RESEARCH PAPER

NANOCARRIER-INTEGRATED MICRONEEDLE SYSTEMS FOR ADVANCED TRANSDERMAL DRUG DELIVERY: RECENT PROGRESS, THERAPEUTIC APPLICATIONS, AND FUTURE PERSPECTIVES

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ABSTRACT
Transdermal drug delivery systems (TDDS) provide a non-invasive alternative to conventional oral and injectable therapies by improving patient compliance, minimizing systemic adverse effects, and bypassing first-pass metabolism. However, the stratum corneum acts as a major barrier limiting the permeation of hydrophilic and high-molecular-weight therapeutics. Recently, nanocarrier-loaded microneedle (MN) systems have emerged as a promising strategy to overcome these limitations and enhance transdermal delivery efficiency. This review discusses the design, functional characteristics, and therapeutic potential of various microneedle platforms, including solid, coated, dissolving, hollow, and hydrogel-forming systems integrated with nanocarriers such as lipid nanoparticles, polymeric nanoparticles, metallic nanoparticles, and vesicular carriers. These hybrid systems enhance skin penetration, improve drug stability, enable controlled and stimuli-responsive release, and facilitate targeted intracellular delivery. Their applications in cancer therapy, vaccination, dermatological disorders, chronic diseases, and diagnostic biosensing are critically highlighted. Recent advances in smart and wearable microneedle technologies further support the development of personalized transdermal therapeutics. Despite significant progress, challenges related to large-scale manufacturing, reproducibility, regulatory approval, and long-term nanomaterial safety continue to limit clinical translation.

Keywords: Transdermal drug delivery, Microneedles, Nanocarriers, Nanoparticles, Controlled drug release, Skin permeation, Smart drug delivery, Biosensing.
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Introduction

Conventional transdermal drug delivery system and its limitation

The Transdermal Drug Delivery System (TDDS) is a non-invasive, painless medication administration technique that is found to be superior to other traditional delivery methods. The TDDS is a type of Minimally Invasive Drug Delivery Systems (MIDDS) which compared to conventional medication delivery techniques, have several benefits, and offer a patient-friendly, minimally invasive alternative for treating a variety of ailments.[1]

In TDDS, the medication enters the systemic circulation through the layers of the skin and is administered in a discrete dosage form using a skin-patch or other transdermal delivery techniques. TDDS system aid in the delivery of many different therapeutic substances, particularly in the areas of pain management, cardiovascular disorders, central neurological systems, etc. This delivery system has been recognized as a successful alternative of Several routes of administration, including oral, parenteral, intravenous, intramuscular, hypodermal injections, and other invasive delivery methods.[2]

Most macromolecules cannot pass through the skin barrier; however, some larger molecules can still pass through passively because cutaneous absorption depends on physicochemical characteristics like the degree of ionization and the partition coefficient in addition to molecular size.[3] Specifically, non-ionized substances or molecules with an intermediate partition coefficient can easily dissolve in the stratum corneum's (SC) lipophilic matrix before diffusing across the intercellular channel.[4]

Acting as the outermost layer of skin, the SC prevents effective therapeutic drug transport over the skin.[5] This layer is made up of corneocytes embedded in a dense, mortar-like matrix of ceramides, cholesterol, and free fatty acids, forming a highly controlled barrier that prevents passing of molecules larger than 500 Daltons or with poor hydrophilic-lipophilic balances.[6] Drug molecules at the skin-formulation interface partition into the stratum corneum, whereas molecules from the bulk formulation redistribute to keep the interfacial balance.[7] Lipophilic medicines are best given

from hydrophilic carriers via partitioning. The rate of redistribution is determined by formulation characteristics such as viscosity. Drug dissolving in particle systems has a further impact on the early stages of cutaneous delivery.[8]

Microneedles (MNs) are made up of micrometre-scale structures placed in patches that allow a variety of compounds to be delivered via the skin. MNs for drug delivery are typically 50-1000 μm in height, allowing them to pierce the SC and deliver the medicine straight to the blood vessels in the dermis. This method avoids stimulating the dermal nerves, preventing deep tissue injury or pain.[9]

Utilizing the self-assembling characteristics of surfactants, nanocarrier systems ranging from lipid-based nanoparticles to vesicular systems like niosomes encapsulate medications and shield them from deterioration, making easier for them to pass through the dermal barrier.[10] Microneedle patches with nanocarriers are one of the most effective ways to improve transdermal penetration.[11]

