# USE OF MICRONEEDLE TECHNIQUE IN TDDS: A REVIEW ARTICLE

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## ABSTRACT

**Introduction**: Transdermal drug delivery administers medication through the skin, surpassing other methods with its advantages. Techniques like needles or creams can be ineffective due to a protective layer on our skin. To overcome this, scientists have developed microneedles - tiny needles that deliver medicine regardless of size! Made from materials like silicon and metals, these tools are used for medical purposes and enhancing appearance by placing cosmetics beneath the skin's surface. Microneedles revolutionize drug delivery procedures and aesthetics, offering endless opportunities for improving healthcare outcomes and physical features."

**Method**: This review aimed to summarize the use of microneedle technique for drug delivery through the skin, compare it with other techniques, and highlight its advantages. It is important to note that no human or animal studies were conducted by any of the authors; instead, their findings are based on information from previous studies.

**Result**: Microneedles are a trendy method for administering medicine through the skin, simplifying medication intake. They come in various materials and shapes and have been proven to greatly assist individuals with health problems. In summary, microneedles are versatile tools that could significantly enhance healthcare outcomes.

**Conclusion**: MN devices can release medicine through the skin nonstop, creating new treatment options. But more research is needed to completely understand how well they work. Plus, there are limits that need fixing in transdermal MN delivery methods.

**Keywords**: Microneedle1, TDDS2, drug delivery3, technique4, microneedling5.

## 1. INTRODUCTION:

The most common ways to give medicine through the skin are with needles or creams. Needles can hurt, so some people don't like them. Creams aren't as effective because they don't go into your body very well. The skin has three layers: the outer layer, middle layer, and innermost layer. The outer layer is a big barrier that only lets certain kinds of medicines pass through it easily. Scientists have been studying different ways to make topical creams work better by using tiny carriers called nanocarriers or patches on your skin [1-4]. microneedles, which are tiny needles on a small patch. They can deliver medicine through our skin and help solve problems with other methods like regular needles or patches. Some medicines don't go through the skin well enough to work properly, but scientists have made new technology using these microneedles that lets big molecules get into our skin better. This makes the medicine work faster and more effectively! Using these microneedle devices has many benefits: quicker results, easier for patients to use themselves, higher absorption of drugs in our bodies, and less differences between people when it comes to how much drug gets absorbed. But there are some limitations too – some people might be allergic or irritated by them because their skin is sensitive. Also, since these needles

are really thin compared to hair strands, they could break off inside your skin if you're not careful. Overall, though this new technology helps create pathways for bigger molecules to enter our body's system efficiently so we can benefit from certain medications! Other ways like electricity or chemicals may improve permeability but don't always work well for large-sized molecules. "As a result, the development of these ultra-thin needles signifies an important step ahead in improving drug delivery and perfecting medical treatments." [2, 5, 11, 12]

Microneedles have been studied as an alternative method for drug delivery. These small needles arranged on patches cause minimal pain when applied to the skin and offer advantages such as faster action of medication and improved absorption into the body for treating illnesses. However, individuals with sensitive skin may experience irritation or allergic reactions when using these patches. Microneedles provide a painless way to deliver medicine through the skin compared to regular needles in transdermal drug delivery systems (TDDSs). This article discusses how microneedles can effectively administer different medications and highlights areas of further research needed before widespread use becomes possible.

