Drug Design, Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Review of Microneedle Technology for Targeted Therapeutics in Vitiligo: Design Principles, Application Prospects

Yihui Yu[1], Wei Li[1,2], Qian Li[1,2], Wenyan Liu[1,2], Sanquan Zhang[1,2], Xibao Zhang[1,2], Jingyao Liang[1,2]

[1]Institute of Dermatology, Guangzhou Medical University, Guangzhou, 510095, People's Republic of China; [2]Department of Dermatology, Guangzhou Dermatology Hospital, Guangzhou, 510095, People's Republic of China

Correspondence: Jingyao Liang; Xibao Zhang, Email ljy20221228@163.com; gzpfbfzs@163.com

Abstract: Vitiligo is a chronic autoimmune disorder characterized by depigmented patches of the skin. The treatment of vitiligo remains challenging, partly owing to the lack of efficient drug delivery system. Microneedles (MNs), an ideal transdermal drug delivery system, have emerged as promising drug delivery platform for vitiligo. Recently, the emergence of novel MNs with increased biocompatibility, including hydrogel and hollow MNs, further enhance the translational value of MNs in the treatment of vitiligo. However, up-to-date review of these advancements remains lacking. This review aims to summarize the most recent studies of MN-based drug delivery systems for vitiligo, highlighting the translational potential of MNs as a therapeutic platform for the treatment of vitiligo in the near future.

Keywords: vitiligo treatment, microneedle design, advanced applications

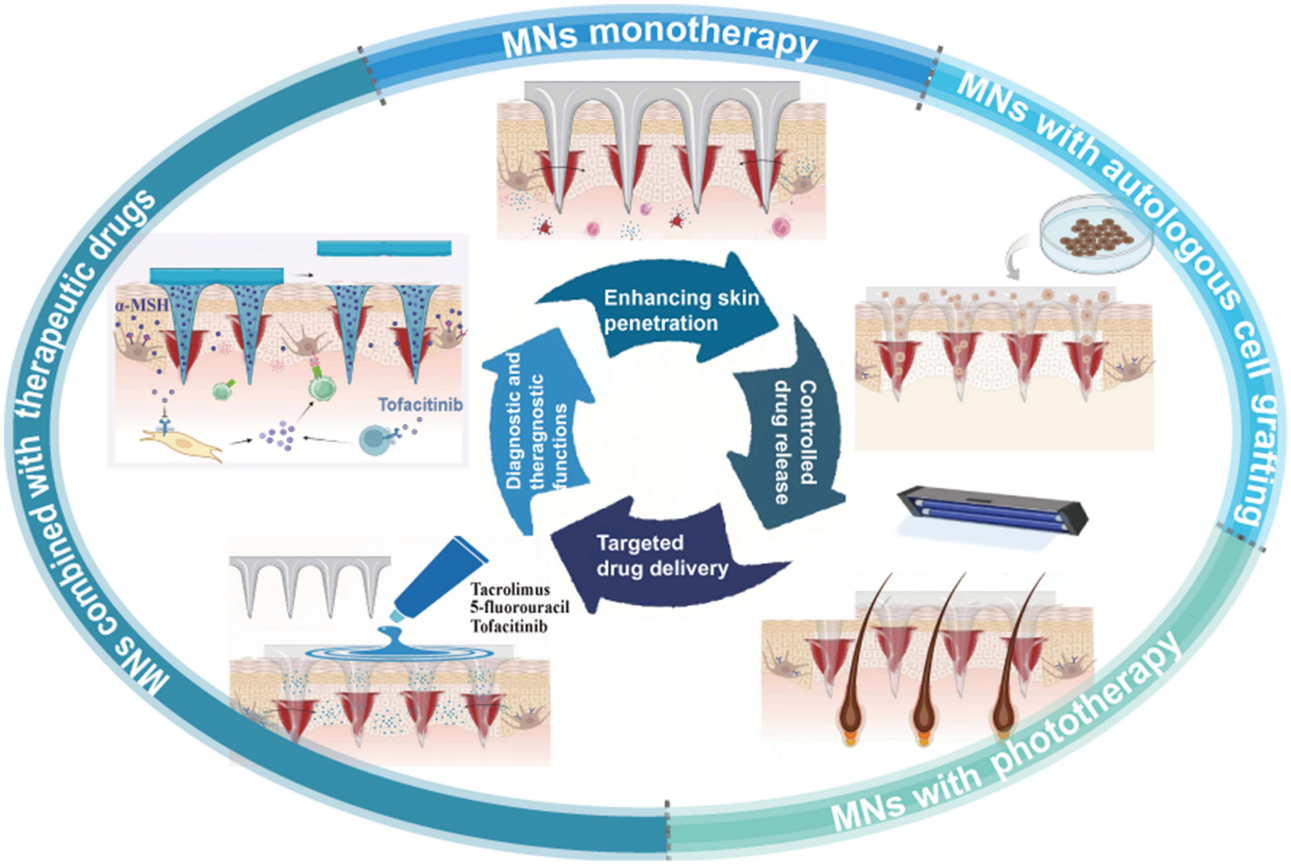
Introduction

Vitiligo is a dermatological condition characterized by the acquired depletion of melanocytes, which leads to the appearance of white macules in the skin.[1] The current understanding of the etiology of vitiligo is associated with the overactivation of the immune cells, specifically the activation of $CXCR3^{+}CD8^{+}$ cytotoxic T cells.[2] Several anti-inflammatory therapeutics, including tofacitinib (JAK-STAT inhibitor) and tacrolimus (calcineurin inhibitor), have been widely used to combat vitiligo in clinical application. However, given that the $CXCR3^{+}CD8^{+}$ T cells are mainly located in the dermal-epidermal junction, it remains challenging for the therapeutics to be effectively delivered to the targeted region. In addition, systemic medications have the potential to induce undesirable adverse effects, whereas topical ointments and creams exhibit limited permeability, subsequently reducing their clinical efficacy. As a result, there is an increasing demand for more effective and safe targeted treatments for vitiligo.

Recently, microneedles (MNs) have caught significant attention as a transdermal drug delivery method. MNs are micrometer-sized needles that increase the diffusivity of the drug to the stratum corneum (SC) by creating micron-size pores in the skin. Specifically, solid MNs can reach to the dermal-epidermal junction of the skin, and was the first MNs that applied clinically to treat skin diseases, including vitiligo. Previous review that analyzed the efficacy and safety of solid MNs in treating vitiligo found that solid MNs can significantly improve vitiligo lesion without causing observable side effect, suggesting that solid MNs may serve as an alternative treatment for vitiligo for patients whose resistant to conventional therapies.[3] Recently, new types of MNs have been developed, including hollow MNs, coated MNs, dissolving MNs and hydrogel MNs, all of which further improve the bioavailability and drug delivery efficacy of MNs in skin diseases, including vitiligo. Here, we aim to summarize the latest research on MNs-based drug delivery systems for vitiligo, highlighting the translational potential of MNs as a therapeutic platform for the management of vitiligo in the near future.

Received: 25 November 2023
Accepted: 27 August 2024
Published: 3 November 2024

Graphical Abstract



Method

All the studies included in this review were searched on PubMed (https://pubmed.ncbi.nlm.nih.gov), Web of Science (https://webofscience.clarivate.cn/) and Embase (https://www.embase.com/) with keywords including the combination of "microneedle" and "vitiligo" or "microneedle" only, respectively. Searched results (research article and review article) regarding the application of microneedles in vitiligo were all included in this review independent of the year of publication.

Microneedles

Advancements in microfabrication technology have enabled the precise design of MNs, tailored for delivering both low- and high-molecular-weight biotherapeutics or extracting blood and interstitial fluid (ISF) through the skin.[4,5] The formulation of MNs has garnered considerable interest from academic researchers and pharmaceutical companies, leading to the patenting of diverse MNs designs for transdermal drug delivery. Currently, the patent landscape for MNs is primarily focused on applications in oncology, cosmetics, ophthalmology, diabetes therapy, and vaccination.

Classification

MNs are primarily classified into five categories: solid, coated, hollow, dissolving, and hydrogen MNs, based on their composition, configuration, and the morphology of their shafts and tips[6] (Table 1).