Functional Benefits of Microneedles in Transdermal Delivery

The combination of nanotechnology and microneedle (MN) systems offers a potentially revolutionary approach to precision medicine and next-generation drug delivery, with a rapidly growing range of applications in both therapeutic and diagnostic fields.[12] From a therapeutic standpoint, nanocarrier-loaded microneedles make it possible to effectively deliver a variety of bioactive molecules transdermally, such as vaccines, peptides, proteins, nucleic acids, small-molecule medications, and gene-editing constructs.[7] These molecules typically encounter issues like poor permeability, instability, and systemic side effects.[13] The platform may be used to administer drugs in a sustained, targeted, and less invasive manner, which has great promise for addressing localized and chronic diseases such as diabetes, cancer, neurological disorders, dermatological issues, and infectious diseases.[14] Because nanomaterials are so versatile, they may also be used to incorporate smart release mechanisms and stimuli-responsive mechanisms, which enable regulated therapeutic dosage in response to physiological triggers like temperature, pH, glucose levels, or inflammatory biomarkers.[15,15,16]

Search methodology

A comprehensive literature search was carried out using PubMed, Scopus, Web of Science, and Google Scholar for papers published between 2008 and 2026. The keywords were "microneedles," "nanocarriers," "transdermal drug delivery," and similar Boolean combinations. Peer-reviewed publications, reviews, and pertinent preclinical/clinical research in English were selected based on their relevance to microneedle-nanocarrier integration. Selected papers were further reviewed using reference lists and classified according to microneedle type, nanocarrier system, and therapeutic use.

Skin Barrier and Design Principles for Transdermal Delivery

Usually, the size and hydrophobicity/hydrophilicity index of active ingredients and medications determine their ability to pass across the SC barrier.[17] In general, hydrophilic actives with large molecular weights have lower permeabilities across the SC barrier than smaller molecules with hydrophobic characteristics.[18] However, numerous of passive and active techniques, such as the use of electrical impulses, ultrasound, chemical penetration enhancers, and others, have been developed to overcome around this limitation. In order to improve solute/drug penetration, these techniques usually involve any form of SC barrier depletion.[19]

Passing through the SC, the epidermis' outermost layer, is crucial for effective medication permeation. Medicinal substances can enter this barrier mainly through two recognized routes. Trans-epidermal route, which involves moving of molecules through the skin's cellular matrix.[20] There are two ways it can happen: direct drug absorption into and through individual skin cells, which works especially well for hydrophobic substances because of the lipid-rich environment of cell membranes. Another means of absorption involves moving via the interstitial gaps between neighboring cells in the extracellular matrix.[21]

The most popular technique for transdermal delivery of biologics in both recent and historical clinical trials is microneedles. Similar to traditional needles, which require skin piercing for systemic distribution, microneedles work similarly. With a maximum size of a few hundred micrometers, microneedles are made to be sufficiently sharp

to penetrate without damaging the SC, allowing for systemic drug absorption. [20,22] Many of the same benefits as the conventional transdermal patch are provided by microneedles, including the ability to be applied by patients themselves, low pain and discomfort, and substantially enhance patient compliance and convenience.[23]

Not all APIs are appropriate for transdermal medication delivery. Percutaneous absorption is influenced by the drug's molecular weight, solubility, partition coefficient, dissociation constant, and other physical and chemical characteristics, as well as the type of carrier vehicle and skin condition.[24,25] APIs with molecular weights between 400 and 500 Daltons that are sufficiently soluble in lipids and water can penetrate the skin. About 400 Daltons or less is the ideal molecular weight for an API meant for a TDDS.[26]

Microneedles for transdermal drug delivery

Microneedles (MNs) form tiny pores in the skin, which allow medications to reach the skin's deeper layers without breaching the SC.[27] Slender needles, measuring 10–2000 μm in length and 10–50 μm in width are functional characteristics of MNs.[28] As the microneedles come into alignment with the skin, some of them are designed to disintegrate, while others remain in place to enhance drug absorption. The main benefit of MNs is its great skin penetration efficiency, which allows for painless medication delivery, improved patient compliance, and the benefit of self-administration.[29] Furthermore, a variety of medications, including small molecular weight medications, oligonucleotides, DNA, peptides, proteins, and even inactivated viruses, can be delivered locally or systemically through the skin using a variety of selection of needle materials.[30]

