Materials Chemistry Horizons REVIEW

Polymeric and Composite-based Microneedles in Drug Delivery: Regenerative Medicine, Microbial Infection Therapy, and Cancer Treatment

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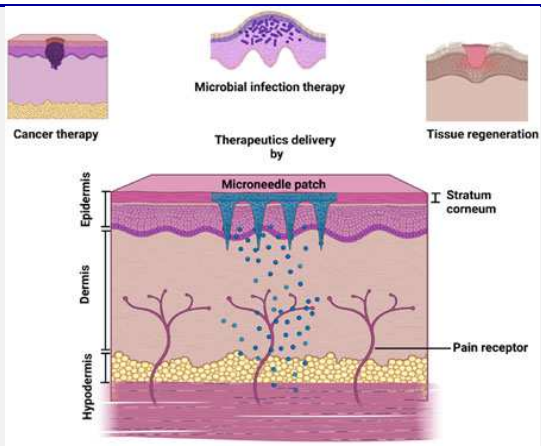
Mater. Chem. Horizons, 2023, 2(2), 113-124 10.22128/mch.2023.645.1036 OPEN ACCESS

ABSTRACT
Microneedles (MNs) are microscopic, needle-like structures employed in drug delivery through the skin. They are non-invasive and cause minimal to no pain at the site of insertion into the skin. MNs can be used to successfully deliver both small and large molecules to people who need them. Polymeric MNs have recently been combined with nanomaterials in order to construct flexible nanocomposite systems, allowing their use in biomedicine to be expanded. The literature has provided in-depth evaluations of MN patch technology, which has led to a dramatic rise in the number of scholarly articles on this topic. This review introduces different nanocomposite-based MN applications in the fields of tissue regeneration, microbial infection, and cancer therapy. Also, the prospects and challenges of nanocomposite-based MNs are briefly discussed.



Keywords: Microneedle patch, nanocomposite, cancer therapy, regenerative medicine, microbial infection therapy

1. Introduction

Currently, MN patches have become a research hotspot in biomedicine due to their noninvasive method of transdermal administration [1-3]. MN patches can avoid the common adverse effects associated with the oral administration of conventional medications. Also, they elude digestive system damage and first-pass hepatic effects but also the drawbacks associated with subcutaneous injections, such as needle infection and pain feeling [4, 5]. MNs drug delivery is illustrated in **Figure 1** compared to other transdermal and injection drug delivery routes. Extensive research on various MN patches has been conducted in recent years. MNs arrays are often fabricated from silicon, metals, and polymers [6, 7]. Among them, polymeric MNs have attracted significant interest in the biomedicine areas due to their distinctive benefits, which include high drug loading capacity, excellent biocompatibility, nontoxicity, great biodegradability, and a straightforward and affordable production technique [8, 9]. Polymeric MNs could be in different forms of ones such as dissolvable, solid, swellable, and composite-based forms. In the case of dissolvable MNs, after insertion, MNs array dissolves rapidly in the skin, releasing the drug and biomolecules, leaving no sharp residue. Despite dissolvable polymers' promising properties, they typically possess very weak mechanical properties. The necessity to combine biocompatibility, powerful mechanical qualities, and quick dissolution severely restricts the selection of polymers [10].

Nanocomposites, composed of nanoscale particles in a polymer, metal, or ceramic matrix, are one of the technical advancements of the twenty-first century that have lived up to the expectation [11, 12]. Because of their superior mechanical, optical, thermal, electrochemical, biodegradable, and biocompatible qualities, nanocomposites have significant potential in almost all industrial areas. Nanomaterials have recently been combined with polymeric MNs to create nanocomposites, expanding their biomedical applications [13, 14]. This combination provides the nanocomposite hydrogel the benefits of both systems, such as mechanical properties, proper flexibility, improved local nanomaterial retention, and other impressive properties such as tailored biodegradation, tissue adhesiveness, as well as thermal, light, and electrical responsiveness while minimizing the disadvantages of each system [11, 15]. Some

Received: January 12, 2023
Received in revised: March 19, 2023
Accepted: March 26, 2023

polymers which are widely used in MN fabrication, such as polyvinylpyrrolidone (PVP) and carboxymethylcellulose (CMC) associated with a harsh process of production and have a low elastic modulus around 1 Gpa [5, 16-18]. As a result, enhancing the mechanical characteristics of dissolving polymer MNs may improve therapeutic effectiveness, versatility, simplicity of production, and quick skin dissolution[19].

