et al.,* 2012).

Different fabrication techniques have been created, and each has its own set of benefits and drawbacks.

5.1 Photolithography

Photolithography is a prevalent method for making MNs, especially for silicon micro needles. A photoresist coating that is sensitive to light is applied to a silicon wafer, and the wafer is then exposed to ultraviolet (UV) light, leading to the formation of the desired patterns, which are then eroded to reveal the microscopic needle structures underneath. Photolithography allows precise control over the size, shape and needle dimension, which makes it a very suitable technique for both hollow and solid MNs. The cost of the procedure, however, is high and it also requires cleanroom facilities, which makes it unfeasible for mass production (Henry *et al.,* 1998; Oliveira *et al.,* 2024).

5.2 Moulding techniques

Moulding is a technique that is most often used in the manufacture of polymer-based MNs, such as dissolving and hydrogel-forming MNs. A master template is prepared, and then negative moulds are made, typically of polydimethylsiloxane (PDMS), which is a very common material used for the manufacturing of negative moulds in this process. After that, the polymers are poured into the negative moulds, they are cured or solidified, and then the MNs are removed from the moulds. Moulding allows one to produce MNs quickly at a low cost, and in any desired shape or size, but the technique also demands the utmost precision in the manufacturing process to avoid the pitfalls of bubble formation and needle deformation (Donnelly *et al.,* 2012; Lee *et al.,* 2020).

5.3 Laser etching/ablation

Laser-based fabrication involves removing material from a substrate using focused laser beams to create microneedle structures. This method provides high precision and rapid prototyping, and is suitable for metal, silicon, and polymer MNs. Limitations include high equipment costs and potential surface roughness, which may affect mechanical strength (Larrañeta *et al.,* 2016).

5.4 3D Printing/additive manufacturing

Recent advances in additive manufacturing have enabled the fabrication of MNs *via* stereolithography (SLA), two-photon polymerisation and fused deposition modelling. 3D printing allows customisation of geometry, complex shapes, and rapid prototyping, and is particularly advantageous for hybrid and stimuli-responsive MNs. Challenges include resolution limits and material biocompatibility considerations (Nguyen and Banga, 2025; McCrudden *et al.,* 2014).

5.5 Micromilling

Micromilling, which is a mechanical precision milling method, is used to produce MNs from metals or polymers. This method offers high mechanical strength and reproducibility, and this technique is suitable for hollow MNs requiring fluid channels. However, micro-milling is a slow process and thus not suitable for production at a high throughput level (Bao *et al.,* 2022).

5.6 Polymer casting and hot embossing

One of the methods to produce MNs in polymer casting is pouring of polymer melts or solutions into a mould followed by curing or solidification. Hot embossing is another method that makes use of heat and pressure to imprint MN features onto polymer sheets. Both these methods are inexpensive and also allow the use of biodegradable polymers, which makes them suitable for dissolving and hydrogel MNs. Nevertheless, there are still limitations with respect to the needle tip sharpness and the possibility of deformation during the demoulding process (Donnelly *et al.,* 2012; Parhi, 2023).

Table 2: Comparative overview of fabrication techniques

Fabrication method	Material	Advantages	Limitations	Typical MN type
Photolithography	Silicon, metal	High precision, reproducibility	Expensive, cleanroom required	Hollow, solid
Moulding	Polymer, PDMS	Low cost, high-throughput	Bubble formation, deformation	Dissolving, hydrogel
Laser etching/ablation	Metal, silicon, polymer	Rapid prototyping, precision	Expensive, surface roughness	Solid, hollow
3D Printing/additive	Polymer, resin	Complex shapes, customised design	Material limitations, resolution	Hybrid, smart/stimuli-responsive
Micromilling	Metal, polymer	High mechanical strength, reproducibility	Time-consuming, not high-throughput	Hollow, coated
Polymer casting and hot emboss	Biodegradable polymer	Cost-effective, versatile	Tip sharpness, needle deformation	Dissolving, hydrogel

The method of fabricating needles influences their sharpness, strength, biocompatibility, and drug loading which have a direct impact on clinical outcomes. For instance, Dissolving MNs for insulin demand biodegradable polymers with precise tip geometry, on the other hand, hollow MNs for chemotherapy need robust metallic needles to bear the injection pressures. Fabrication optimization leads to safe, efficient, and consistent drug delivery.

6. Therapeutic relevance of microneedles in transdermal drug delivery

Microneedles have changed the way drugs are delivered through the skin by allowing the application of a wide range of therapeutic agents in a manner that is almost painless, efficient, and controlled. Their use is widespread, from pharmaceuticals to biomedical applications, cosmetics and even diagnostic innovations, while cumulative supportive evidence is still emerging in clinical and commercial contexts (Donnelly *et al.,* 2012; Prausnitz and Lanzer, 2008).