A study investigates the creation of dissolving microneedles using ulvan, a naturally occurring sulfated polysaccharide, to enhance transdermal medication administration by getting past the SC barrier. In vitro models are used to systematically assess the shape, mechanical strength, insertion efficiency, dissolution behavior, drug loading, penetration, and biocompatibility of ulvan-based microneedles that are fabricated utilizing a two-step casting process. The microneedles effectively penetrate the dermis, dissolve within minutes, and significantly improve the delivery and sustained release of both low- and high-molecular-weight drugs while retaining good cellular compatibility, demonstrating their potential as an efficient and minimally invasive TDDS for pharmaceutical and cosmeceutical applications.[31]

Solid MNs

Solid microneedles (MNs) are used as a skin pretreatment method to temporarily disturb the SC and increase skin permeability before medication delivery.[32] This system use the 'poke and patch' technique to construct microchannels. These microchannels increase medication permeability by permitting diffusion from a formulation directly into the skin layer.[33]

Coated MNs

The coated MNs approach involves coating MNs with a drug solution or dispersion and using the coat-and-poke concept to diffuse the drug to the epidermal layers following insertion.[34] The predominant technique to develop coated microneedles is dip coating; nonetheless, it is intricate because to the necessity for meticulous supervision to ensure the proper immersion of the MNs into the dipping solution. Alternative approach of coating is through spray coating and aerosol coating methods.[33]

Dissolving MNs

Dissolving microneedles (MNs) work by a poke-and-release process. When inserted into the skin, the biodegradable matrix, which is typically made up of polymers or sugars, dissolves, allowing for regulated release of encapsulated medications or vaccinations.[35] The most popular method for creating dissolving microneedles is microcasting or micromolding. This method involves utilizing a centrifuge or vacuum to fill a microneedle with a material's solution, slurry, or suspension.[36]

Hollow MNs

Hollow microneedles (MNs) are miniature versions of traditional hypodermic needles that work on a poke-and-flow principle. Drug distribution is accomplished via a pressure-driven flow of liquid formulation. They have an interior lumen that allows liquid medication formulations to be pressed into the skin.[33] Hollow MNs can be used to constantly administer a medication formulation that is kept in a reservoir or by forming holes in the skin to collect bodily fluids. When using Hollow MNs, standard flow-control instruments like syringes and micropumps can be utilized to regulate the medication flow rate intentionally.[37]

Table 1 Comparison of Microneedle Types, Functional Characteristics, and Clinical Relevance

Based on their functional performance, drug loading technique, and structural design, the **Table 1** lists the many kinds of microneedle (MN) systems. In addition to offering unique benefits in terms of clinical application, release kinetics, and drug delivery efficiency, each MN design has unique drawbacks in terms of mechanical strength, manufacturing, and dosage capacity.

Microneedle Type	Structural Design & Drug Loading Strategy	Advantages	Limitations	Major Clinical / Therapeutic Applications	Reference
Solid Microneedles	Fabricated from metals, silicon, or rigid polymers; create microchannels in skin followed by external drug application ("poke-and-patch" approach).			• Risk of channel closure before full drug absorption	[38]

		• Minimal formulation complexity		• Enhancement of topical drug permeation	
Coated Microneedles	Drug coated as a thin film on the needle surface; rapid dissolution after insertion enables immediate drug release.			• Rapid therapeutic administration (e.g., analgesics, peptides)	[39, 40]

		• Minimally invasive	• Stability issues during storage		
Dissolving Microneedles	Made from biodegradable or water-soluble polymers encapsulating drugs within the matrix; needles dissolve after insertion.				[41]

		• Enhanced stability of biologics	• Polymer selection influences release kinetics	• Dermatological and cosmetic therapy	
Hollow Microneedles	Contain internal microchannels enabling active or passive infusion of liquid drug formulations.				[42]

		• Suitable	• Potential leakage and structural fragility		

		for macromolecules and nanoparticle suspensions		• Infusion of biologics and nanomedicines	
Hydrogel-Forming Microneedles	Crosslinked polymer networks that swell upon insertion and act as drug diffusion conduits connected to external reservoirs.		• Manufacturing complexity	Biosensing and theranostic applications	[43]