Biodegradable polymer nanocomposites, such as chitosan-reduced graphene oxide nanocomposites and carboxymethylcellulose-layered double hydroxide nanocomposites, have been reported for use in MNs array to increase mechanical strength and introduce novel functionality, such as electrical conductivity to facilitate iontophoretic drug delivery [10, 20]. In addition to providing mechanical and electrical properties, graphene nanoparticles in nanocomposites have also improved drug release behaviors while preserving the biodegradability of the polymer [21, 22]. MNs array-based nanocomposite has been utilized for therapeutic various fields due to their superior benefits. In this review, applications and recent advances of MNs array-based nanocomposite are briefly reviewed through the fields of cancer therapy, microbial infection therapy, and regenerative medicine. Moreover, their challenges and prospects are discussed.

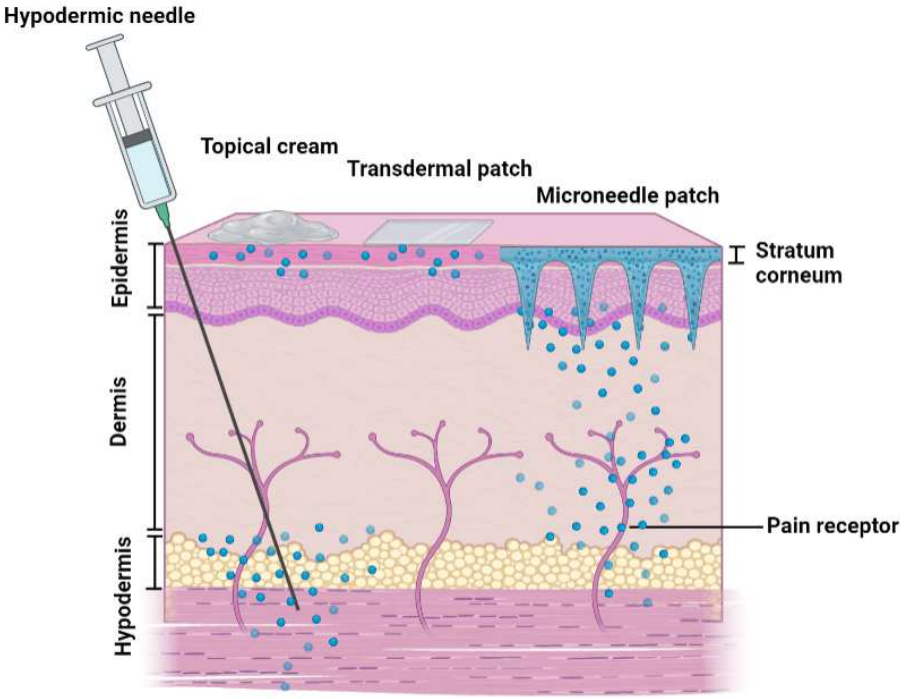


Figure 1. Efficacy and mechanism of action of the MN patch compare to other transdermal drug delivery systems.

2. Microbial infection therapy

Skin is the body's largest organ, which plays a vital role in promoting health and preventing the penetration of pathogenic agents. The role of skin as a barrier is complicated and includes different parts, such as the physical, chemical, immunological, and microbiome barriers. In the physical barrier role, the stratum carenum as a tight junction does not prevent the entry of small molecules and pathogenic microbes. The chemical barrier role refers to keratinocytes producing a wide range of antimicrobial peptides for a right and fast immune response [23]. Immunological Barrier roles include multiple functions, such as innate and adaptive immune cells protecting the skin against pathogens and sensing danger signals. In the microbiota barrier, the outermost layer of the cutaneous barriers, including bacteria, fungi, and viruses, is a barrier to prevent infection by harmful pathogenic microbes. This microbiota barrier metabolizes the host's proteins and lipids and produces bioactive molecules [24]. Despite all this, microbial infection from the skin is an unavoidable subject, and the best remedy is via skin.