Table 1 Summary of Materials, Properties of Various Microneedles, and Their Application Potential in Vitiligo Therapy

Classification	Materials Selection	Drug-Loading Capacity	Penetration Capacity	Controlled Drug Release	Side Effect	Pain	Suitable for what Types of Vitiligo
Solid MNs (poke and patch)	Silicon; Stainless steel; Metallic glass	–	High	–	High	High	Generalized vitiligo
Coated MNs (coat and poke)	Silicon; Stainless steel; Polymers	Low	High	–	High	High	–
Hollow MNs (poke and flow)	Silicon; Glass; Polymers	Low	Low	–	High	Medium	Localized and stable vitiligo
Dissolving MNs (poke and release)	Maltose; Carboxymethyl cellulose	Medium	Medium	–	Low	Low	Localized vitiligo
Hydrogel MNs (poke and release)	Polymers; Silk	Medium	Medium	Yes	Low	Low	Faciocervical, acral, mucosal and localized vitiligo

Solid MNs

Solid MNs are commonly fabricated from materials like silicon, stainless steel, metallic glass, polymers, and others. Notably, metallic glasses possess exceptional mechanical properties comparable to traditional metals, and while also offering the flexibility of thermoplastic molding, similar to polymers.[7] Numerous studies have emphasized their favorable attributes, including biocompatibility, biodegradability, and antibacterial properties.[8–10] Manufacturing solid MNs involves various methods, including laser micromachining, electrodeposition, wet etching, and molding processes. In an effort to achieve simpler and high-throughput fabrication methodologies, prior research has introduced novel methods such as thermoplastic drawing of metallic glass and the utilization of KOH etching to create sidewall etch angles in oriented silicon wafers.[7,11] Solid MNs devoid of drug content are primarily utilized to generate microchannels on the skin surface, thereby enhancing skin permeability for subsequent topical treatments. Historically, this approach has been considered slow and ineffective for delivering hydrophobic drugs, owing to their poor solubility and the rapid closure of aqueous microchannels. However, the current study has identified that the drug-pretreatment "patch and poke" strategy, utilizing oscillating MNs, significantly enhances drug penetration. This methodology relies on the mechanical insertion of the drug and effectively addresses the challenges associated with drug solubility and pore closure.[12]

Coated MNs

Coated MNs are consist of a solid-core MN structure coated with a film containing water-soluble inactive excipients and active drugs.[13] Water-soluble excipients fulfil a dual role in the coating of MNs, facilitating the coating process and enabling the detachment of the film from the microneedle surface. Selection of a coating excipient should adhere to specific criteria, including solid state at room temperature, biocompatibility, and rapid disintegration upon skin penetration. Crucial properties sought in the coating process are attaining uniform coating and the ability to selectively coat only the MN shafts while leaving the MN array base substrate uncoated.[14,15] To date, dip-coating and inkjet-coating methods have emerged as the most promising techniques for achieving selective coating of MN shafts while preventing contamination of the base substrate.[16,17]

Hollow MNs

Hollow MNs are typically fabricated from ceramics, metals, silicon, or glass, featuring a void cavity within each needle and a bore at the tip of each needle. In contrast to other types of MNs, most reported hollow MNs are designed to be connected to a syringe, serving as both a drug reservoir and a pumping device.[18,19] The primary advantage of hollow MNs lies in their greater drug delivery capacity when compared to solid, coated, and dissolving MN arrays. The predominant manufacturing method for hollow MNs involves micro-electro-mechanical systems (MEMS), including processes such as lithography, laser cutting, metal electroplating, etching, and micro-molding.[20] Recently, 3D printing has been employed to achieve superior printing resolutions, enabling the creation of customizable and intricate structures

at reduced cost and increased printing speed compared to previous techniques.[21] The current research focused on establishing the feasibility of employing hollow MNs for painless and minimally invasive drug or vaccine delivery, in addition to their potential applications in monitoring applications.[21–23]

Dissolving MNs

The manufacturing process for dissolving MNs involves encapsulating the drug within a carrier matrix, achieved through techniques such as micro-molding, droplet air drying, and lithography/3D printing.[24–26] Upon penetration of the SC, the carrier matrix comprising the needle structure dissolves, enabling the release of encapsulated drugs. The mechanical properties, drug loading capacity, and drug release characteristics of dissolving MNs are dependent on the strength, solubility, and biocompatibility of the matrix polymer employed in their fabrication.

Commonly reported matrix materials include hyaluronic acid (HA), polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), resin, and polysaccharides compounds.[27] These materials possess unique properties that contribute to the efficacy and functionality of MN devices. For instance, photo-curable resin is notable for its ability to be directly mixed with solid pharmaceutical agents, enaling polymeric porous MN structures. This approach eliminates the need for aqueous drug dispersions, which can restrict the drug loading capacity of the MN array. Polysaccharides, a versatile category of biopolymers, are intriguing due to their ability to modulate biological functions. Polysaccharide-based MNs offer multifaceted benefits in addressing complex pathophysiological conditions and facilitating bioprinting, making them promising candidates for advancements in sensing, drug delivery, and biologics restoration.

The utilization of dissolving MNs constitutes a one-step procedure, as they do not require subsequent removal after application. They possess potential applications spanning a wide range of medical domains, including vaccine administration, diagnosis and monitoring, cancer treatment, diabetes management, and the management of inflammatory skin conditions.[28]

Hydrogel MNs

Hydrogel MNs, a novel variant, exhibit distinct principles compared to other MNs due to their unique water absorption and swelling properties.[29] Upon insertion into the skin, hydrogel MNs rapidly absorb interstitial fluid, leading in the swelling and the creation of an unobstructed pathway for drug permeation.[30] Drugs can be loaded by incorporating them into the polymeric structure during the manufacturing process or by loading them into a separate reservoir and subsequently attaching it to the MNs as a substrate.[31]

The development of hydrogel MNs aims to overcome the biocompatibility challenges associated with silicon or metallic MNs. It is widely that Conventional MNs are acknowledged to potentially exhibit cytotoxicity.[32] Penetration disrupts the skin barrier, eliciting an immune response against the MNs as foreign entities.[33] Polymers have emerged as the most extensively employed and highly desirable materials for hollow hydrogel MNs due to their possession of both biocompatibility and biodegradability properties. Polymer material is a noteworthy poly (methyl vinyl ether-co-maleic acid) (PMVE/MA), known for its remarkable attributes including high mechanical strength, excellent biocompatibility, low toxicity, and antimicrobial properties.[34]

Controlled drug release is a highly desirable trait in the utilization of MNs. Hydrogel MNs achieve this control by modulating the crosslinking density of the matrix material. An increase in crosslinking, achieved by increasing the weight percentage of crosslinker, can result in a slower and more prolonged rate of drug release.[35] PVA is a commonly used polymer, often employed in the tailoring of desired properties for hollow HMs through blending with various other polymers, including dextran, carboxymethyl cellulose, and chitosan. The integration of dextran into PVA has been observed to significantly improve sustained and controlled drug release. Another noteworthy material is poly (N-isopropyl acrylamide) (PNIPAm), which exhibits a reversible conformational change from linear to coiled in response to temperature fluctuations. A matrix material utilizing carboxylic end capped PNIPAm grafted onto gelatin has been developed to fabricate highly crosslinked hydrogel MNs patches. These thermo-sensitive hydrogel MNs offer the capability for precisely tunable drug release upon application to the skin.[36]

Design of MNs

Various designs of MNs have been utilized, tailored specifically to enhance treatment outcomes for diverse applications throughout the evolution of MN technology. Multiple designs have been developed to optimize treatment outcomes .

Enhancing Skin Penetration

Several parameters must be carefully considered to achieve an optimal balance between the MNs' shape and array and their efficacy in skin penetration. These parameters include geometric features, material selection, and fabrication feasibility. Geometric features, including length, base width, tip radius, and inter-needle spacing, are pivotal in attaining this balance. Inadequate length may impede MN from penetrating to adequate depths, whereas excessively long needles may heighten the risk of activating pain receptors. A previous study demonstrated a sevenfold surge in pain scores from 5% to 37%, when MN length was augmented from 480 to 1450 μm. Conversely, the utilization of standard hypodermic needles resulted in a pain score of 100%.[37] Solid MNs with lengths ranging from 600 to 1100 μm have demonstrated superior efficacy in drug delivery to the epidermal and dermal regions.[38] In various research studies involving hydrogel MNs, lengths typically spanning from 500 to 800 μm have been employed.[35] The base width of needles is also a critical factor in skin penetration. A width within ranging from 200 to 300μm has been established as optimal choice for effective skin penetration and minimally invasive drug delivery.[39] The force required for skin penetration exhibits a linear increase in relation to the tip radius, and penetration efficiency is maximized when the tip radius remained below 7.5 μm.[40] Cone and pyramid needle shapes are often preferred due to their superior skin penetration capabilities compared to other shapes.