The importance of our protective outer layer called stratum corneum makes delivering medicine challenging via pills alone; hence doctors explore options like administering them directly through our skins instead- one being micro needling that causes less discomfort yet efficiently delivers medicines within us making it highly beneficial future treatment approach. Transdermal drug delivery systems (TDDSs) are advantageous over other methods due to their painless nature while ensuring better efficacy and absorption rates for certain drugs administered externally rather than ingested orally. The development of microneedle technology has enabled scientists overcome challenges posed by layers if human epidermis which acts likes a natural barricade against external substances. Microneedles not only allow effective penetration without causing any significant sensory response but also revolutionize TDD system opening up new prospects towards more efficient treatments. Patches used in transdermal drug administration bypass liver metabolism allowing controlled release up to 7 days however this route isn't suitable for all types of medicines since human ski forms strong barriers inhibiting entry. In order enhance permeability ultrasound waves or minute needle structures known as microneedles have been developed. Micro needles provide painless delivery of potent medicament without penetrating to deep into skin; they are also employed in vaccination and transfer of other substances inside body. Microneedles are minute needles composed of various substances such as silicon, metals, and polymers. They possess the capability to administer medication by puncturing the skin. Researchers have devised microneedles that disintegrate or decompose within the body subsequent to dispensing medicine. Certain specialized types of microneedles can even facilitate modifications in drug absorption through dermal layers. The utilization of microneedles presents a highly encouraging and effective substitute for conventional approaches towards pharmaceutical administration, thereby ushering in a transformative era in medical science. Microneedles essentially create minuscule pathways in our skin allowing medicines to reach specific targets within our bodies effectively and efficiently. The different types include

solid microneedles which puncture tiny holes in your skin coated ones with medication applied onto them dissolving one's release medicine gradually while disappearing rapidly separating where only part remains after application can easily be removed by you lastly hollow type injects liquid directly under your dermis. Micorneeedling has vast applications ranging from administering vaccines or insulin shots, to delivering cosmetics beneath our skins aiming for enhanced appearance. [6, 7, 8, 9, 10]

An approximate discussion is collected for varied transdermal medicine delivery systems in Table 1. Topical creams typically only reach the skin's surface with a low drug absorption rate (10-20%) [3]. Transdermal patches face low bioavailability due to the stratum corneum barrier, which can be somewhat improved with permeation enhancers (though still limited) [4]. Hypodermic needles deliver drugs deep into the dermis but are very painful and lead to poor patient compliance, offering high drug delivery (90-100%) [5]. Microneedle patches, however, bypass the stratum corneum barrier and painlessly deliver 100% of the loaded drug into the Epidermis or upper Dermis layer [5].

### *1.1.1 Table1. Comparison B/W topical cream, transdermal patch, hypodermic needle and microneedle drug delivery system*

| | **Topical cream** | **Transdermal patch** | **Hypodermic needle** | **Microneedle** |
|---|---|---|---|---|
| **Description** | Emulsion/ emulgel/ cream/ ointment | Adhesive patch to be placed on the skin | Fine hollow tube having a sharp tip with small opening at the end | Micron sized needles are aligned on the surface of the small patch |
| **Onset of action** | Slow | Slow | Faster | Faster |
| **Pain** | Painless | Painless | Painless | Painless |
| **Bioavailability** | Poor | Insufficient | sufficient | Sufficient |
| **Patient compliance** | Less | Better | Less | Better |
| **Self-administration** | possible | Possible | Not possible | Possible |
| **Mechanism of delivery** | Permeation through skin pores | Drug has to cross the stratum corneum barrier so poor diffusion of large molecules | Drug placed directly in the dermis | Bypass stratum corneum and drug placed directly into epidermis or dermis hence enhanced permeability |

## 2. TYPES OF MICRONEEDLES BASED ON THEIR DELIVERY STRATEGIES:

There are various types of microneedles. Solid microneedles, for example, use a poke with patch method and are used to treat the skin before other procedures. Coated microneedles involve applying a drug solution onto the needle surface using a coating technique. Dissolving microneedles are made from biodegradable polymers that break down over time. Hollow microneedles contain

the drug solution and deliver it into the dermis layer of the skin.

A) The tens are applied to thousands of MNs as a pore-forming pretreatment. Then, a traditional drug formulation is put on the surface of the skin. B) The coat-and-poke method involves coating solid MNs with a water-soluble drug. During administration, the drug coating dissolves and gets deposited in the skin. C) In the poke-and-release approach, non-water soluble MNs are injected into the skin. Over time, they slowly release their enclosed therapeutic agent while remaining on top of the patch after application. D) The poke-and-flow technique includes microneedles that have holes allowing for drugs to flow across them onto or through the skin's surface. E) With poke-and-dissolve strategy biodegradable or water-soluble drug-encapsulated MNs dissolve within and deliver their loaded therapeutic agents into the skin. [44]