		• Compatible with high-dose			
		delivery			
Nanocarrier-Integrated / Hybrid Microneedles	Incorporate nanoparticles (liposomes, SLNs, polymeric NPs, metallic NPs) within or coated onto micro				[44]

	needles for targeted and stimuli-responsive delivery.	Improved permeation and bioavailability • Multifunctional therapeutic capability	• Long-term nanomaterial safety concerns		

				• Precision and personalized medicine	

Nanocarriers and their incorporation into microneedles

Nanoparticles (NPs) / nanocarriers can target damaged tissue or provide control over medication release in addition to improving the skin penetration of small/biomacromolecular therapeutic agents.[45] NPs have also been used in imaging, biosensing, and the treatment of skin conditions because of their special optical, photothermal, and superparamagnetic properties as shown in Figure 1. The distribution of NPs across the SC, the primary skin barrier, has proven difficult despite their ubiquitous transdermal use.[46] Recently, microneedle array (MN) technology has shown encouraging results in the administration of several formulations, particularly NPs to deliver therapeutic compounds that are both hydrophilic and hydrophobic.[47]

A study demonstrates a synergistic strategy that overcomes the primary limitations of DNA vaccine delivery, such as limited immunogenicity and poor skin penetration, by combining cationic nanocarriers with microneedle (MN)-based physical enhancement. Hollow microneedles showed superior efficacy among the evaluated techniques by directly avoiding the SC through a "poke-and-flow" mechanism, enhancing plasmid DNA (pOVA) permeation up to 64-fold in comparison to passive diffusion. By facilitating effective DNA condensation, protection from nuclease degradation, and increased cellular uptake, the addition of cationic nanocarriers such as polyethylenimine (PEI), Lipofectamine 2000, and Superfect further improved intracellular delivery. PEI (1:1 ratio) demonstrated the highest transfection efficiency because of its ideal nanoscale size and proton sponge-mediated endosomal escape.

Once the barrier was bypassed, nanocarriers did not significantly change dermal penetration; however, they were crucial in enhancing biological results, as demonstrated by noticeably greater IgG responses in vivo when compared to naked DNA, with hollow MN-mediated delivery outperforming traditional subcutaneous administration. Notably, dendrimer-based carriers demonstrated relatively lower but sustained responses, while Lipofectamine-based systems demonstrated decreased *in vivo* efficacy due to serum instability. Overall, the work shows that combining hollow microneedles with tailored nanocarriers, PEI—offers a safe, highly effective, and minimally invasive platform for improving transdermal gene delivery and vaccination results.[48]

A drug delivery system comprising poly (lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) loaded with dexamethasone (DEX) and integrated into sodium alginate (SA) microneedles (MNs) has been investigated. Nanoprecipitation was used to yield drug-loaded PLGA NPs with a high encapsulation yield. Pattern of controlled release over 120 hours is shown by these systems. A modified vacuum-deposition micromolding process was used to load the resultant DEX-NPs into the tips of dissolving MNs. When evaluated against various static stresses, the NP-MNs outperformed their counterparts (SA-MNs) in terms of mechanical strength and insertion capabilities into the skin-simulant parafilm model.[49]

Nanoparticles (NPs) are tiny particles that range in size from 1 to 100 nm.[50] Large surface area-to-volume ratio, high mobility in free state, and electronic properties affected due to quantum effects are three main characteristics they have. Although nanoparticles have been proved to be effective medication transporters, formulation remains a significant hurdle. Due to the effects of Ostwald ripening and Brownian motion, they tend to aggregate when in solution.[51]

Types of NPs loaded in NPs MNs

Gold NPs

Gold NPs are made up of gold atoms that have unique optical and electrical capabilities due to their nanoscale size.[52] These characteristics render them relevant in a variety of sectors, particularly healthcare and technology. Gold nanoparticles are utilized in medicine to enhance targeted therapy and bioavailability.[53] They are also used in photothermal and photodynamic therapy to eliminate cancer cells by localized heating when exposed to specific light wavelengths.[54]

El-Sayed *et al.* addressed the drawbacks of systemic nanoparticle delivery, including poor tumor targeting and off-target toxicity, by designing polyethylene glycol (PEG)-stabilized gold nanostars (GNSs) and incorporating them into dissolving polyvinylpyrrolidone (PVP) microneedles (MNs) to enable localized photothermal therapy for melanoma. To enable to maximize near-infrared (NIR) plasmon resonance, the GNSs were synthesized using a seed-mediated approach with regulated $AgNO_3$ concentration and PEG functionalization. Physicochemical

characteristics, cytocompatibility, and photothermal efficiency were then assessed under 808 nm irradiation.