Material selection is crucial for optimizing skin penetration, a vital aspect that can be broadly categorized into three main types: inorganic materials, metal materials, and polymer materials. Inorganic MNs, composed of materials like silicon, glass, and ceramics, exhibit exceptional mechanical strength, enabling effective skin piercing for drug delivery. However, these inorganic MNs have certain limitations, including the time-consuming fabrication process, suboptimal biocompatibility, and susceptibility to fragility.[41] Metallic materials possess remarkable hardness, which reduces the risk of mechanical failure in inorganic MNs. Commonly used metallic materials include stainless steel, titanium, and tungsten. However, these materials have the potential to contaminate biohazardous waste during their use. Recently, polymer materials have gained popularity due to their inherent biocompatibility, cost-effectiveness, and ability to regulate drug release. The controlled drug-release properties of polymers can be precisely adjusted by manipulating factors like concentration, molecular weight, crosslinking density, and charge characteristics. The diverse range of crosslinking techniques and chemical modifications allows polymers to be seamlessly integrated with various types of drugs, resulting in hydrogels. Notable examples of polymers include poly (methyl methacrylate) (PMMA), poly-L-lactic acid (PLA), poly-glycolic acid (PGA), poly-lactic-co-glycolic acid (PLGA), cyclic-olefin copolymer, poly (vinyl pyrrolidone), and sodium carboxymethylcellulose.[42] Hydrogels, including HA and chitosan, exhibit relatively modest mechanical properties, typically measuring below 1 MPa, and possess a shorter degradation duration, usually ranging from a few hours to several weeks. These properties render hydrogels highly suitable for applications requiring a slow drug release rate. MNs crafted from these polymers may not match the strength of metal materials but they are significantly more durable than glass and ceramics.

Controlled Drug Release

The predominant controlled release modes include long-acting release and stimulus-responsive release. Long-acting MN delivery systems are highly suitable for management of chronic illnesses, primarily due to their sustained and precisely controlled release mechanisms. These advanced drug delivery technologies offer the capability to administer drugs precisely to where they are most needed, thereby reducing the risk of elevated systemic toxicity exposure.[43] To extend drug retention at the application site, MNs can be modified to exhibit enhanced mucosal adhesion properties. PVA possesses robust adhesive characteristics, making it an ideal choice for developing a topical adhesive system for controlled drug release. By covalently attaching retinoids to hydrophilic PVA, this polymer-drug conjugate can effectively achieve controlled release of retinoids.[44] Additionally, drug release can also be finely controlled by manipulating the wettability of the polymer, which can be achieved through techniques such as electro-spinning or plasma technology.[45] Variations in surface wettability were achieved through pattern-assisted enhancement of surface hydrophobicity, a technique that has the potential to mitigate the initial burst release of drugs.

Stimulus-responsive drug delivery, an emerging and promising drug delivery system, offers the potential for on-demand drug release and enhanced therapeutic effectiveness. Cross-linked HA emerges as a prevalent material used in the construction of stimulus-responsive MNs. These MNs can establish a stable internal environment while modulating mechanical strength to meet the requirements of various stimulus-responsive drug delivery systems.[46] Stimulus-responsive MNs release drugs in response to a range of endogenous and external triggers, including but not limited to pH-based, enzymatic, thermal, photic, electrical, or mechanical stimuli.[47,48] The acidic pH level of the skin (pH < 5.5) is crucial for maintaining homeostasis and its barrier function. Any disruption in this pH equilibrium can potentially result in cutaneous diseases, such as atopic dermatitis (pH 7–9). Consequently, pH responsive MNs exhibit significant promise in managing skin disorders associated with pH dysregulation. Among the various types of stimuli-responsive materials, thermosensitive polymers, such as polycaprolactone, N-isopropyl acrylamide, and poloxamer, are widely recognized as prevalent options.[49] Thermosensitive materials, characterized by a low melting point, undergo a transition from a solid to a liquid state upon exposure to a heat source, resulting in the release of the encapsulated drugs. Three distinct heat sources are utilized to induce this phase transition: a thermal heater, photothermal agents, and changes in body temperature.[50,51] These thermosensitive MNs exhibit the capability to precisely regulate drug release, thereby enabling accurate and sustained drug delivery for chronic diseases, such as diabetes.

Targeted Drug Delivery

Targeted drug delivery is a crucial approach for precise treatment, characterized by its ability to prolong drug retention time and the reduction of toxic side effects. Among the most commonly used strategies, targeted skin delivery via MNs carrying nanocarriers equipped with targeting ligands is particularly noteworthy.[52] The development of ligands that specifically target pathological cells or tissues can significantly enhance specificity towards these targets, ultimately improving the efficacy of transdermal drug delivery and enhancing drug retention in the skin.[53] For example, psoriasis is characterized by the overexpression of CD44 protein, which functions as a receptor for HA on the surface of affected skin. The utilization of HA as a ligand for CD44 offers a promising approach for the development of targeted drug delivery systems. Furthermore, the interaction between HA and CD44 plays a pivotal role in regulating the proliferation and differentiation of keratinocytes, while also influencing lipid secretion, ultimately contributing to the maintenance of homeostasis in the skin permeability barrier.[46]

MN techniques themselves constitute effective site-targeted delivery strategies for precise treatment. When combined with drugs, these exogenous targeting sites can effectively bypass gastrointestinal degradation and hepatic first-pass metabolism. This approach has the potential to reduce dosage requirements and minimize systemic side effects. Notably, antimicrobial transdermal MN patches are emerging as a viable option for delivering antibacterial, antifungal, or antiviral agents, effectively serving as direct platforms for combating pathogens.[54]

Delivering drugs to specific skin layers has the potential to enhance drug targeting and minimize drug wastage. Recent studies have revealed that tip-loaded dissolving MNs, also known as layered MNs, effectively provide a solution to this requirement. These tip-loaded MNs consist of two distinct layers: a tip layer containing the active medication and a base layer composed entirely of pure dissolving material. The drugs are concentrated in the tips of the MNs, where they dissolve into the skin to sustain drug release, significantly reducing drug consumption. The base layer primarily serves to provide adequate strength for skin penetrating.[55]

Diagnostic and Theranostic Functions

The ISF surrounding cells within bodily tissues presents a promising reservoir of biomarkers that closely mimic those found in the blood.[56] As the largest organ covering the body's surface, the skin offers a vast platform for obtaining physiological information from the ISF.[57] However, the SC serves as a fundamental barrier, impeding the identification of biomarkers and the absorption of medications. To overcome this challenge, there has been a growing focus on MNs-based transdermal biosensing in the ISF.[58] MN patches can penetrate the skin, creating microchannels that enable sampling biomarker molecules or direct detection in the ISF. MNs-based transdermal diagnostic strategies can be categorized into two approaches: in vivo sampling of ISF for in vitro testing and in vivo capture for direct detection in ISF. Specifically, the latter method utilizes MNs as a crucial sensing component for direct biomarker detection in ISF. Consequently, this method offers promising advantages,

including closed-loop control, simplification, and self-administration.[59] Based on the sensing mechanism, in vivo MNs-based detection methods encompass electrochemical, fluorometric, colorimetric, and Raman approaches.