6.1 Vaccine delivery

Vaccination is probably the application of MNs that has been most extensively studied. MNs give non-invasive, pain-free vaccine administration, thus improving compliance and immunogenicity.

Examples include:

- **Influenza vaccines**

  Coated and dissolving MNs have been shown to induce stronger immune responses than intramuscular injections (Kim *et al.,* 2012).

- **Measles, polio, and rubella vaccines**

  The use of dissolving MN patches allows for the vaccines to be stored at room temperature; thus, their distribution in areas with limited resources becomes possible.

- **COVID-19 vaccines**

  Recent studies are being conducted to find out how MNs can help with the delivery of mRNA and protein subunit vaccines during rapid immunization campaigns.

6.2 Diabetes management (insulin and GLP-1 delivery)

MNs provide painless, self-administered insulin delivery, improving glycaemic control and improved patient compliance.

Examples include:

- Dissolving MNs encapsulating insulin for rapid release.
- Glucose-responsive smart MNs releasing insulin automatically in response to hyperglycaemia (Oliveira *et al.,* 2024).
- GLP-1 delivery for type 2 diabetes using polymeric MNs.

6.3 Analgesics and pain management

Hydrogel-forming and dissolving MNs enable controlled release of analgesics, such as:

- Lidocaine and local anaesthetics for minor surgical procedures.
- NSAIDs for chronic musculoskeletal pain.
- Opioids in controlled, sustained-release MN patches.These approaches reduce systemic side effects and improve patient comfort (Larrañeta *et al.,* 2016).

6.4 Cancer therapy

MN technology allows localized chemotherapy and immunotherapy, minimising systemic toxicity. Examples include:

- Doxorubicin-loaded MNs for skin cancers.
- Immunotherapeutic MN patches delivering checkpoint inhibitors.
- Combination MN systems for simultaneous drug and immunomodulator delivery (Wang *et al.,* 2023; Guillot *et al.,* 2020).

6.5 Cosmetic and dermatological applications

MNs are widely used in aesthetic medicine, including:

- Hyaluronic acid delivery for skin rejuvenation.
- Anti-wrinkle peptides for collagen stimulation.
- Transdermal delivery of depigmenting agents for hyperpigmentation. Dissolving and hydrogel MNs improve skin penetration without pain or scarring (Nguyen and Banga, 2025; Parhi, 2023).

6.6 Hormone and contraceptive delivery

MN patches are being explored for:

- Oestrogen, progesterone, and testosterone delivery in hormone replacement therapy.
- Long-acting contraceptives, including levonorgestrel, *via* dissolving MNs, enabling monthly or quarterly administration (Larrañeta *et al.,* 2016).

6.7 Antimicrobial and antiviral applications

MN systems facilitate localized delivery of antimicrobials, reducing systemic toxicity and improving efficacy:

- Antibiotics for bacterial skin infections.
- Antivirals for herpes simplex virus or cytomegalovirus.MNs enhance drug penetration into infected tissues, overcoming skin barriers (Prausnitz and Lanzer, 2008).

6.8 Biologics and macromolecule delivery

- MNs enable the transdermal delivery of proteins, peptides, monoclonal antibodies, and nucleic acids, which are otherwise difficult to administer orally due to enzymatic degradation: Insulin, vaccines, growth factors, and antibodies.
- siRNA and DNA-based therapies *via* coated or dissolving MNs.Potential applications in gene therapy and personalised medicine (Donnelly *et al.,* 2012).

6.9 Diagnostic and monitoring applications

Emerging MN technologies are being developed for interstitial fluid sampling and biosensing:

- Continuous glucose monitoring using hollow or hydrogel MNs.
- Biomarker detection for diseases such as cancer or infection.Point-of-care diagnostics through minimally invasive MN sampling.