The modified nanostars demonstrated considerable melanoma cell destruction (>90%) upon irradiation, strong NIR absorption (~800 nm), high heat generation (~65–66°C), and biocompatibility. Nanoparticle stability, mechanical integrity, and photothermal performance is maintained after being included in PVP-based dissolving MNs. This resulted in effective skin insertion, quick dissolution (~3 min), and localized temperature elevation (~63 °C) in pig skin. Overall, the work shows that PEG-stabilized GNS-loaded MNs offer an effective and minimally invasive platform for targeted intradermal administration of photothermal medicines, improving superficial tumor therapeutic precision.[55]

Liposomes/Niosomes

Liposomes are spherical vesicles made of lipid bilayers that may transport both hydrophilic and hydrophobic medicines, improving bioavailability and lowering toxicity.[56] They are the most popular nanocarriers for active compounds because of their high biocompatibility, biodegradability, and minimal immunogenicity. Liposomes increase drug solubility and allow for regulated distribution, with the capacity to change surfaces for targeted, prolonged, and sustained release.[57]

Polymeric NPs

Natural polymers like albumin, gelatin, chitosan, and alginate compose natural polymeric nanoparticles. These natural polymers are typically extracted and then subjected to various purifying processes.[58] These naturally occurring polymers' tendency to form hydrogels makes them perfect transporters for proteins, peptides, oligonucleotides, and water-soluble medications.[59]

Kim *et al.* synthesized retinol-loaded chitosan nanoparticles by ion complexation and examined their size, shape, and encapsulation as a polymeric nanocarrier for topical/transdermal administration. The nanoparticles (50–200 nm) maintained the medication in an amorphous encapsulated state, showed good reconstitution and loading efficiency, and greatly increased retinol solubility (>1600-fold). These findings demonstrate that chitosan-based nanoparticles improve stability and solubility and are appropriate carriers for TDDS applications.[60]

Solid lipid NPs

Solid lipid nanoparticles (SLNs) are typically made of safe, biodegradable lipidic components. SLNs are special because they can carry a variety of medications, including genetic material (DNA/siRNA), vaccine antigens, large biomacromolecules (polysaccharides, etc.), and tiny drug molecules. Both hydrophilic and lipophilic drugs can be loaded by these tiny molecules.[61]

SLNs' adaptability in several fields of research and development is leading to the emergence of several therapeutic patents because of their low risk/benefit ratio.[62] SLNs have been tested and patented for their ability to transport anticancer drugs (Methotrexate, Docetaxel), antitubercular drugs (Rifampicin, Isoniazid, Pyrazinamide), vitamins, topical medications (minoxidil, Roxithromycin, Tazarotene), anti-inflammatory and antioxidant agents (curcumin), enzymes (catalase), low molecular weight heparin (LMWH), and several other therapeutic molecules.[63]

Singha *et al.* explored the use of nanoparticle-based transdermal administration by creating Neratinib-loaded solid lipid nanoparticles (SLNs) that were mixed into dissolving microneedles to overcome poor solubility and bioavailability constraints. The SLNs were prepared by hot homogenization and characterized for particle size (~209 nm), entrapment efficiency (~87%), morphology, and controlled release behavior. They were then integrated into polymeric microneedles and evaluated for ex vivo skin permeation and in vitro cytotoxicity.