Microbial infection in the MN category can be discussed from two viewpoints; first, different kinds of MN that are conceptualized for drug delivery to deliver a broad range of low molecular weight drugs and may cause infection; second, MNs that are used to prevent or eliminate this trauma. In some research, microbial penetration for MN punctures was studied and demonstrated that residual holes left by MNs significantly cause less infection than hypodermic needle punctures. Nearly no microorganisms crossed the viable epidermis in MN-punctured skin [25].

Indeed, the maximum level of infection with a hundred MN array is non-problematic infection. Another kind of microbial attack could occur by MNs when a long-term drug delivery patch poorly sticks to desired tissue which can limit their application and cause increased infection. This limitation may be mitigated by an octopus's and mussel's bioinspired MN. In a study, the good adhesion to the surface by an MN patch's idea was obtained from covalent and noncovalent chemical interactions between an adhesive protein derived from the mussel and the tissue [26]. In another research, a loop of octopus suction-cup-resembling concave chambers surrounding each MN was designed. At the same time, these inner dome-like protuberances motivated researchers to adhere MNs to wet and dry surfaces [27]. Another preventive approach in this field is the basic material of MNs. For example, a MN fabricated from a polydopamine hydrogel can render the tips and base of MNs with antimicrobial effects against common bacteria such as *Escherichia coli* [28].

Conversely, combating infections is another known task of MNs [29]. Skin infection includes three stages that involve three parts of the skin layer, while deeper skin layer infection is more serious [30]. In this regard, antimicrobial MNs opened a new horizon for treating this problem. For achieving this purpose, three main strategies are the usage of antimicrobial polymers, nanoparticles, or MNs integrated with living organisms. Antimicrobial polymers benefits from chemical stability and possess low cytotoxicity. At the same time, they are capable of preventing the growth of bacteria, fungi, and viruses and can eliminate drug-resistant microbes by disrupting microbial membranes [31]. On the other hand, antimicrobial nanoparticles-based inorganic nano-compounds such as Au, Ag, CuO, ZnO, TiO_2, MgO, Fe_2O_3, MgO, and CaO nanoparticles[32, 33], as well as antimicrobial polymeric nanomaterials such as quaternary ammonium polyethyleneimine, are used to prepare this category of MNs [34]. And for instance, as a living for infection therapy, virus, and bacterial-loaded MNs can be pointed out [35].

The main three categories in the field of antimicrobial therapy are antibacterial, antifungal, and antiviral MNs. Bacterial infection is the most prevalent infection involving humankind these days. To treat bacterial bio-networks connected to surfaces, MN needs to penetrate the extracellular polymeric substances of the bio-network and disrupt its structure. One of the examples, for this reason, is the gelatin nanoparticles drug encapsulation strategy. These degradable nanoparticles may deliver a broad range of antimicrobial therapeutics to biofilm-contaminated sites, resulting in lower off-target toxicity and a faster wound-healing process compared to direct chloramphenicol administration [36]. The next category belongs to antifungal MNs. As a recent example, *Candida* fungus, causing a red, scaling, itchy rash on the skin, and MN patch-loaded Amphotericin B demonstrated concentration-dependent activity against it [37]. Another attractive application of antifungal MNs is based on MNs integrated with probiotic bacteria; it treats the fungal infection. In this regard, lactobacillus encapsulated in the dissolvable sodium carboxymethyl cellulose, and the results are satisfactory (**Figure 2**). Even though it was mentioned before, there are five different kinds of barriers in the skin, but viruses cause various skin ailments despite all of them. As a serious problem in today's world, the human papillomavirus (HPV) Viral wart is a proliferation of skin. A microneedle-based suggestion for overcoming this disease is polylactic acid and poly(lactic-co-glycolic acid) coated with bleomycin and capable of puncturing the thickened, heavily keratinized skin associated with HPV and treatment of the patient [38].