Patients often display significant individual differences in drug absorption and bodily responses. MNs-mediated theranostic systems seamlessly integrate MNs-based disease diagnosis, offering promising clinical applications.[60] The operational mechanism of MNs-based theranostic systems comprises three key steps: detection of physiological biomarkers, precise calculation of drug dosages, and the subsequent on-demand drug delivery. These MNs-mediated theranostic systems can be classified into two main types: open-loop and closed-loop systems, depending on whether they rely on direct or indirect feedback mechanisms.[61] The MNs-based open-loop theranostic system exhibits limitations in providing immediate diagnostic and therapeutic feedback. In this system, either the patient or medical personnel serve as intermediaries, determining the administration dosage based on the data obtained from the analysis. Conversely, closed-loop MNs-mediated theranostic systems facilitate autonomous self-administration through a self-constructed control algorithm, thereby eliminating the need for human intervention.[62] The administration strategy involves the MNs-based diagnostic component accurately monitoring physiological signals, while the MNs-based therapeutic component possesses the ability to dynamically adjust drug release dosages based on real-time feedback data.[63]

Pathogenesis and Treatment Mechanisms of Vitiligo

Recently, the understanding of the mechanism underlying vitiligo has progressed, revealing the involvement of autoreactive cytotoxic $CD8^+$ T cells that target melanocytes. This targeting leads to disease progression through the local production of IFN-γ. Subsequently, neighboring fibroblasts secrete chemokines, which are induced by IFN-γ, to further recruit T cells to the skin via a positive-feedback loop.[2] Therefore, successful re-pigmentation in vitiligo necessitates the achievement of two treatment objectives: suppressing autoimmunity and promoting the regeneration of melanocytes from their stem cell niche within the hair follicle. Targeted immunotherapy utilizing immunosuppressants is employed to inhibit cytokine signaling. Concurrently, phototherapy and analogues of alpha-melanocyte-stimulating hormone (α-MSH) are administered to enhance melanocyte proliferation and migration. Moreover, relapse commonly occurs upon discontinuation of treatment, attributed to autoreactive resident memory T cells.[64] Current treatment strategies focus on eradicating these cells to achieve long-lasting benefits.

MNs in the Treatment of Vitiligo

MNs have emerged as an innovative approach for the treatment of dermatological diseases. The plasticity of MNs facilitates the creation of diverse lesion configurations, particularly beneficial for treating localized, stable vitiligo lesions (Figure 1). Conversely, diseases like atopic dermatitis, characterized by lesions with indistinct boundaries, pose significant challenges for MN-based therapeutic strategies. Moreover, the pathological changes in vitiligo primarily occur in the epidermal and superficial dermal layers, allowing for easy accessibility by microneedles. Furthermore, unlike psoriasis, vitiligo lesions do not exhibit hyperkeratosis, thus maintaining the consistency and length of microneedles during insertion. The unique combination of these factors highlights the potential of MNs as a targeted and efficient modality for the treatment of vitiligo. Furthermore, the application of MNs demonstrate the capacity to modulate vitiligo-related immune disorders.[65] Several findings validate that MNs significantly enhance the effectiveness of vitiligo repigmentation, both when used alone and in combination with other therapeutic modalities (Table 2).

MNs Monotherapy

The utilization of MNs affords precise regulation of penetration, thereby negating the necessity for additional topical anti-infective therapy. Notably, these characteristics surpass needling therapy, an alternative efficacious approach for promoting re-pigmentation in cases of unresponsive, stable vitiligo.[77] To assess the efficacy of MNs monotherapy, two clinical trials were conducted, focusing on the treatment of localized stable vitiligo.[78,79] A more favorable response in re-pigmentation was achieved through MNs monotherapy, administered over twelve sessions with 2-week intervals, comparable to the outcomes achieved with twice-daily application of 0.1% tacrolimus ointment for a duration of 6 months.[78] A plausible explanation is that MNs induce microlesions, which trigger the recruitment of platelets and neutrophils, releasing various growth factors and inflammatory mediators, ultimately leading to the migration and

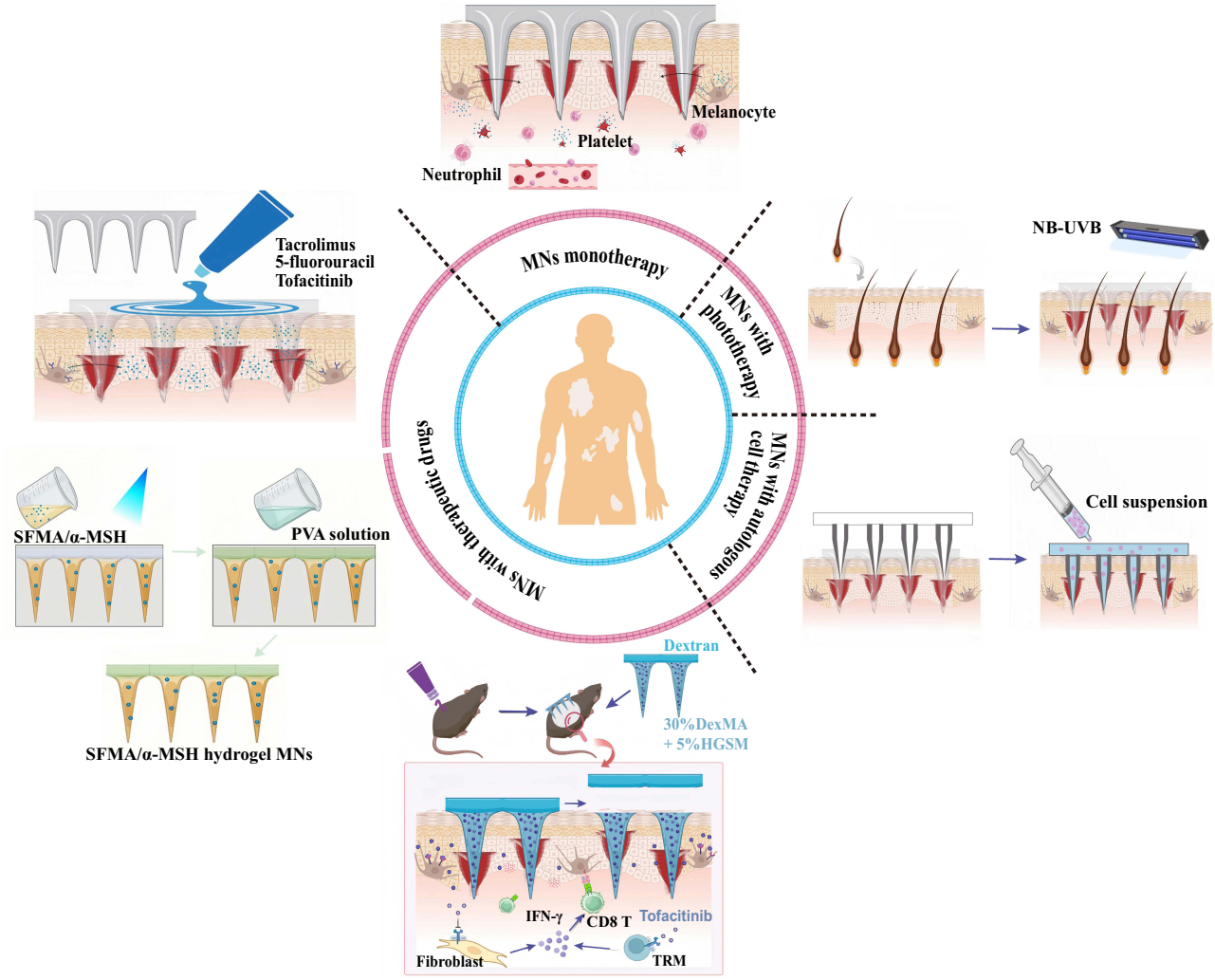


Figure 1 MNs-based strategies for vitiligo treatment. (**a**) MNs monotherapy generates microlesions in the skin, triggering a localized immune response characterized by the recruitment of platelets and neutrophils to the site of MN application. This immune response leads to the release of various growth factors and inflammatory mediators, ultimately resulting in the migration and activation of melanocytes. (**b**) Transdermal drug delivery is enhanced by MNs, facilitating targeted delivery to affected skin areas and potentially improving treatment outcomes. (**c**) Combining hollow MNs with autologous cell suspension grafting remarkably increases regimentation by improving the delivery of melanocyte-containing cell suspensions into targeted areas. (**d**) Combining MNs with phototherapy significantly enhances treatment effectiveness by creating microlesions in the skin, improving the penetration of phototherapy, and accelerating regimentation in vitiligo-affected areas (some of contents were Created in BioRender. Yu, Y. (2024) BioRender.com/j311097).

activation of melanocytes. Additionally, this mechanical trauma could induce melanophore aggregation by damaging the epidermis's basal cell stratum of the epidermis, potentially leading to post-inflammatory hyperpigmentation. Collectively, these factors have the potential to enhance and stimulate melanogenesis.[80]