The system showed sustained drug release (~80% over 24 hours), increased skin penetration, and improved anticancer efficacy compared to free drug, indicating better cellular uptake and lower systemic toxicity. These results demonstrate that SLN-loaded microneedle systems greatly improve drug solubility, permeability, and targeted delivery, confirming their potential as a successful TDDS platform based on nanoparticles as shown in **Figure 1.**[64]

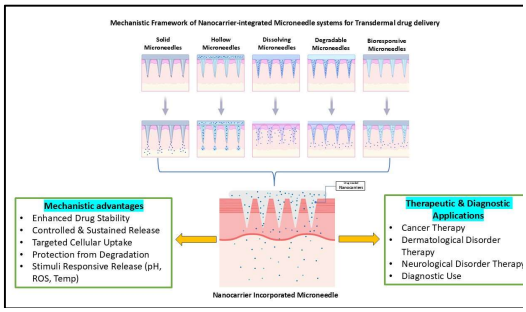

Figure 1 Mechanistic framework of nanocarrier integrated microneedle systems for transdermal drug delivery

Therapeutic Applications and Translational Evidence of nanocarriers integration with microneedles

Cancer

There are notable synergistic results when MNs technology is used in conjunction with immunotherapy, gene therapy, chemotherapy, and photodynamic therapy to treat cancer.[65] By enhancing antigen distribution to antigen-presenting cells (APCs), like cutaneous dendritic cells, MNs in immunotherapy improve immune response to cancer vaccines and encourage local immunological activation.[66] Precise immunological regulation can also be facilitated by the local delivery of immune checkpoint inhibitors via MNs.[67] MNs in gene therapy provide for the effective transport of RNA interference molecules or tumor-suppressor genes, improving the selectivity of gene editing for tumor cells while overcoming the low transfection effectiveness of in vitro approaches and possible toxicity of viral vectors.[68] Using biodegradable MNs or nanoparticle encapsulation, MNs enable continuous drug release during chemotherapy while facilitating localized drug delivery, reducing systemic toxicity and adverse effects.[69]

Researchers designed a dissolving microneedle patch loaded with folic acid-conjugated silver nanoparticles for the transdermal administration of letrozole in the treatment of breast cancer.[70] Chitosan-based microneedles (575 µm height, 10×10 array) with great mechanical strength (1.41 N), high drug entrapment efficiency (95.7%), and excellent skin penetration without irritation were successfully integrated with the nanoparticles (≈87 nm). Ex vivo permeation revealed significantly improved letrozole transport (≈84%) in comparison to traditional ointment, while in vitro release tests showed sustained drug release over 48 hours following Korsmeyer-Peppas kinetics. The system's potential as a safe, targeted, and minimally invasive platform for breast cancer treatment was highlighted by cytotoxicity experiments on MCF-7 cells, which showed increased anticancer activity (IC_{20} = 50 µM) and a 3.2-fold higher targeted uptake due to folate receptor-mediated administration.[71]

Dermatological Disorders

Acne Treatment

Acne is the most common skin condition and a very common chronic inflammatory dermatosis. It is a long-term inflammatory disease of the pilosebaceous unit brought on by a variety of interrelated factors.[72] The pathogenic mechanisms include dysbiosis of the cutaneous microbiota centered on Cutibacterium acnes (previously Propionibacterium acnes), abnormal keratinization of the follicular duct, excessive sebum production, and ensuing inflammatory cascades.[73]

Eugenol-loaded hyaluronic acid dissolving microneedles (E@P-EO-HA-MNs) with polydopamine nanoparticles (PDA NPs) as photothermal agents were created by Wang *et al.* At the points of the microneedles, eugenol-loaded PDA (EO@PDA) was placed. Rapid heating caused by 808 nm NIR irradiation destroyed sebaceous glands and inhibited *Propionibacterium acnes (P. acnes)*, which decreased inflammation. After HA disintegration, more eugenol was embedded in the needle matrix for sustained release, which promoted skin healing and had long-lasting antibacterial and anti-inflammatory properties.[74]

Psoriasis Treatment

A common immunoinflammatory skin disorder, psoriasis is characterized by aberrant skin thickness that prevents drug penetration and complicates standard topical drug delivery.[75] Through designing a transdermal medication formula, one can intend to improve the effectiveness of psoriasis treatment. By improving topical medicine absorption through skin penetration, microneedles (MNs) can enhance therapeutic outcomes.[76]

Zhou *et al.* created a ROS-responsive methotrexate prodrug (MTX-TK-HA) that targets hyperproliferative keratinocytes through CD44, providing a new treatment for psoriasis. PLA-mPEG (Poly (lactic acid)–methoxy polyethylene glycol) was used to nano-precipitate the prodrug into nano-assemblies, which were then added to

dissolving microneedles (MNs). CD44-mediated endocytosis becomes feasible by the efficient penetration of psoriatic skin by these mechanically strong, hyaluronic acid-based MNs. ROS-induced MTX release decreased keratinocyte growth by blocking the NF-κB pathway. This synergistic prodrug–MN approach dramatically reduced psoriatic inflammation in an animal model, suggesting enhanced transdermal delivery for psoriasis and other ROS-related conditions.[77]