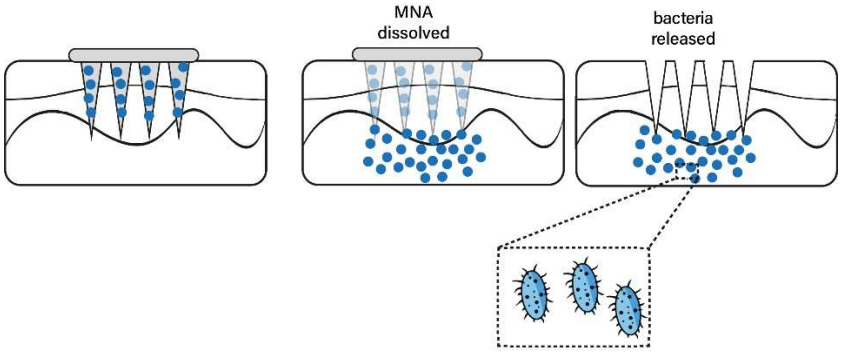


Figure 2. MNs deliver encapsulated bioactive functional probiotics into local skin to improve skin health and immunity

3. Tissue engineering

Tissue engineering is a fast-progressing therapeutic approach to help humankind who suffer from tissue or organ damage or loss to regenerate and repair that obstacle rapidly and efficiently. MNs are known for their widely employed transdermal drug and vaccine delivery systems [39]. However, due to their precision progress in fabrication techniques in the 1990s, their application grew daily in every single part of medical research and tissue engineering. In the early

steps, they draw attention to overcoming the epidermis as a barrier to the transdermal drug delivery systems [40]. But gradually, the mesmerizing application of these micro miracles infiltrates tissue engineering for application to different organs and tissue.

MN can occupy a certain position in tissue engineering for many reasons, such as portability, semi-invasiveness, safety, and painlessness [5]. One major application is skin wound repair, for example, a chitosan MN array patch that could intelligently control drug release and effectively promote tissue regeneration in wound healing [41]. Another usage is to gain the benefit of MNs as prostheses to deliver chemical agents precisely to the defined regions of tissue or even to the interior of cells. This specific delivery to the tissue is far better than spread over distances with just convection rates or drug diffusion penetration distance determined by the physicochemical properties of the agent and the tissue [42, 43].

For instance, a vascular drug administration reported applying a curved-based MN to direct drug delivery to blood vessels by penetrating its external surface [44, 45]. Another example in this context is tissue regeneration, in particular for the treatment of skin wounds, with the design of a detachable hybrid MN depot for delivering mesenchymal stem cells [46]. For this reason, a hybrid MN with poly(lactic-co-glycolic) acid shell and encapsulating mesenchymal stem cells are embedded in a Gelatin methacryloyl hydrogel core to ease MN penetration and protect the encapsulated cells. The poly(lactic-co-glycolic) acid shell's degradation starts after removing of detaching MN substrate, and mesenchymal stem cells migrate to the target tissue and release regenerative factors. Another mesmerizing wound healing application is herb MN patches. In a study, a novel herbal patch fabricated by poly (ethylene glycol) diacrylate MNs include: integrating the herbal extracts, *Premna microphylla*, and *Centella asiatica* was introduced. This MN shows excellent performance in anti-oxidant, anti-inflammatory, and anti-bacterial activity while being very capable of raising relevant growth factor gene expression in fibroblasts (**Figure 3**).