MNs Combined with Therapeutic Drugs

MNs are regarded as an optimal adjuvant due to their capacity to create microchannels that facilitate the transdermal delivery of therapeutic drugs across the SC. This capability has been highlighted by two comprehensive systematic reviews.[3,66]

Calcineurin inhibitor, such as tacrolimus and pimecrolimus, have been utilized in the treatment of vitiligo, where they inhibit calcineurin in T-cells, thereby preventing the production and release of pro-inflammatory cytokines activated by these T-cells. Moreover, these inhibitors promote melanocyte migration with minimal impact on melanocyte proliferation.[67,81] A study demonstrated a significantly higher re-pigmentation rate of 66.6% among patients treated with MNs and tacrolimus, compared to a rate of only 33.3% observed in the topical tacrolimus groups.[78] Howyda et al[82] further demonstrated the superior efficacy and tolerability of MNs combined with tacrolimus over tacrolimus ointment

Table 2 Overview the Studies of MNs Application in the Treatment of Vitiligo

Application method	MNs Type	Combined with Therapy	Research Type	Vitiligo Type	Results	Reference
MNs monotherapy	Solid MNs	–	Case series	Localized and stable	17/30 patients achieving repigmentation	[66]
	Solid MNs	–	Case series	Localized	5/22 patients achieving repigmentation	[67]
MNs with therapeutic drugs	Solid MNs	Tacrolimus	Case series	Localized and refractory	12/24 achieving repigmentation over 75% in MNs with Tacrolimus group, while 7/24 in Tacrolimus alone group	[3]
	Solid MNs	Vitamin D	Case series	Stable	52% achieving repigmentation over 50% in MNs with vitamin D group, while 40% in MNs alone group	[68]
	Solid MNs	5-fluorouracil	Case report	Stable	75% repigmentation	[69]
	Hydrogel MNs	Tofacitinib/ α-MSH loaded	Basic research	–	Significantly promote the repigmentation of vitiligo mice and reduce localized inflammation	[70]
	Hydrogel MNs	α-MSH loaded	Basic research	–	Enhance the synthesis of melanin and transportation of melanin granules to surrounding cells	[71]
MNs with autologous cell suspension grafting	Hollow MNs	Non-cultured epidermal cell suspension (NCES)	Case report	Faciocervical	50% repigmentation	[72]
	Hollow MNs	Non-cultured epidermal cell suspension (NCES)	Case report	Acral	Combination of MNs, NCES transplantation and topical 5-FU produced far more re-pigmentation (84%) than NCES monotherapy (40%)	[73]
MNs with phototherapy	Solid MNs	NB-UVB	Case series	–	No benefit in enhancing repigmentation	[74–76]

https://doi.org/10.2147/DDDT.S449381

alone. Notably, patients receiving combination therapy displayed an upregulation of c-kit expression in the vitiliginous epidermis. C-kit, a cell surface receptor that regulates melanocyte survival and proliferation, is closely associated with the loss or dysfunction of melanocytes in depigmented regions. These findings emphasize the pivotal dual role of MNs, acting as an adjuvant and as promoters of melanocyte proliferation and migration from perilesional sites to depigmented patches.[3] Furthermore, the combination of topical vitamin D analogs, such as cholecalciferol, with MNs treatment have been shown to enhance melanocyte functionality and viability, thereby promoting repigmentation.[83]

Recent evidence suggests that intradermal 5-fluorouracil (5-FU) administration has potential for effectively inducing re-pigmentation in vitiligo patients resistant to conventional treatments.[84] It has been established that 5-FU stimulates dermal fibroblasts to release CXCL12, thereby promoting the chemotactic migration of melanocytes expressing CXCR4.[85] Kumar et al[69] utilized derma-rollers with MNs along with topical 5-FU solution to effectively manage stable vitiligo, yielding remarkable re-pigmentation outcomes. The combined use of MNs and 5-FU demonstrated a synergistic effect, leading to superior re-pigmentation outcomes and increased patient satisfaction compared to the combination of MNs and tacrolimus, especially in acral regions.[86] In refractory pediatric vitiligo cases, the combination of MNs with low-dose oral corticosteroids and topical 5-FU exhibited significant efficacy.[87] Furthermore, this combination of MNs and 5-FU has proven effective in improving vitiligo, likely due to its ability to up-regulate the expression of matrix metalloproteinase 2 (MMP2) in depigmented areas. MMP2, synthesized by keratinocytes during epidermal remodeling, has been found to enhance melanocyte migration.[88]

The oral and topical formulations of tofacitinib, a selective inhibitor of JAK1 and JAK3, have shown effectiveness in treating vitiligo.[89,90] As a pathogenesis-directed therapy, the effectiveness of tofacitinib in promoting re-pigmentation can be attributed to its downregulation of IFN-γ signaling.[91] The utilization of MNs provides numerous advantages, including enhanced targeted drug release and mitigation of tofacitinib-associated side effects. It was observed that dissolving tofacitinib-loaded MN arrays resulted in the delivery of 835 μg/cm² of the drug into the dermis over a 24-hour period, whereas the topical cream only delivered 143.98 μg/cm².[92] This finding indicates a significant potential for the treatment of vitiligo. α-MSH is a neuroendocrine hormone that stimulates melanin production and protects melanocytes from oxidative stress.[93,94] A decrease in α-MSH expression levels has been observed in the serum and skin lesions of patients with vitiligo.[95] Chong et al[71] demonstrated that silk fibroin methacrylate (SFMA)/α-MSH hydrogel MNs significantly promote melanin synthesis, facilitate melanin granule transportation to surrounding cells, and enhance epidermal re-pigmentation. In our recent study, hydrogel MNs composed of dextran methacrylate (DexMA) and cyclodextrin-adamantane host-guest assembly polymer (HGSM) were utilized to encapsulate tofacitinib and α-MSH. This approach significantly enhanced re-pigmentation in both skin and hair in an animal model of vitiligo.[70]

MNs with Autologous Cell Suspension Grafting

Cutaneous cell suspension grafting has emerged as a promising treatment modality for vitiligo. Nonetheless, clinical translation of cell therapy faces various challenges, including the need to deliver an adequate number of cells to the designated site while maintaining their viability and functionality. Conventional transdermal delivery methods entailed the use of ablative lasers or skin dermabrasion as an initial procedure before the topical application of cell suspension. However, these methods are associated with several limitations, including the risk of scaring and infection, and challenges in achieving a uniform distribution of cell suspension.[72,96] In contrast, hollow MNs offer a safe, novel, and minimally invasive approach for the uniform delivery of functional cells into the skin. A study conducted by Gualeni et al[73] revealed that hollow MNs with a length of 500 μm and a bore size of 75 μm are potentially more suitable for delivering cells to the skin. The combination of MNs and epidermal keratinocyte-melanocyte cell suspension has exhibited significant re-pigmentation in the facial region of vitiligo patients after a 6-month treatment protocol.[74] Acral vitiligo is acknowledged as a difficult and refractory form of the condition, often resistant to both medical and surgical treatments, including transplantation. A study by Albalat et al[75] observed that the combination of MNs, non-cultured epidermal cell suspension (NCES) transplantation, and topical 5-FU led to significantly higher re-pigmentation rates (84%) compared to NCES monotherapy (40%), indicating its potential as an effective treatment for refractory vitiligo.

MNs with Phototherapy

NB-UVB is widely considered as the most effective phototherapy for treating vitiligo. A recent study indicates that combining MNs or CO_2 laser with hair transplantation, followed by NB-UVB, achieved comparable therapeutic efficacy in treating refractory palmar-plantar vitiligo.[76] However, several other studies have reported no additional benefits when combining MNs with NB-UVB.[68,97] Similar to CO_2 laser, MNs enhance the levels of pro-pigmentary cytokines and promote skin cell proliferation.[76]

Conclusion

With the progression of clinical trials involving MNs-based products, it is evident that MNs represent an efficient and well-tolerated method for the treatment of vitiligo. Their ability to modulate melanocyte migration and proliferation has significant potential. Notably, the combination of MNs with other therapeutic approaches has exhibited promising synergistic effects on treatment outcomes. However, further research is necessary to optimize the design and materials of MNs, enhancing their compatibility with the skin and ensuring the sustained release of therapeutic agents. Additionally, clinical trials should assess the therapeutic potential of MNs in a diverse population of vitiligo patients, including individuals with different skin types and disease severities. Addressing these research gaps will further unlock the potential of MNs in revolutionizing the treatment paradigm for vitiligo and other dermatological conditions.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Funding

This study was supported by Guangzhou Basic Research Plan Jointly Funded by the City, School (Hospital), and/or Enterprise (Grant No.SL2022A03J00202 and 2023A03J0472); the Medical Science and Technology Research Foundation of Guangdong Province (Grant No. A2022052).