Table 3: Summary of microneedle applications

Application area	MN type(s) used	Drug/agent delivered	Clinical relevance
Vaccines	Coated, dissolving	Influenza, measles, COVID-19	Improved immunogenicity, pain-free delivery
Diabetes	Dissolving, smart glucose-responsive	Insulin, GLP-1	Self-regulated therapy, enhanced compliance
Analgesics	Hydrogel, dissolving	Lidocaine, NSAIDs, opioids	Controlled pain relief, reduced side effects
Cancer therapy	Hollow, coated, dissolving	Doxorubicin, immunotherapies	Localised delivery, reduced systemic toxicity
Cosmetic/dermatology	Dissolving, hydrogel	Hyaluronic acid, peptides	Skin rejuvenation, anti-ageing
Hormones/contraceptives	Dissolving, coated	Oestrogen, progesterone, testosterone, levonorgestrel	Sustained hormone therapy, contraception
Antimicrobial/antiviral	Coated, hollow, dissolving	Antibiotics, antivirals	Targeted infection treatment
Biologics/macromolecules	Coated, dissolving, hollow	Proteins, peptides, antibodies, siRNA, DNA	Oral alternative for macromolecule delivery
Diagnostics/monitoring	Hollow, hydrogel	Glucose, biomarkers	Minimally invasive real-time monitoring

7. Limitations of microneedles in transdermal drug delivery

Even though microneedles have remarkable transdermal drug delivery potential, several limitations are still in the way for their wide-scale clinical and commercial applications. These limitations cover a variety of aspects such as mechanical, biological, pharmaceutical, manufacturing, and regulatory challenges (Donnelly *et al.,* 2012).

7.1 Mechanical limitations

Needle breakage: MNs can break during the insertion process, especially the dissolving and hydrogel types. In this case, fragments might be left behind in the skin, which raises safety concerns. Thus, it may be necessary to perform polymer engineering to make it safer by being better designed or by using reinforcement.

Insufficient strength: Soft polymer or hydrogel MNs might not be able to penetrate the skin in the tougher skin areas, resulting in inefficiency of drug delivery.

Tip blunting: Repeated or improper application may blunt the tips of the needles, which leads to penetration being compromised and inconsistent dosing of the drug.

7.2 Drug loading and dosage limitations

Limited drug capacity: For MNs, the volume of drugs that can be encapsulated is minimal, which is very costly, especially for macromolecules or high-dose therapeutics, and hence the use of multiple patches or more polymer volume is required (Donnelly *et al.,* 2012).

Rapid release *vs.* sustained delivery: Some MN types, such as coated MNs, release drugs very fast, and this limits the therapeutic effect from being sustained unless hybrid or hydrogel systems are used.

7.3 Skin-related limitation

- **Skin irritation and allergic reactions:** Biodegradable polymers or adhesives may trigger local irritation, erythema, or allergic responses in sensitive individuals (Larrañeta *et al.,* 2016).
- **Variability in skin properties:** Differences in thickness, hydration, elasticity, and hair density between patients can affect MN insertion, penetration depth, and drug absorption.
- **Microbial infection risk:** Though minimally invasive, microchannels can act as entry points for pathogens, particularly if MNs are reused or improperly sterilised.

7.4 Manufacturing and technical challenges

- **Scalability issues:** High-precision fabrication methods such as photolithography, laser etching, or 3D printing can be expensive and difficult to scale for mass production (Guillot *et al.,* 2020).
- **Reproducibility concerns**: Ensuring consistent needle geometry, sharpness, and drug loading across large batches remains challenging.
- **Material limitations:** Biodegradable polymers must balance mechanical strength, dissolution rate, and biocompatibility, which can limit MN design options.
- **Shelf-life and stability:** MNs containing biologics or vaccines may have stability issues under varying temperature and humidity conditions.

7.5 Clinical and regulatory limitations

- **Patient compliance:** Though minimally invasive, incorrect self-application may reduce efficacy or cause injury.
- **Regulatory hurdles:** MNs are considered combination products of a device and drug, requiring complex regulatory approval processes including safety, efficacy, and sterility evaluations (Bao *et al.,* 2022).

Table 4: Summary of microneedle limitations

Limitation category	Specific issues	Clinical/manufacturing impact
Mechanical	Needle breakage, tip blunting, insufficient strength	Reduced penetration, safety risks
Drug loading	Limited capacity, rapid release vs sustained delivery	May require multiple patches, suboptimal dosing
Skin- related	Irritation, variability, infection risk	Affects safety, efficacy, patient acceptability
Manufacturing/technical	Scalability, reproducibility, material limitations, stability	Increased cost, production challenges
Clinical/regulatory	Regulatory hurdles, compliance, cost-effectiveness	Limits market translation and adoption
Advanced/smart MNs	Complexity, limited long-term data	Potential malfunction, regulatory challenges

- **Cost-effectiveness:** High-precision MN fabrication and specialised packaging can increase production costs, affecting accessibility in low-resource settings.

7.6 Limitations in advanced and smart MNs

- **Limited long-term clinical data:** Many advanced MNs, including hybrid or smart designs, have limited long-term human studies, restricting regulatory approval and clinical adoption.
- **Complexity of smart MNs:** Stimuli-responsive MNs, while innovative, involve complex polymer chemistry, integrated sensors or nanoparticles, increasing the risk of malfunction or unpredictable drug release.