Researchers created a multilayer dissolving microneedle device for need-based treatment of Psoriatic arthritis, which allows for the simultaneous targeting of skin and joint lesions. Tacrolimus was added to the interlayer to help retain the epidermis, while diclofenac was added to the tip layer to reach deeper tissues and the articular cavity. Permeation tests demonstrated depth-specific drug localization, which outperformed non-layered mixed-drug systems. *In vivo* data revealed significant reductions in psoriasis severity, joint inflammation, cartilage degradation, and pro-inflammatory cytokines, indicating a successful dual-site therapeutic action.[78]

Chronic And Neurological Disorders

MNs system allows for the targeted, minimally invasive, and prolonged transdermal administration of medications that frequently have systemic adverse effects or poor oral bioavailability, aiding in treatment of neurological and chronic conditions. Through painless, self-applicable forms, MN systems improve patient adherence by facilitating controlled medication administration for chronic ailments, including diabetes, cardiovascular diseases, and hormonal disorders.[79] MNs are investigated for the delivery of neuroprotective drugs, peptides, and other biologics in the setting of neurological illnesses. These biologics usually encounter issues with systemic degradation and blood–brain barrier permeability.[80,81] Dissolving and hydrogel-forming MN platforms improve therapeutic effectiveness while eliminating fluctuations associated with traditional methods by permitting steady-state plasma concentrations and lowering dose frequency. The combination of nanocarrier-loaded MN arrays with stimuli-responsive materials is also emphasized as a means of achieving better pharmacokinetic profiles and precise dosage for the long-term treatment of neurodegenerative and chronic illnesses.[82,83]

Diagnostic Applications

MNs for diagnosis can be classified into four types: electrochemical biosensors, direct extraction of interstitial fluid (ISF) via hollow MNs, direct absorption via coated, porous, swellable hydrogel MNs, and analyte capture on the MNs' surface.[84]

Diagnosis-Oriented Biosensor

MN-based electrochemical biosensors that use surface-functionalized and metallized solid microneedles to detect analytes in target samples, such as glucose, lactate, alcohol, and medicinal drugs, can reflect the body's current states and transform biochemical data into analytical signals in the form of current or voltage. The linear detection range, reaction time, sensitivity, selectivity, limit of detection (LOD), and stability of the sensor can all be used to assess its performance.[85]

Yuan *et al.* investigate electrochemical biosensors based on microneedles (MN) as a minimally invasive and effective platform for real-time biomarker monitoring in interstitial fluid (ISF). Their research demonstrates the benefits of MN systems, such as their appropriateness for wearable and point-of-care applications, quick and sensitive electrochemical signal transduction, direct ISF access, and painless skin penetration. Overall, it shows how MN-based electrochemical biosensors can be used for decentralized, sensitive, and ongoing biomarker monitoring.[86]

Diagnosis-Oriented ISF Extraction

In MN-based direct ISF extraction, ISF can be extracted via capillary action, vacuum, or suction via the hollow MNs bore. Hydrogel MNs' 3D cross-linked network structure allows them to absorb ISF through swelling.[87] The acquired ISF can be analyzed using both laboratory equipment and built-in sensors.[88]

To facilitate minimally invasive contact with interstitial fluid through the skin, a conductive hydrogel microneedle system using nanostructured materials was created.[89] To provide both structural integrity and electrochemical activity, the platform was constructed utilizing a dopamine–hyaluronic acid hydrogel matrix integrated with a conductive polymer (PEDOT: PSS) and in situ generated Ag–Pt nanoparticles. *In vitro, ex vivo*, and *in vivo* models, the obtained microneedle array showed efficient skin penetration, stable operation, and sensitive real-time detection capacity.[90] The work

demonstrates how nanoparticles can be effectively embedded within microneedle architectures, providing important material and fabrication insights pertinent to the design of nanocarrier-integrated microneedle systems for transdermal applications, despite being primarily intended for biosensing rather than drug delivery.[91]