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Ezzedine K, Eleftheriadou V, Whitton M, van Geel N. Vitiligo. *Lancet*. 2015;386(9988):74–84. doi:10.1016/s0140-6736(14)60763-7
2. Khaitan BK, Sindhuja T. Autoimmunity in vitiligo: therapeutic implications and opportunities. *Autoimmun Rev*. 2022;21(1):102932. doi:10.1016/j.autrev.2021.102932
3. Salloum A, Bazzi N, Maalouf D, Habre M. Microneedling in vitiligo: a systematic review. *Dermatol Ther*. 2020;33(6):e14297. doi:10.1111/dth.14297
4. Faraji Rad Z, Prewett PD, Davies GJ. An overview of microneedle applications, materials, and fabrication methods. *Beilstein J Nanotechnol*. 2021;12:1034–1046. doi:10.3762/bjnano.12.77
5. Atefi N, Ziaeifar E, Seirafianpour F, et al. Evaluation of efficacy and safety of vitiligo treatment with micro-needling combined with N-Acetylcysteine and micro-needling alone: a double-blinded randomized controlled clinical trial. *J Cosmet Dermatol*. 2024;23(6):2220–2230. doi:10.1111/jocd.16274
6. Queiroz MLB, Shanmugam S, Santos LNS, et al. Microneedles as an alternative technology for transdermal drug delivery systems: a patent review. *Expert Opin Ther Pat*. 2020;30(6):433–452. doi:10.1080/13543776.2020.1742324
7. Hu Z, Meduri CS, Ingrole RSJ, et al. Solid and hollow metallic glass microneedles for transdermal drug-delivery. *Appl Phys Lett*. 2020;116(20). doi:10.1063/5.0008983
8. Liu Z, Huang L, Wu W, et al. Novel low Cu content and Ni-free Zr-based bulk metallic glasses for biomedical applications. *J Non-Cryst Solids*. 2013;363:1–5. doi:10.1016/j.jnoncrysol.2012.09.026
9. Zberg B, Uggowitzer PJ, Löffler JF. MgZnCa glasses without clinically observable hydrogen evolution for biodegradable implants. *Nat Mater*. 2009;8(11):887–891. doi:10.1038/nmat2542
10. Chu JP, Liu T-Y, C-L L, et al. Fabrication and characterizations of thin film metallic glasses: antibacterial property and durability study for medical application. *Thin Solid Films*. 2014;561:102–107. doi:10.1016/j.tsf.2013.08.111
11. Howells O, Blayney GJ, Gualeni B, et al. Design, fabrication, and characterisation of a silicon microneedle array for transdermal therapeutic delivery using a single step wet etch process. *Eur J Pharm Biopharm*. 2022;171:19–28. doi:10.1016/j.ejpb.2021.06.005
12. Sabri A, Ogilvie J, McKenna J, et al. Intradermal delivery of an immunomodulator for basal cell carcinoma; expanding the mechanistic insight into solid microneedle-enhanced delivery of hydrophobic molecules. *Mol Pharm*. 2020;17(8):2925–2937. doi:10.1021/acs.molpharmaceut.0c00347

13. Kim Y-C, Park J-H, Prausnitz MR. Microneedles for drug and vaccine delivery. *Adv Drug Deliv Rev*. 2012;64(14):1547–1568. doi:10.1016/j.addr.2012.04.005
14. Jin M, Jeon WJ, Lee H, et al. Preparation and evaluation of rapid disintegrating formulation from coated microneedle. *Drug Deliv Transl Res*. 2022;12(2):415–425. doi:10.1007/s13346-021-01046-w
15. Ingrole RSJ, Gill HS. Microneedle coating methods: a review with a perspective. *J Pharmacol Exp Ther*. 2019;370(3):555–569. doi:10.1124/jpet.119.258707
16. Gill HS, Prausnitz MR. Coated microneedles for transdermal delivery. *J Control Release*. 2007;117(2):227–237. doi:10.1016/j.jconrel.2006.10.017
17. Caudill CL, Perry JL, Tian S, et al. Spatially controlled coating of continuous liquid interface production microneedles for transdermal protein delivery. *J Control Release*. 2018;284:122–132. doi:10.1016/j.jconrel.2018.05.042
18. Bolton CJW, Howells O, Blayney GJ, et al. Hollow silicon microneedle fabrication using advanced plasma etch technologies for applications in transdermal drug delivery. *Lab Chip*. 2020;20(15):2788–2795. doi:10.1039/d0lc00567c
19. Cárcamo-Martínez Á, Mallon B, Domínguez-Robles J, et al. Hollow microneedles: a perspective in biomedical applications. *Int J Pharm*. 2021;599:120455. doi:10.1016/j.ijpharm.2021.120455
20. Bariya SH, Gohel MC, Mehta TA, Sharma OP. Microneedles: an emerging transdermal drug delivery system. *J Pharm Pharmacol*. 2012;64(1):11–29. doi:10.1111/j.2042-7158.2011.01369.x
21. Yeung C, Chen S, King B, et al. A 3D-printed microfluidic-enabled hollow microneedle architecture for transdermal drug delivery. *Biomicrofluidics*. 2019;13(6):064125. doi:10.1063/1.5127778
22. Miller PR, Narayan RJ, Polsky R. Microneedle-based sensors for medical diagnosis. *J Mater Chem B*. 2016;4(8):1379–1383. doi:10.1039/c5tb02421h
23. van der Maaden K, Heuts J, Camps M, et al. Hollow microneedle-mediated micro-injections of a liposomal HPV E7(43-63) synthetic long peptide vaccine for efficient induction of cytotoxic and T-helper responses. *J Control Release*. 2018;269:347–354. doi:10.1016/j.jconrel.2017.11.035
24. Lee K, Lee CY, Jung H. Dissolving microneedles for transdermal drug administration prepared by stepwise controlled drawing of maltose. *Biomaterials*. 2011;32(11):3134–3140. doi:10.1016/j.biomaterials.2011.01.014
25. Kim JD, Kim M, Yang H, et al. Droplet-born air blowing: novel dissolving microneedle fabrication. *J Control Release*. 2013;170(3):430–436. doi:10.1016/j.jconrel.2013.05.026
26. Pere CPP, Economidou SN, Lall G, et al. 3D printed microneedles for insulin skin delivery. *Int J Pharm*. 2018;544(2):425–432. doi:10.1016/j.ijpharm.2018.03.031
27. Zhang L, Guo R, Wang S, et al. Fabrication, evaluation and applications of dissolving microneedles. *Int J Pharm*. 2021;604:120749. doi:10.1016/j.ijpharm.2021.120749
28. Sartawi Z, Blackshields C, Faisal W. Dissolving microneedles: applications and growing therapeutic potential. *J Control Release*. 2022;348:186–205. doi:10.1016/j.jconrel.2022.05.045
29. Hutton ARJ, Kirkby M, Van Bogaert T, et al. Transdermal administration of nanobody molecules using hydrogel-forming microarray patch technology: a unique delivery approach. *Macromol Mater Eng*;2024:2400029. doi:10.1002/mame.202400029
30. Hou X, Li J, Hong Y, et al. Advances and prospects for hydrogel-forming microneedles in transdermal drug delivery. *Biomedicines*. 2023;11(8):2119. doi:10.3390/biomedicines11082119
31. Migdadi EM, Courtenay AJ, Tekko IA, et al. Hydrogel-forming microneedles enhance transdermal delivery of metformin hydrochloride. *J Control Release*. 2018;285:142–151. doi:10.1016/j.jconrel.2018.07.009
32. Cheung K, Das DB. Microneedles for drug delivery: trends and progress. *Drug Delivery*. 2016;23(7):2338–2354. doi:10.3109/10717544.2014.986309
33. Duarah S, Sharma M, Wen J. Recent advances in microneedle-based drug delivery: special emphasis on its use in paediatric population. *Eur J Pharm Biopharm*. 2019;136:48–69. doi:10.1016/j.ejpb.2019.01.005
34. Romanyuk AV, Zvezdin VN, Samant P, et al. Collection of analytes from microneedle patches. *Anal Chem*. 2014;86(21):10520–10523. doi:10.1021/ac503823p
35. Turner JG, White LR, Estrela P, Leese HS. Hydrogel-forming microneedles: current advancements and future trends. *Macromol Biosci*. 2021;21(2):e2000307. doi:10.1002/mabi.202000307
36. Li JY, Feng YH, He YT, et al. Thermosensitive hydrogel microneedles for controlled transdermal drug delivery. *Acta Biomater*. 2022;153:308–319. doi:10.1016/j.actbio.2022.08.061
37. Gill HS, Denson DD, Burris BA, Prausnitz MR. Effect of microneedle design on pain in human volunteers. *Clin J Pain*. 2008;24(7):585–594. doi:10.1097/AJP.0b013e31816778f9
38. Yan G, Warner KS, Zhang J, et al. Evaluation needle length and density of microneedle arrays in the pretreatment of skin for transdermal drug delivery. *Int J Pharm*. 2010;391(1–2):7–12. doi:10.1016/j.ijpharm.2010.02.007
39. Lin Y-H, Lee IC, Hsu W-C, et al. Rapid fabrication method of a microneedle mold with controllable needle height and width. *Biomed Microdevices*. 2016;18(5):85. doi:10.1007/s10544-016-0113-8
40. Römgens AM, Bader DL, Bouwstra JA, et al. Monitoring the penetration process of single microneedles with varying tip diameters. *J Mech Behav Biomed Mater*. 2014;40:397–405. doi:10.1016/j.jmbbm.2014.09.015
41. Waghule T, Singhvi G, Dubey SK, et al. Microneedles: a smart approach and increasing potential for transdermal drug delivery system. *Biomed Pharmacother*. 2019;109:1249–1258. doi:10.1016/j.biopha.2018.10.078
42. Lyu S, Dong Z, Xu X, et al. Going below and beyond the surface: microneedle structure, materials, drugs, fabrication, and applications for wound healing and tissue regeneration. *Bioact Mater*. 2023;27:303–326. doi:10.1016/j.bioactmat.2023.04.003
43. Tekko IA, Permana AD, Vora L, et al. Localised and sustained intradermal delivery of methotrexate using nanocrystal-loaded microneedle arrays: potential for enhanced treatment of psoriasis. *Eur J Pharm Sci*. 2020;152:105469. doi:10.1016/j.ejps.2020.105469
44. Castleberry SA, Quadir MA, Sharkh MA, et al. Polymer conjugated retinoids for controlled transdermal delivery. *J Control Release*. 2017;262:1–9. doi:10.1016/j.jconrel.2017.07.003
45. Nair K, Whiteside B, Grant C, et al. Investigation of plasma treatment on micro-injection moulded microneedle for drug delivery. *Pharmaceutics*. 2015;7(4):471–485. doi:10.3390/pharmaceutics7040471