8. Future prospects of microneedles in transdermal drug delivery

Microneedles are a revolutionary method of transdermal drug delivery, and continuous research is gradually opening new therapeutic, diagnostic, and commercial avenues for them. Although there are drawbacks at present, a number of innovations and approaches are expected to improve MN performance, safety, and use in both medical and commercial areas (Donnelly *et al.,* 2012).

8.1 Smart and stimuli-responsive microneedles

The development of smart MNs is a major focus, with systems capable of responding to physiological stimuli such as glucose, pH, temperature, or specific biomarkers. For instance:

- **Glucose-responsive MNs** for insulin delivery in diabetes offer self-regulated therapy, reducing the risk of hypoglycaemia.
- **pH-sensitive MNs** can release chemotherapeutics specifically in acidic tumour microenvironments.
- **Temperature-responsive MNs** allow on-demand release of analgesics or hormones.These systems promise precision medicine, personalised therapy, and reduced systemic side effects.

8.2 Integration with nanotechnology and advanced drug carriers

MNs are increasingly being combined with nanocarriers to improve drug stability, targeting, and controlled release:

- **Micelles and liposomes** for sustained release of hydrophobic drugs.
- **Lipid nanoparticles (LNPs)** and polymeric nanoparticles for vaccine and nucleic acid delivery.
- **Nanocrystals or dendrimers** to enhance solubility and bioavailability.

This integration enhances efficacy for macromolecules and biologics, expanding MN applications in oncology, immunotherapy, and chronic diseases (Nguyen and Banga, 2025).

8.3 3D Printing and customised microneedles

Advances in additive manufacturing allow the production of patient-specific MNs with customised geometry, length and density for individual skin types or therapeutic needs. This approach supports:

- Rapid prototyping and optimisation of MN designs.
- Hybrid and multi-functional MNs combining coated, dissolving, and hydrogel features.
- On-demand manufacturing for emergency vaccine deployment or personalised therapies (Oliveira *et al.,* 2024).

8.4 Combination therapy and multi-drug delivery

Future MN systems may enable simultaneous delivery of multiple therapeutics in combination, such as:

- Chemotherapy and immunotherapeutic agents for synergistic cancer treatment.
- Analgesics along with a combination of anti-inflammatory drugs for chronic pain management.
- Multi-antigen vaccines in a single Microneedle patch for broader immunisation coverage.

Combination MNs can improve treatment efficacy and patient compliance.

8.5 Long-term and chronic disease management

Hydrogel-forming and smart MNs provide the potential for sustained and programmable drug release over days or weeks, ideal for chronic conditions such as:

- Diabetes (insulin, GLP-1)
- Hormone replacement therapy
- Pain management in musculoskeletal disorders

These MN systems reduce the need for frequent injections, improving adherence and quality of life (Kim *et al.,* 2012).

8.6 Diagnostic and theranostic applications

Emerging MN systems integrate diagnostic capabilities with drug delivery, forming theranostic platforms:

- Continuous monitoring of glucose, electrolytes, or biomarkers.
- Real-time feedback to trigger drug release.
- Point-of-care diagnostic devices combining sampling, sensing, and therapy.

Such MN-based theranostics could redefine personalised medicine and improve early disease detection (Bao *et al.,* 2022).

8.7 Commercial translation and global health applications

Future MN deployment is expected to:

- Enable thermostable vaccine patches suitable for distribution in low-resource regions.
- Reduce medical waste compared to traditional needles.
- Facilitate self-administration, increasing compliance and accessibility.
- Support rapid response to pandemics, as seen in research for influenza and COVID-19 vaccines.

8.8 Regulatory and standardisation efforts

Efforts are underway to establish standardised protocols for MN fabrication, testing, and clinical evaluation, which will accelerate regulatory approval and commercialisation. Standardisation will address:

- Sterility and safety requirements
- Mechanical strength and drug release validation
- Long-term stability and shelf-life of MN products

The main direction for the development of microneedle technology will be the mixture of intelligent systems, nanotechnology, 3D printing and theranostics along with mass production and regulatory standardization. These changes are ready to change the way drugs are delivered through the skin, making it easier for patients to take their medicine and open up more clinical uses for the technology, thus making MNs a key part of the new wave of therapeutics.

9. Scope of microneedles in transdermal drug delivery

The scope of microneedle technology extends across clinical, pharmaceutical, research, and commercial domains, reflecting its versatility and transformative potential in modern therapeutics (Donnelly *et al.,* 2012).