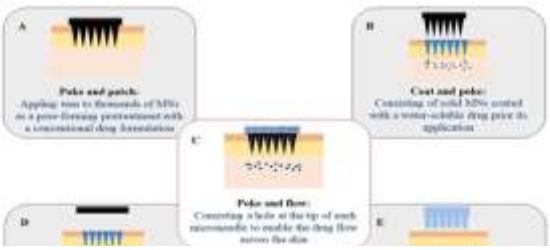

**Figure1. A schematic representation of delivery approaches using various types of microneedle arrays (MNs): (A) poke-and-patch (solid MNs), (B) coat-and-poke (coated MNs), (C) poke-and-flow (hollow MNs), (D) poke-and-dissolve (dissolvable MNs), and (E) poke-and-release (hydro gel forming MNs).**

### 2.1 Solid microneedles:

Are commonly used to create pores in the skin, allowing drugs to enter more effectively. These needles penetrate into the skin and form tiny channels through which the drug can directly access deeper layers of the skin. This method increases the permeation of drugs and can have both local or systemic effects. Researchers have developed various types of solid microneedles using different materials such as silicon, gold-coated silicon, poly lactic acid, and stainless steel. By studying these different materials, they found that biodegradable polymer solid microneedles made from poly lactic acid had enough strength to pierce through a protective layer on top of our skin (stratum corneum) while enhancing drug absorption. Stainless steel micro-needles were also tested for their ability to deliver specific medications like captopril and metoprolol tartrate with promising results. In summary: Solid microneedle technology is effective at increasing drug delivery by creating small openings in the skin's surface; it has been studied extensively using various material compositions including silicone-based structures coated with gold nanoparticles as well as bioresorbable polymers like poly-lactic-acid (PLA). Additionally, researchers looked into delivering medication via stainless steel needle arrays resulting in improved outcomes specifically for captopril & metoprolol tartrate administration. [1, 26, 27, 30, 31, 32]

### 2.2 Coated microneedles:

Are surrounded by a drug solution or dispersion layer. The drug is then dissolved from the coating and delivered quickly. The amount of drug that can be loaded depends on the thickness of the coating and needle size, which is usually small. Baek et al successfully loaded lidocaine onto poly L-lactide (PLLA) microneedle arrays, with rapid release in phosphate buffer saline and stability for 3 weeks. Coated microneedles have also been used to deliver multiple agents simultaneously using different formulations and drugs, as demonstrated by Li et al who achieved co-delivery of water soluble and insoluble dyes at once. Chen et al coated PLA microneedles with

sulforhodamine B, achieving approximately 90% efficiency in delivering the drug continuously according to in-vitro studies conducted on mice. [1, 26, 33, 34, 35]

**2.3Dissolving microneedles:**

Made of biodegradable polymers are used to release drugs into the skin. Unlike other methods, these microneedles do not need to be removed after insertion. The polymer degrades inside the skin and controls drug release, making it a good option for long-term therapy with improved patient compliance. Mixing the polymer and drug together is an important step in creating effective dissolving microneedles. Different techniques have been developed to enhance drug delivery efficiency, such as using rapidly separating or bubble-filled microneedle designs. These modifications allow for rapid drug delivery while controlling its release kinetics within seconds of insertion into the skin. [1, 27, 36, 37, 38, 39]

**2.4 Hollow microneedles:**

Are small needles that have a space inside where drugs can be filled? They are used to directly deposit the drug into the skin, specifically in the epidermis or upper dermis layer. These types of needles are commonly used for large molecules like proteins and vaccines. The flow rate and release pressure of the drug can be adjusted for rapid injection if needed. Hollow microneedles allow for a larger dose of medication because more drugs can fit inside them, but it is important to maintain a constant flow rate while administering medication with these needles. [1, 28, 29]