46. Kang H, Zuo Z, Lin R, et al. The most promising microneedle device: present and future of hyaluronic acid microneedle patch. *Drug Delivery*. 2022;29(1):3087–3110. doi:10.1080/10717544.2022.2125600
47. Detamornrat U, Parrilla M, Domínguez-Robles J, et al. Transdermal on-demand drug delivery based on an iontophoretic hollow microneedle array system. *Lab Chip*. 2023;23(9):2304–2315. doi:10.1039/d3lc00160a
48. Roussel S, Udabe J, Bin Sabri A, et al. Leveraging novel innovative thermoresponsive polymers in microneedles for targeted intradermal deposition. *Int J Pharm*. 2024;652:123847. doi:10.1016/j.ijpharm.2024.123847
49. Tobin KV, Fiegel J, Brogden NK. Thermosensitive gels used to improve microneedle-assisted transdermal delivery of naltrexone. *Polymers*. 2021;13(6). doi:10.3390/polym13060933
50. Makvandi P, Ali GW, Della Sala F, et al. Biosynthesis and characterization of antibacterial thermosensitive hydrogels based on corn silk extract, hyaluronic acid and nanosilver for potential wound healing. *Carbohydr Polym*. 2019;223:115023. doi:10.1016/j.carbpol.2019.115023
51. Jiang S, Bian J, Shi X, Hu Y. Thermosensitive microneedles capable of on demand insulin release for precise diabetes treatment. *Macromol Biosci*. 2023;23(9):e2300018. doi:10.1002/mabi.202300018
52. Sun MC, Xu XL, Lou XF, Du YZ. Recent progress and future directions: the nano-drug delivery system for the treatment of vitiligo. *Int J Nanomed*. 2020;15:3267–3279. doi:10.2147/ijn.S245326
53. Srinivasarao M, Low PS. Ligand-targeted drug delivery. *Chem Rev*. 2017;117(19):12133–12164. doi:10.1021/acs.chemrev.7b00013
54. Jamaledin R, Yiu CKY, Zare EN, et al. Advances in antimicrobial microneedle patches for combating infections. *Adv Mater*. 2020;32(33):e2002129. doi:10.1002/adma.202002129
55. Zhuang J, Rao F, Wu D, et al. Study on the fabrication and characterization of tip-loaded dissolving microneedles for transdermal drug delivery. *Eur J Pharm Biopharm*. 2020;157:66–73. doi:10.1016/j.ejpb.2020.10.002
56. Heikenfeld J, Jajack A, Feldman B, et al. Accessing analytes in biofluids for peripheral biochemical monitoring. *Nat Biotechnol*. 2019;37(4):407–419. doi:10.1038/s41587-019-0040-3
57. Kolluru C, Williams M, Chae J, Prausnitz MR. Recruitment and collection of dermal interstitial fluid using a microneedle patch. *Adv Healthcare Mater*. 2019;8(3):e1801262. doi:10.1002/adhm.201801262
58. Al Sulaiman D, Chang JYH, Bennett NR, et al. Hydrogel-coated microneedle arrays for minimally invasive sampling and sensing of specific circulating nucleic acids from skin interstitial fluid. *ACS Nano*. 2019;13(8):9620–9628. doi:10.1021/acsnano.9b04783
59. Abdullah H, Phairatana T, Jeerapan I. Tackling the challenges of developing microneedle-based electrochemical sensors. *Mikrochim Acta*. 2022;189(11):440. doi:10.1007/s00604-022-05510-3
60. Yang J, Zheng S, Ma D, et al. Masticatory system-inspired microneedle theranostic platform for intelligent and precise diabetic management. *Sci Adv*. 2022;8(50):eabo6900. doi:10.1126/sciadv.abo6900
61. Chen W, Tian R, Xu C, et al. Microneedle-array patches loaded with dual mineralized protein/peptide particles for type 2 diabetes therapy. *Nat Commun*. 2017;8(1):1777. doi:10.1038/s41467-017-01764-1
62. Cahill EM, O'Cearbhaill ED. Toward biofunctional microneedles for stimulus responsive drug delivery. *Bioconjugate Chem*. 2015;26(7):1289–1296. doi:10.1021/acs.bioconjchem.5b00211
63. Yang J, Yang J, Gong X, et al. Recent progress in microneedles-mediated diagnosis, therapy, and theranostic systems. *Adv Healthcare Mater*. 2022;11(10):e2102547. doi:10.1002/adhm.202102547
64. Frisoli ML, Essien K, Harris JE. Vitiligo: mechanisms of pathogenesis and treatment. *Annu Rev Immunol*. 2020;38(1):621–648. doi:10.1146/annurev-immunol-100919-023531
65. Xu P, Xiao W, Xu K, et al. Potential strategy of microneedle-based transdermal drug delivery system for effective management of skin-related immune disorders. *Eur J Pharm Biopharm*. 2024;195:114148. doi:10.1016/j.ejpb.2023.11.013
66. Bailey AJ-M, Li HO-Y, Zheng D, et al. Microneedling as an adjuvant to local therapies for vitiligo: a systematic review and meta-analysis. *Dermatol Surg*. 2021;47(9):1314–1316. doi:10.1097/dss.0000000000003048
67. Lee KY, Jeon SY, Hong JW, et al. Endothelin-1 enhances the proliferation of normal human melanocytes in a paradoxical manner from the TNF-α-inhibited condition, but tacrolimus promotes exclusively the cellular migration without proliferation: a proposed action mechanism for combination t. *J Eur Acad Dermatol Venereol*. 2013;27(5):609–616. doi:10.1111/j.1468-3083.2012.04498.x
68. Kaur A, Barman KD, Sahoo B, Choudhary P. A comparative interventional study of narrowband ultraviolet B alone and narrowband ultraviolet B in combination with microneedling in patients with stable vitiligo. *Photodermatol Photoimmunol Photomed*. 2022;39(4):357–363. doi:10.1111/phpp.12847
69. Kumar A, Bharti R, Agarwal S. Microneedling with Dermaroller 192 needles along with 5-fluorouracil solution in the treatment of stable vitiligo. *J Am Acad Dermatol*. 2019;81(3):e67–e69. doi:10.1016/j.jaad.2018.12.066
70. Liang J, Yu Y, Li C, et al. Tofacitinib combined with melanocyte protector α-MSH to treat vitiligo through dextran based hydrogel microneedles. *Carbohydr Polym*. 2023;305:120549. doi:10.1016/j.carbpol.2023.120549
71. Chong S, Wei C, Feng L, Guo R. Silk fibroin-based hydrogel microneedles deliver α-msh to promote melanosome delivery for vitiligo treatment. *ACS Biomater Sci Eng*. 2023;9(6):3368–3378. doi:10.1021/acsbiomaterials.3c00284
72. Lagrange S, Montaudié H, Fontas E, et al. Comparison of microneedling and full surface erbium laser dermabrasion for autologous cell suspension grafting in nonsegmental vitiligo: a randomized controlled trial. *Br J Dermatol*. 2019;180(6):1539–1540. doi:10.1111/bjd.17464
73. Gualeni B, Coulman SA, Shah D, et al. Minimally invasive and targeted therapeutic cell delivery to the skin using microneedle devices. *Br J Dermatol*. 2018;178(3):731–739. doi:10.1111/bjd.15923
74. Nilforoushzadeh MA, Nouri M, Alavi S, et al. Combination of epidermal keratinocyte-melanocyte cells suspension and microneedling: safe surgical approach in vitiligo. *J Cosmet Dermatol*. 2022;21(10):4669–4676. doi:10.1111/jocd.14987
75. Albalat W, Elsayed M, Salem A, et al. Microneedling and 5-flurouracil can enhance the efficacy of non-cultured epidermal cell suspension transplantation for resistant acral vitiligo. *Dermatol Ther*. 2022;35(10):e15768. doi:10.1111/dth.15768
76. Feily A, Firoozifard A, Sokhandani T, et al. Follicular transplantation, microneedling, and adjuvant narrow-band ultraviolet-b irradiation as cost-effective regimens for palmar-plantar vitiligo: a pilot study. *Cureus*. 2020;12(4):e7878. doi:10.7759/cureus.7878
77. Zawar VP, Karad GM. Needling in unresponsive stable vitiligo. *J Am Acad Dermatol*. 2016;75(5):e199–e200. doi:10.1016/j.jaad.2016.05.033
78. Ebrahim HM, Albalate W. Efficacy of microneedling combined with tacrolimus versus either one alone for vitiligo treatment. *J Cosmet Dermatol*. 2020;19(4):855–862. doi:10.1111/jocd.13304