Performance and safety assessment

Reliability on microneedle-based delivery system can be guaranteed by characterizing it's mechanical, pharmacological, and biological abilities to ensure clinical safety. Microneedles should be structurally strong enough to penetrate the SC without infringement.[92] Loading accuracy, stability tests in regulated temperature and humidity environments, homogeneity, and release kinetics are important factors that needs to be determine for improved drug delivery.[93] To assess biocompatibility, in vivo dermatological investigations and in vitro cytotoxicity tests are used. By avoiding stimulation of deeper dermis nerves, MNs minimizes discomfort and improves patient acceptance.[94]

Collectively, these studies suggest that nanocarrier incorporation enhances not only permeation but also intracellular delivery efficiency.

Conclusion

Non-invasive techniques such as TDDS are proven to be useful and effective in terms of improved drug delivery and patient compliance. By incorporation macromolecules in nanocarrier loaded microneedles systems inherent barrier properties of the SC can be overcome significantly. Different varieties of MNs, including solid, coated, dissolving, hollow, and hydrogel-forming systems, show unique functional benefits over other system by enabling the delivery of a variety of therapeutic agents, ranging from complex biologics to tiny molecules.

The functional benefits of these systems involve enhanced drug stability, controlled release, and targeted administration, with the physical permeation enhancement through skin barrier. Nanocarriers like lipid-based nanoparticles, polymeric systems, metallic nanoparticles, and vesicular carriers improves intracellular uptake, shielding of labile molecules, and drug release on stimulus response.[95]

These systems proven to be effective in a variety of applications, such as cancer treatment, dermatological problems, immunization, and chronic diseases management.[96] Nanocarrier-integrated microneedle systems provide a flexible and minimally invasive platform that has the potential to replace traditional transdermal therapies with more effective, patient-friendly, and focused treatment modalities.[97]

Future aspects

To determine the pharmacological and therapeutic viability of this system, various studies have been conducted, even though there are still a number of crucial fundamental issues that must be resolved in order to advance the clinical application of laboratory discoveries.[98]

Significantly, the clinical translation of NPs incorporated MNs becomes difficult due to the complex manufacturing process and loading of MNs.[99,100] Therefore, it is important to develop low-cost, reliable MN-based formulations to ensure their successful translation. Long-term toxicity of these drug delivery systems will be a major concern to look forward while researching in these field to ensure safety and balancing the risk-benefit ratio for improved patient compliance.[101]

Future studies should focus on eliminating the lacking in translation from preclinical to clinical employment of nanocarrier incorporated microneedle based transdermal system. Much more sophisticated material engineering techniques should be studied to evolve the functional characteristics, such as the use of stimuli-responsive and smart polymers for accurate medication release in response to physiological triggers like pH, temperature, and biomarker levels.

Author contributions:

The authors confirm their contributions to the manuscript as follows: study conception and design were performed by Anadi Tiwari; data collection was carried out by Peeyush Bhardwaj; and both authors contributed equally to the analysis and interpretation of the results. All authors reviewed and approved the final version of the manuscript.

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List of abbreviations:

APCs – Antigen Presenting Cells
API – Active Pharmaceutical Ingredient
DEX – Dexamethasone
GNSs – Gold Nanostars
IgG – Immunoglobulin G
ISF – Interstitial Fluid
LMWH – Low Molecular Weight Heparin
LOD – Limit of Detection
MIDDS – Minimally Invasive Drug Delivery Systems
MNs – Microneedles
MTX-TK-HA – Methotrexate–Thioketal–Hyaluronic Acid
NF-κB – Nuclear Factor kappa B
NIR – Near Infrared
NPs – Nanoparticles
pOVA – Plasmid Ovalbumin
PEI – Polyethylenimine
PEDOT:PSS – Poly(3,4-ethylenedioxythiophene):Polystyrene Sulfonate
PEG – Polyethylene Glycol
PLA-mPEG – Poly(lactic acid)–methoxy polyethylene glycol
PLGA – Poly(lactic-co-glycolic acid)
PVP – Polyvinylpyrrolidone
ROS – Reactive Oxygen Species
SA – Sodium Alginate
SC – Stratum Corneum
SLNs – Solid Lipid Nanoparticles
TDDS – Transdermal Drug Delivery System

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