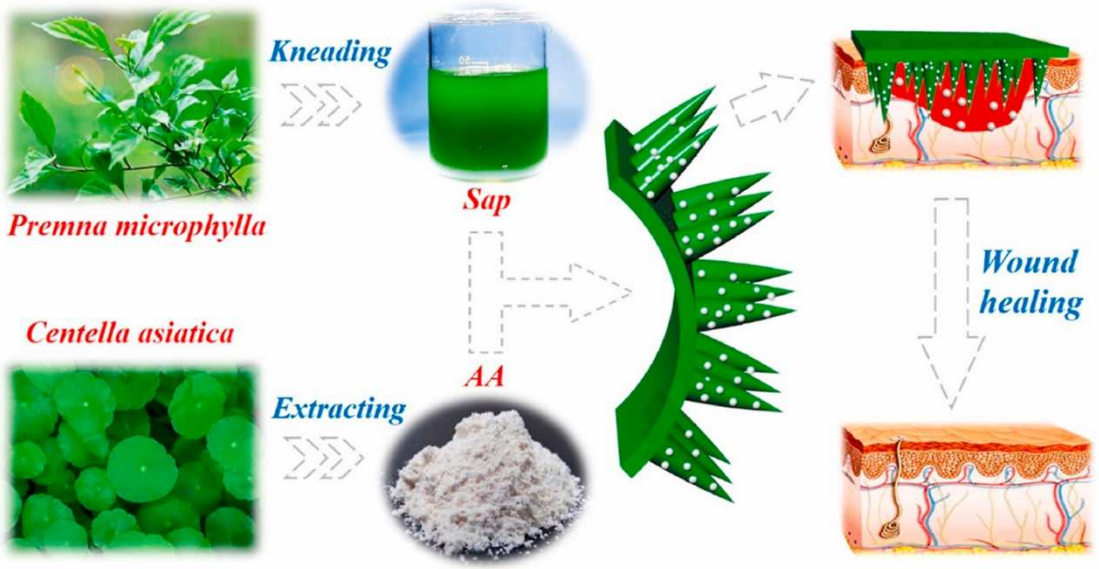


Figure 3. The application of herbal MN patches derived from the extractives of Chinese herbs for wound healing. Reprinted from [47] under open access license.

A fact of MN usage in the drug delivery sector is that drugs delivered with this method with DNA- and protein-based pharmacologic agents cannot be administered orally or through the skin because of their fast metabolization in the digestive system or breathing system before reaching systemic circulation [48]. To prove this case, a Lego-like interlocking MNs array was proposed that was created with a two-photon induced polymerization method and exhibited a non-linear stress-strain response and demonstrated penetration without fracture when tested against pork skins [49].

The next application related to a physical non-viral gene delivery method for tissue engineering is microinjection based on MNs for direct nucleic acid delivery. It took place in the toolbox of cell biologists and bioengineers [50]. In the first report, a glass-based MN injected nucleic acids directly into the cellular cytoplasm [51]. After that, MN-based injection became tedious due to the few cells that could be transfected; in the meantime, cellular biologists took good advantage of it for making transgenic animals illuminating functions of uncharacterized genes [52]. A successful

report in this branch is a single MN used for transfecting rat and mouse ova for creating transgenic animals and facilitating somatic nuclear transfer [53].

Another use report in the MN category for tissue engineering is based on the scaffolding role of MNs. A key factor in nearly all methods of tissue fabrication is making a three-dimensional biomaterial framework that mimics the extracellular matrix known as a scaffold that helps the damaged tissue restore facile while controlling building block behavior [54]. In this regard, a less-known approach confers the functional characteristics of living tissues with temporary scaffold approaches [55]. The minute method in this field are MNs assisted bioprinting which fabricates a tissue with different cellular building blocks such as microspheroids[56].