Increasing the size of hollow microneedle bore may increase flow rate but compromise strength and sharpness. To address this issue, metal coatings can be applied to strengthen the needle; however, this makes them sharper. Researchers have developed different variations of hollow microneedles: Mishra et al created aligned silicon substrate-based ones measuring 500-600 µm long with an outer diameter of 100 µm achieving a flow rate at specific pressure differences. Maaden et al fabricated fused silica hollow microneedles using hydrofluoric acid etching which allowed automated delivery system overcoming hypodermic needle drawbacks by injecting minimal amounts into skin. Suzuki's team designed mosquito-inspired hollow microeedels showing improved penetration capability on human skin compared mosquitoes' action itself. [40, 41]

**2.5 Hydro gel-forming microneedles:**

Are new types of needles made from polymers that can absorb water and swell when inserted into the skin? This creates channels between the blood vessels and drug patch, allowing for controlled release of medication. These microneedles also have flexible sizes and shapes, making them easy to sterilize and remove from the skin. Researchers have studied their use in transdermal administration of metformin, which showed improved delivery with fewer gastrointestinal side effects compared to oral intake. Cross-linked polymers are also used to create swell able microneedles for drug delivery purposes. [42, 43]

**3. Material for MicroneedleFormulation:**

The main reason for producing MNs is their ability to penetrate the skin without

breaking or bending. Various factors, such as material, manufacturing method, and design have been considered in addressing the challenge of MN production. Different types of materials like silicon, metals, ceramic, and polymers have been used to make various kinds of MNs. A combination of these materials has also been employed for biomedical purposes such as drug delivery and tissue engineering. Silicon was one of the first materials used for making MNs due to its flexibility that allows easy customization. However, silicon fabrication can be time-consuming and costly with a risk of causing fractures on the skin. Metals are chosen because they possess good biocompatibility and mechanical properties compared to other materials. Stainless steel was among the earliest metal utilized followed by titanium but there's a possibility it may cause allergies when applied on skins. Ceramic substances like alumina offer superior chemical properties which makes them suitable choices while fabricating an arrayed type micro needle however; this substance lacks tensile strength hence might create problems during application. Polymers provide excellent biocompatibility at low cost but they lack strength compared to silicon or metals thus usually being deployed in dissolvable/hydro gel-forming arrays etc., Poly lactic acid (PLA), Poly (methyl methacrylate) (PMMA), poly(carbonate), polystyrene alongside SU-8 photo resist were some examples. [46-60]

***3.1.1 Fabrication techniques: The choice depends on the kind, shape, and material of the microneedle. Different methods are used for different types of microneedles as listed in Table 2. [61, 62, 63]***

| Type of microneedles | Fabrication techniques |
|---|---|
| **Solid microneedles** | |
| **Silicon microneedles** | Solid microneedles Silicon dry-etching process. Isotropic etching, Anisotropic wet etching, Dicing a silicon substrate and then acid etching Three-dimensional laser ablation, |
| **Metal microneedles** | Laser cutting, Wet etching.<br>Metal electroplating methods. |
| **Polymer microneedles** | Photolithography. |
| **Ceramic microneedles** | Ceramic micro moulding and sintering lithography. |
| **Coated microneedles** | Dipping or spraying the microneedles with an aqueous solution of microneedles increased viscosity to retain more formulation during drying and which contains a surfactant, the active agent and a stabilizing agent. Microneedles can be dipped one time or more than one time into a coating solution, each individual microneedle can be dipped into a microwell containing drug solution or a film of drug solution previously formed on the roller can be applied. Layer-by-layer coating techniques. |
| **Dissolving microneedles** | Micro moulding. |
| **Hollow microneedles** | Micro-electromechanical systems (MEMS) techniques-laser micromachining, deep reactive ion etching of silicon, an integrated lithographic moulding technique, deep X-ray photolithography, wet chemical etching and micro-fabrication. |

## 4. Mechanical Characterization of Microneedles:

During the design phase of MNs, it is crucial to consider their mechanical properties in relation to the force applied during epidural insertion. Various types of mechanical tests should be conducted on MNs for characterization purposes, such as axial force, transverse force, base plate breakage, and insertion force. These tests help determine the strength and failure points of the needles. Several studies have been carried out to examine the relationship between mechanical characterization and manufacturing parameters for MNs. The most common test is axial force testing which involves applying vertical forces to both needle tips and the base of an array with an aim at determining needle failure forces that can provide information about expected needle insertion forces. Transverse Force Testing measures resistance while parallelly pressing against microneedle bottom metal mill surface along y-axis direction; this measurement relates closely with bending behaviour upon penetration into irregular skin surfaces. Furthermore, carrying out Insertion Tests

are significant since unlike Axial Forces they offer accurate measurements & require different subject's skins. This allows researchers studying drug release through actual interaction rather than just simulations. [64, 65, 66]