9.1 Clinical scope

- MNs offer a pain-free alternative to hypodermic injections, improving patient compliance in chronic diseases such as diabetes, hormone replacement therapy, and pain management.
- **Vaccine delivery:** MN patches allow mass immunisation campaigns, including in resource-limited settings, with reduced cold-chain dependency and improved thermostability.
- **Localized therapy:** MNs enable targeted delivery of chemotherapeutics, analgesics, and dermatological agents, reducing systemic side effects.
- **Theranostics:** Integration with biosensing allows MNs to simultaneously monitor biomarkers and deliver therapy, expanding personalised medicine applications.

9.2 Research and educational scope

- **Drug delivery studies:** MNs provide an excellent platform for studying transdermal pharmacokinetics, drug diffusion pathways, and delivery efficiency.
- **Materials science research:** Investigation of biodegradable polymers, hydrogels, and stimuli-responsive materials is accelerated by MN development.
- **Vaccine and biologics research:** MNs facilitate exploration of novel vaccine formulations, peptide drugs, and nucleic acid delivery, offering translational research opportunities.
- **Educational applications:** MNs are increasingly included in pharmacy, biomedical engineering, and medical curricula, demonstrating innovative drug delivery principles.

9.3 Commercial and industrial scope

- **Pharmaceutical industry:** MNs represent a growing segment for next-generation transdermal systems, with potential for insulin patches, vaccine patches, and cosmetic MNs.
- **Cosmetic and dermatology market:** Hydrogel and dissolving MNs are being commercialised for anti-ageing, skin hydration, and peptide delivery.
- **Global health applications:** MNs have the potential to simplify vaccine distribution, particularly in remote areas, and reduce sharps waste.
- **Startups and innovation hubs:** Numerous companies are exploring MN-based products, reflecting high commercial and translational potential (Nguyen and Banga, 2025).

9.4 Regulatory and policy scope

- The adoption of MNs is expected to drive standardisation in combination product regulations, covering drug-device interactions, sterility, and mechanical testing.
- Regulatory acceptance will expand the global market reach, fostering innovation in both developed and developing countries.

9.5 Market potential

- The microneedle market is projected to grow substantially due to increasing demand for painless drug delivery, self-administration, and novel vaccines.
- Expanding applications in chronic disease management, oncology, cosmetic dermatology, and theranostics provide diverse commercial opportunities.
- MNs may also reduce healthcare costs by minimising needle-stick injuries, improving compliance, and reducing hospital visits. MN technology is very broad in its scope, as it has applications in clinical, regulatory, educational, and commercial domains. Thus, it is the global healthcare delivery system, along with the next generation of therapeutics, that microneedle technology has already become involved in and will continue to be so in the future with continuous development of smart systems, nanotechnology, and 3D printing.

10. Conclusion

Microneedling (MNs) has crossed the boundaries of traditional routes of drug delivery and has become an innovative research tool for transdermal delivery. They let the drug get through efficiently by

creating microchannels in the stratum corneum layer of the skin. This method has become a suitable one for the delivery of a huge variety of drugs, including small molecules, biologics, vaccines, and hormones. Advances in MNs types such as solid, hollow, coated, melting, hydrogel-forming and smart designs have made tailored drug release possible depending on the required profile, from rapid, sustained or even stimuli-responsive delivery. MNs have demonstrated applications across vaccination, diabetes management, pain control, oncology, cosmetic dermatology, hormone therapy, antimicrobials, and diagnostic monitoring; hence, the vastness of their clinical relevance is highlighted. On the downside, although MNs have plenty of advantages, they still have a mechanical strength issue, drug loading limitations, skin variability, manufacturing scalability and regulatory approval. The development of smart, hybrid, and nanotechnology integrated MNs combined with fabrication and standardization improvements that are already in the works will eventually lead to the removal of these barriers. With their potential for enhanced patient compliance, precision therapy, global vaccine distribution, and theranostic applications, MNs are poised to play a pivotal role in next-generation transdermal drug delivery and personalised medicine.

Availability of data and material

All data are provided within the manuscript.

Authorship contribution statement

Safura Ayesha Mujeeb: Contributed to conceptualization, supervision, methodology, validation, manuscript reviewing and editing, and overall guidance throughout the study. **Syeda Alvia Faizan:** Contributed to data curation, investigation, formal analysis, software handling, visualization, and manuscript writing. **Ayesha Maryam:** Contributed to investigation, data collection, methodology, literature review, validation, and manuscript writing. **Azmath Begum:** Contributed to data curation, formal analysis, literature review, manuscript reviewing and editing, and project administration.

Consent for publication

All authors gave their full consent for publication and submission to this journal.

Conflict of interest

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Ethics approval

Not applicable.

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