A report for constructing temporary scaffold shapes by bioprinting and fusing micro spheroids is for repairing cartilage tissue. This method is one of the subcategories of bottom-up fabrication that can overcome some cons in this part of tissue engineering, such as impairment in host scaffold integration or toxicity response to the scaffold, a prevalent issue in this field. Nevertheless, the meticulous control of obtained shape or desired outcome in a nonuse scaffold is challenging. To surmount this obstacle, a modular design uses small building blocks to improve the units' manageability that can be precociously implanted into a desired tissue. As an example of this type of tissue engineering, spheroids with the fusion to each other capability, placed in a specific arrangement for gain to a final tissue, can be mentioned. This subset of bioprinting which is inspired by a Japanese traditional art called the "Kenzan" method (stalks of floral become firmed upon a bed of metallic needles), puts up microspheres(MS) with a distinctive spatial organization with temporary support containing MNs [57]. In this method, the initial assumption is that MS held up in a determined position on the MN array for fusing into a neotissue over time in a temporary scaffold manner. Indeed, the MN array role is defined as a transient scaffold system to maintain MS orientation while the tissue becomes mature and ready to remove from the MN array. The printer worktable includes various parts named management and printing areas. The first area (management) contains two different parts, such as; a transport unit and plate management, which have different capabilities; a storage magazine that collects up to ten spheroid containing multiwell plates, and a waste magazine is provided for the spheroid-inspected and used plates.

For this reason, a capture unit needed with two cameras named in **Figure 3** as the upper and lower camera installed in the printing area and the MN in the top position captured by the upper camera while the plates well and spheroids present there and the spheroid suction nozzle tip captured with the lower camera. The reason for benefiting from two cameras in the bioprinter is to take photographic images for analyzing the MN position and the spheroids' properties and conditions before printing and measuring their size and shape. For further explanation, a mono MS was cultured in a well of a plate shown in **Figure 4**. Cellular MS was picked up with the suction tip of a robotic arm and then skewered upon a single MN in the array.

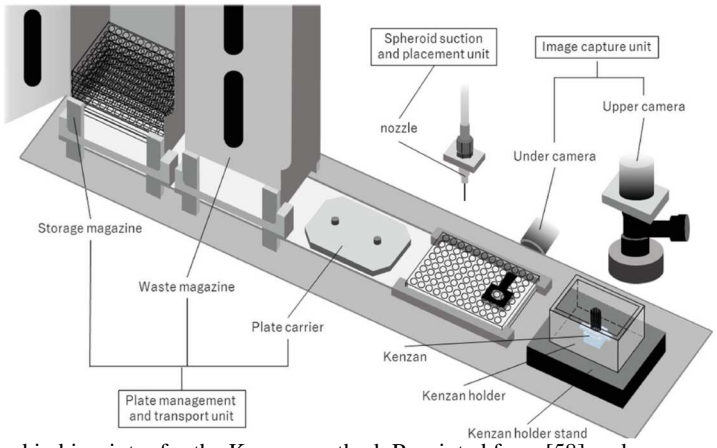


Figure 4. Equipment employed in bioprinter for the Kenzan method. Reprinted from [58] under open access license.

Finally, after self-aggregation, a high-density cellular structure (see **Figure 5**) resulted and was ready to use. This MN-based method ablated the bio-ink bioprinting limitation, such as cell density. In contrast, cell density was close to the highest theoretical cell density in this approach, and tissue benefited from an adequate amount of cells for faster generating complex structures.

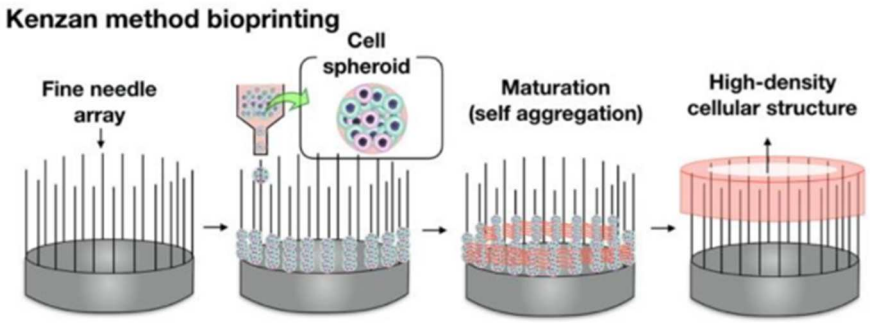


Figure 5. Schematic illustrations of the traditional methods of the Kenzan method. Reprinted from [59] under open access license.