### *4.1.1 Table 3. Overview of mechanical characterization of microneedles. [45]*

| | Description | Importance | Limitations |
|---|---|---|---|
| Axial force | In a vertical way apply force into the needle tip(X-axis) | For the tip of the needle determine the failure force | Not accurate simulation |
| Transverse force | In a parallel way apply force into the base of microneedle (Y-axis) | For the needle base determine the failure force | Not accurate simulation |
| Insertion test | Apply the needle into the rat, pig, or human skin | Actual force on the skin is determined. Ability to release the drug | Required a skin resourse |

## 5. Microneedle Applications Combination with NPs:

### 5.1 MN-Assisted NP Delivery in Cancer Chemotherapy:

Although new strategies for cancer treatment have been developed, chemotherapy remains an important therapeutic method. Nanomaterials have been studied as carriers for anti-cancer drugs to improve their effectiveness and availability. However, using these drugs systemically can cause serious side effects. To overcome this issue, local targeted drug delivery (TDD) of nanocarriers loaded with anti-cancer agents can be used to prevent systemic toxicity. One challenge in TDD is that the skin layers hinder the penetration of nanocarriers. This problem can be solved by using microneedles (MNs), which provide a minimally invasive way of delivering drugs locally through the skin. For example, stainless steel MNs coated with poly (lactic-co-glycolic acid) nanoparticles containing doxorubicin were used for localized drug delivery to oral cavity tumors. Unlike hypodermic needles that result in significant loss of injected volume due to leakage into surrounding tissues or blood vessels; MNs ensure uniform distribution and deposition at their insertion site without any fluid injection process involved. In another study involving cisplatin-loaded lipid nanoparticles mediated by MNs, pH-responsive lipid nanoparticles were designed as carriers for encapsulating cisplatin - leading not only increased solubility but also improved antitumor efficiency when tested on cells grown outside human body ("in vitro"). The combination was then compared against traditional administration methods such as injecting mice directly with either just cisplatin-loaded-MN or nanoparticle-embedded-micro needle systems – showing better tumor response rates from those treated via embedded NPs even though there wasn't comparison made between them alone i.e., no direct assessment comparing standalone nano-particles vs. nano particles delivered thru needling action. Furthermore, it showed absence serum platinum levels indicating its non-toxicity effect towards liver function lung functions kidneys thus ensuring bio safety during therapy. [67, 68, 69]

### 5.2 MN-Assisted NP Delivery in Cancer Immunotherapy:

Focuses on the potential use of microneedles (MNs) and nanoparticles (NPs) to enhance immune responses for cancer treatment. The skin, due to its high density and accessibility of immune cells, is considered an important site for vaccination. Intradermal administration has shown promise in improving antitumor responses against melanoma and prostate cancers. The combination of MNs with NPs offers a method for transcutaneous immunization that stimulates immune responses effectively. In one study, MNs loaded with NPs containing model antigens were used to target specific immune cells called Langerhans cells

(LCs). This approach demonstrated protection against melanoma tumors expressing B16 antigens as well as para-influenza viruses by activating antigen-specific T lymphocytes. Other studies have explored using MNs combined with NPs for cancer vaccination. These approaches showed promising results in preclinical models by topically administering plasmids encoding cancer cell antigens or tumor cell culture-derived antigens loaded into polymeric NPs. Furthermore, combining MN delivery with checkpoint inhibitors or immunosuppressive enzymes may prolong their presence at the tumor site while potentially reducing side effects compared to traditional administration methods. To provide controlled drug release specifically within tumors, researchers integrated HA-based MN patches with pH-sensitive dextran NPs containing anti-programmed death-1 molecules and glucose oxidase enzyme. The enzymatic reaction triggered acidic conditions that caused NP disintegration and subsequent release of anti-programmed death-1 molecules. This approach successfully prevented tumor proliferation in a mouse melanoma model when compared to intra tumoral injection or non-degradable anti-programmed death-1-laden MN patches administered without the enzyme-triggered degradation process. [70-75]