79. Attwa EM, Khashaba SA, Ezzat NA. Evaluation of the additional effect of topical 5-fluorouracil to needling in the treatment of localized vitiligo. *J Cosmet Dermatol*. 2020;19(6):1473–1478. doi:10.1111/jocd.13152
80. Garland MJ, Migalska K, Mahmood TMT, et al. Microneedle arrays as medical devices for enhanced transdermal drug delivery. *Expert Rev Med Devices*. 2011;8(4):459–482. doi:10.1586/erd.11.20
81. Iraji F, Asilian A, Talebzadeh Z, et al. Microneedling in combination with topical pimecrolimus 1% versus topical pimecrolimus 1% for the treatment of refractory stable vitiligo: a randomized clinical trial. *Dermatol Res Pract*. 2021;2021:5652140. doi:10.1155/2021/5652140
82. Ebrahim HM, Elkot R, Albalate W. Combined microneedling with tacrolimus vs tacrolimus monotherapy for vitiligo treatment. *J DermatolTreat*. 2021;32(8):999–1004. doi:10.1080/09546634.2020.1716930
83. Salem MW, Adel Abd El Azim A, Galal SA. Efficacy of topical vitamin D combined with microneedling in the treatment of vitiligo: a comparative study. *J Cosmet Dermatol*. 2023;22(5):1521–1527. doi:10.1111/jocd.15621
84. Zohdy HA, Hussein MS. Intradermal injection of fluorouracil versus triamcinolone in localized vitiligo treatment. *J Cosmet Dermatol*. 2019;18 (5):1430–1434. doi:10.1111/jocd.12820
85. Liao ZK, Hu SH, Han BY, et al. Pro-pigmentary action of 5-fluorouracil through the stimulated secretion of CXCL12 by dermal fibroblasts. *Chin Med J*. 2021;134(20):2475–2482. doi:10.1097/cm9.0000000000001689
86. Mina M, Elgarhy L, Al-Saeid H, Ibrahim Z. Comparison between the efficacy of microneedling combined with 5-fluorouracil vs microneedling with tacrolimus in the treatment of vitiligo. *J Cosmet Dermatol*. 2018;17(5):744–751. doi:10.1111/jocd.12440
87. Marasca C, Fabbrocini G, D'Andrea M, et al. Low dose oral corticosteroids, microneedling, and topical 5-fluorouracil: a novel treatment for recalcitrant pediatric vitiligo. *Pediatr Dermatol*. 2021;38(1):322–323. doi:10.1111/pde.14443
88. Abdou AG, Farag AGA, Rashwan M, Shehata WA. The clinical and pathological effectiveness of microneedling and topical 5-fluorouracil in vitiligo treatment: an association with matrix metalloproteinase 2 immunohistochemical expression. *J Cosmet Dermatol*. 2022;21(5):2153–2161. doi:10.1111/jocd.14388
89. Mobasher P, Guerra R, Li SJ, et al. Open-label pilot study of tofacitinib 2% for the treatment of refractory vitiligo. *Br J Dermatol Apr*. 2020;182 (4):1047–1049. doi:10.1111/bjd.18606
90. Craiglow BG, King BA. Tofacitinib citrate for the treatment of vitiligo: a pathogenesis-directed therapy. *JAMA Dermatol*. 2015;151(10):1110–1112. doi:10.1001/jamadermatol.2015.1520
91. Qi F, Liu F, Gao L. Janus Kinase inhibitors in the treatment of vitiligo: a review. *Front Immunol*. 2021;12:790125. doi:10.3389/fimmu.2021.790125
92. Cárcamo-Martínez Á, Mallon B, Anjani QK, et al. Enhancing intradermal delivery of tofacitinib citrate: comparison between powder-loaded hollow microneedle arrays and dissolving microneedle arrays. *Int J Pharm*. 2021;593:120152. doi:10.1016/j.ijpharm.2020.120152
93. Pillaiyar T, Manickam M, Jung S-H. Recent development of signaling pathways inhibitors of melanogenesis. *Cell Signalling*. 2017;40:99–115. doi:10.1016/j.cellsig.2017.09.004
94. Laddha NC, Dwivedi M, Mansuri MS, et al. Vitiligo: interplay between oxidative stress and immune system. *Exp Dermatol*. 2013;22(4):245–250. doi:10.1111/exd.12103
95. Abdalla MA, Nayaf MS, Hussein SZ. Correlation between serum α-MSH and vitamin D levels in vitiligo patients. *Iranian J Dermatol*. 2020;23 (4):163–167. doi:10.22034/ijd.2020.120836
96. Beltraminelli H, Dietrich N, Hunziker T. Fractional transepidermal delivery: a histological analysis. *Dermatology*. 2011;223(4):321–324. doi:10.1159/000334165
97. Esmat S, Assaf MI, Mohye Eldeen R, et al. Evaluation of needling/microneedling as an adjunct to phototherapy in the treatment of stable acral vitiligo: a comparative clinical and immunohistochemical study. *J DermatolTreat*. 2022;33(5):2621–2628. doi:10.1080/09546634.2022.2062279