### 5.3 MN-Assisted NP Delivery in Photothermal Therapy:

Photo thermal therapy (PTT) is an alternative technique to chemotherapy that uses near-infrared irradiation. It converts light into heat, causing cell injury and membrane damage. PTT can inhibit tumor growth and trigger the immune response without significant side effects. However, when the tumor is deep within tissue, less light reaches it, reducing PTT's effectiveness in eliminating tumors completely. To address this challenge, researchers have developed delivery systems combining chemotherapy drugs with PTT for a synergistic effect. One promising approach is using microneedles (MNs) to deliver both chemotherapeutic drugs and photothermal agents directly to the tumor site. For example, dissolvable hyaluronic acid MNs containing gold nanorods were loaded with DOX-encapsulated nanoparticles as a NIR-responsive agent for cancer therapy. The release of DOX from these MNs could be controlled by NIR light irradiation. Animal studies showed excellent antitumor efficacy and inhibition of tumor growth after treatment with these MNs. Other studies have also explored transcutaneous co-delivery of chemotherapeutic drugs and photothermal agents using MNs. Recently introduced was an MN-based system featuring co-delivery of indocyanine green-loaded chitosan NPs as photosensitizers along with 1-methyl-tryptophan (IDO) blockade. When exposed to NIR laser irradiation, the ICG-NPs generated heat that destroyed tumor cells, releasing antigens stimulating systematic immune responses. When inserted into the tumor site, MNs dissolved and released ICG NPs which caused pre-apoptotic calreticulin (CRT), a signal encouraging uptake of dead cancer cells by antigen-presenting cells (APCs). Heat shock proteins (HSP70) further help e din APC maturation. The simultaneous release of IDO blockade prevented tryptophan degradation into kynurenine. This local co-delivery of ICG-NPs and IDO blockade not only destroyed primary tumor cells but also inhibited growth of distant tumor cells and lung metastases. [76-81]

### 5.4 MN-Assisted NP Delivery in Photodynamic Therapy:

Photodynamic therapy (PDT) is a non-invasive method used to treat tumors and other diseases. It involves using a photo sensitizer and specific light wavelength to generate reactive oxygen species that can kill damaged cells when tissue oxygen is present. Local administration of the sensitizers is preferred over systemic administration due to its higher selectivity for treatment tissues. Various methods, including MNs, have been explored to improve the delivery of photo sensitizers. MN-mediated PDT has shown promise in tumor treatment by enhancing penetration through skin and increasing drug delivery efficiency compared to topical cream formulations or injections alone. Recent studies have also investigated the use of NP formulations loaded with photo sensitizers for controlled delivery and combination therapies, showing enhanced therapeutic efficacy in treating cancer cells both superficially and deep within tissues. Overall, these findings suggest that MN-assisted photodynamic therapy holds great potential as an effective and safer treatment option. [82-95]

### 5.5 MN-Assisted NP Delivery in Delivery of Therapeutic Proteins:

MN technology has provided a groundbreaking solution for delivering proteins. The delivery of therapeutic proteins faces challenges such as degradation and large molecule size. MN technology offers a promising system that can deliver proteins into the systemic circulation by smoothly passing through the skin. In recent years, MN technology has been widely used to effectively deliver various types of proteins including antigens, antibodies, insulin, exendin-4, and lysozyme. For instance, using MNs in insulin delivery has proven to be non-invasive and painless for diabetic patients looking to regulate their glucose levels. There are different approaches in utilizing MNs for protein delivery systems. Hollow MNs have shown promise in clinical trials while dissolving them with micro particles improves mechanical strength and sustained release capabilities compared to pure PVP-based ones. Programmable MNs offer benefits like reducing hypoglycemia risk associated with unnecessary drug release by incorporating smart pH-triggered abilities or integrating MBGs capped with ZnO QDs that respond specifically to glucose levels resulting in controlled insulin release without side effects. The combination of NPs with PN-loaded-MNs is also being explored as it allows fast administration alongside blood-glucose sensing capability which enables basal or hyperglycemic condition-dependent control over continuous insulin release thus improving diabetes management prospects. MNs have potential applications beyond diabetes treatment; they've been utilized successfully so far for transdermal vaccination aiming at treating immunological issues related mainly but not limited only skin tumors where combining transfersomes (containing anti-PD1 antigen & adjuvant) loaded onto functionalized αCD40-targeting-ligand-equipped-MN resulted remarkable improvement on DC maturation along Th1 immune response leading improved T cell activation/infiltration behavior meanwhile mitigating regulatory T cells activity suppressing tumor micro environmental immunity against cancerous dendritic melanoma model sites. Additionally, MicronJet600 hollow capsules were deployed carrying AuNP-conjugated auto-antigen peptides, DCs have shown to uptake AuNPs and further activate the T-cells which opens a new potential for utilizing MN as

immunotherapy solution in future. [96-102, 13-20]

### 5.6 MN-Assisted NP Delivery in Vaccine Delivery:

Most vaccines are currently administered using hypodermic needles, which require skilled administration and careful temperature control during storage and transportation. However, a solution to these issues can be found in the use of microneedles (MNs). MNs painlessly penetrate the skin barrier and improve vaccine delivery while reducing reliance on cold chain storage and reconstitution. They also offer a unique strategy for delivering antigens directly to immune cells within the skin. Studies have shown that MN-based vaccination systems can achieve similar or even higher immunogenicity with less required doses compared to traditional methods. Various strategies involving different types of MNs have been applied successfully with influenza virus vaccines among other formulations such as Human papillomavirus (HPV) vaccines. The combination of nanoparticles (NPs) with MNs has further enhanced antigen stability and controlled release, leading to improved immunogenicity. For instance, encapsulating chicken OVA into PLGA-NPs incorporated in dMNs allowed slow release of antigen specifically targeting lymph nodes occupied by DCs resulting in successful activation against influenza viruses as well melanoma tumors. In another study, intradermal delivery through hollow MNs loaded mono phosphoryl lipid A(OVA), imiquimod (TLR agonists), along with Toll-like receptor were able produce high levels IgG2a antibody response IFN-γ-producing lymphocytes when delivered via Hollow-MNS rather than intramuscular injection. Moreover, Guangsheng et al., compared various nanocarriers like MSNS, liposomes, gelatin NPS etc. they observed liposome induced significantly more CD4+and CD8+ T cell activations comparing others.[44]

### 5.7 MN-Assisted NP Delivery for Gene Therapy:

Gene therapy, which involves replacing a faulty gene with therapeutic nucleic acids, has potential applications in treating various genetic skin disorders, cutaneous cancers, and wound healing. Transdermal DNA delivery offers advantages such as localized administration over a large surface area while bypassing initial metabolism. However, the stratum corneum (SC) poses limitations on transdermal drug delivery (TDD), especially for macromolecules like nucleic acids. To overcome this challenge, different physical techniques including gene gunning, iontophoresis, sonophoresis needle-free liquid jet injections intradermal injection electroporation and micro-needles have been employed to deliver DNA therapeutics through the skin. Among these methods is the use of solid micro-needles arrays that have shown promise for delivering naked plasmid DNA or its combination with nanoparticles (NPs). Studies using blunt-tipped silicon micro-needles demonstrated significantly increased gene expression compared to topical application when introducing bare plasmid DNA encoding firefly luciferase into disrupted mouse skin. Similarly, silicon microneedle-assisted delivery of hepatitis B surface antigen encoding pDNA resulted in robust antibody production compared to intradermal injection alone. The combinatorial use of NPs allows better control over release kinetics gene loading and cellular uptake when delivered via MNs. In one study conducted by Ruan et al., melanoma treatment was achieved by coating MNs with BRAF siRNA complexes combined with cell-penetrating peptide octa arginine (R8). In vivo experiments

showed significant inhibition of melanoma development along with apoptosis induction and suppression of cell proliferation in mice bearing melanoma. Micro-needle arrays are particularly considered for transcutaneous administration of DNA based vaccines. For instance, a double conjugate system consisting polyethyleneimine (PEI) conjugated mannose (Man)and TAT:RRRQRRKKRC-SH cell-penetrating peptide was used to condense DNA vaccines, which were then delivered using solid micro-needles. This approach successfully activated Trp2-specific responses leading to effective immune system activation against B16 melanoma in mice. In the same study, Xu et al. employed MNs for co-delivery of a DNA vaccine and low-dose paclitaxel (PTX) encapsulated within polymeric nano complexes for cancer immune therapy. The PTX/SBE complex acted as an anionic cross linker that self-assembled with cationic mannosylated N, N, N-trimethyl. [21-25]

**6. Future perspective and current challenges:**

The extensive research conducted in recent years on different types of microneedles (MNs) has raised several important issues regarding their use in clinical settings. The application of MNs can potentially raise safety concerns for patients, both in the short-term and long-term.

While there are generally no major complications associated with short-term use, long-term use may result in skin redness and pain depending on factors such as needle size and number. The effectiveness of MNs also depends on the availability of open micropores, which can be affected by an individual's skin type. Recent studies have shown that people from different ethnic backgrounds may experience variations in micropore closure time following MN application.

Another challenge is the large-scale production of MNs, which could hinder their widespread adoption for medical purposes. Other limitations include a lack of specific regulatory guidelines for quality control tests, requirements for human safety during clinical applications, pharmacokinetic evaluations to confirm efficacy and safety, increased production costs due to sterilization processes or aseptic conditions required during manufacturing, specialized machinery and clean room facilities needed upfront investment, and suitable packaging solutions to protect against moisture damage or microbial contamination. These complex production challenges along with various other concerns related to their usage might impede the translation into clinical practice. Therefore, future fabrication methods like 3D printing technologies should be explored since they have potential capabilities to reduce cost. and complexity.

Despite these challenges, Nanoparticle (NP)-laden Microneedles (MN)s are expected show rapid development considering its emerging features promising favorable outcomes. though more investigations need to exploit therapeutic benefits. NPs incorporation within matrix alters mechanical properties resulting it requires characterization using variety of mechanical test. In addition, stability dispersibility, deterioration function needs special attention. Moreover, reliable preclinical model necessary elucidate molecular basis observations. Furthermore, Asepsis, Large scale productions proper storage must kept in mind.

## 7. Conclusion:

The use of minimally invasive techniques for transdermal drug delivery (TDD) has been a challenge, but recent advancements in delivery systems have aimed to overcome the limitations associated with conventional therapies. One promising approach is the use of nanoparticles (NPs), which can act as effective carriers for delivering drugs while reducing side effects and improving skin permeation. NPs also possess unique properties that enable new applications in therapeutics, imaging, and bio sensing.

Micro-needles (MNs)-based delivery systems have gained attention due to their non-invasive and pain-free nature, without causing infections or safety concerns. MNs can transport NPs directly into deeper layers of the skin, leading to improved treatment outcomes for various skin disorders. Combining MNs with NP-containing therapeutic agents offers additional benefits such as enhanced penetration into the skin and controlled release over time.

Although there is still much exploration needed, combining NPs with MNs shows promise in cancer chemotherapy by effectively targeting tumors. These combined systems are also being investigated for vaccination purposes, immunotherapy treatments, and gene delivery methods.

To successfully deliver NPs using MNs, a thorough understanding of factors like NP characteristics and proper strategy development is necessary. The practical aspects should be evaluated reliably through clinical trials. This combination could significantly impact nano medicine's ability to treat both local skin conditions and systemic diseases in an effective manner.

## 8. Author contribution:

All authors made significant contributions to the idea and design, data acquisition, or data analysis and interpretation; took part in drafting the article or critically editing it for essential intellectual content; agreed on the journal to which the article would be submitted; provided final approval of the version to be published; and agreed to be responsible for all aspects of the work.

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The authors state that they do not have any competing concerns.

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