Overall, three different categories of MN discussed in the tissue engineering category include; hollow MN for direct injection or solid MNs that are coated with a drug or nucleic acid for direct application to tissue, and a simple metal MN as a temporary scaffold. Despite the fact MNs are a safe way to deliver nucleic acids to a variety of cell types and pass many of the gene delivery barriers, some disadvantages should be mentioned too, such as; single MNs, which are mostly used for tissue engineering, are time-consuming need used on a larger scale, while this application of MNs need a well-trained operator for injecting the cells with precision and high accuracy for success while assuming that the stiffness of the MNs are strong enough to endure the shear forces of the tissue and do not break themselves and tear the tissue layer or fail to distribute drugs or nucleic acids.

4. Cancer therapy

Cancer is one of the most prevalent diseases with serious mortality risks. Cancer is traditionally treated with chemotherapy, radiation, hormone therapy, and surgery [60]. However, many limitations are associated with these therapeutic approaches, including toxic side effects and limited therapeutic effectiveness [61]. Therefore, it is necessary to conduct further studies to improve the efficacy of therapy and reduce side effects. Drug agents which are used for cancer therapy are clinically limited by serious adverse effects such as cardiotoxicity and multidrug resistance [62, 63]. Nanoparticle-based anticancer therapies have shown great promise, but their limited ability to accumulate inside tumor tissue has slowed their translation into clinical research. Less than 0.7% of the dosage is reported to reach the tumor site, limiting their bioavailability and effectiveness [64, 65]. Furthermore, the great complexity of nanomedicines renders it difficult to scale up the production techniques and ensure reproducible therapeutic effects [66].

In recent years, researchers have been interested in macroscale delivery systems that can be locally implanted into the tumor tissue and avoid all the problems that arise with their systemic delivery. In particular, MN-based devices may be employed to effectively deliver small and macromolecules such as proteins, chemotherapeutics, and genetic material in addition to nanoparticle-based anticancer therapeutics. Utilizing nanocomposite in combination with the polymeric MNs provides efficient cancer-therapeutic MNs.

To this aim, Pei et al. used a two-step casting technique to fabricate composite-dissolving MN patches to treat superficial cancers with chemotherapy and photothermal therapy (PTT). Doxorubicin hydrochloride (DOX) and indocyanine green (ICG) were encapsulated in the polymeric matrix from polyvinylpyrrolidone (PVP). A mesoporous silica nanoparticle (MSN) was also used to increase ICG stability and prevent losing its PTT effectiveness. The procedure was schematically illustrated in **Figure 6**. The findings demonstrated that combining chemotherapy and PTT for PVP@DOX/MSN@ICG MN patches optimally promoted MG-63 cell death *in-vitro* using human osteosarcoma MG-63 cells as an *in-vitro* cell model. The maximum anticancer impact was shown with PVP@DOX/MSN@ICG MN patches *in-vivo* due to the synergistic effects of chemotherapy/PTT. Consequently, composite-dissolving PVP@DOX/MSN@ICG MN patches could be a promising engineered system for superficial tumor therapy [67].

In another study, Zhang et al. created a nanocomposite MN (ZCQ/MN) patch comprising copper/zinc dual-doped mesoporous silica nanoparticles loaded with quercetin (ZCQ) as a combined treatment for androgenic alopecia. After being inserted into the skin, the biodegradable MN gradually dissolves and releases the ZCQ nanoparticles. Quercetin

(Qu), copper (Cu^{2+}), and zinc ions (Zn^{2+}) are released subcutaneously by ZCQ nanoparticles in a manner that works in concert to enhance hair follicle regeneration. The primary pathophysiological phenomena of AGA that are regulated in the mechanism for promoting hair follicle regeneration include the inhibition of dihydrotestosterone, the suppression of inflammation, the promotion of angiogenesis, and the activation of hair follicle stem cells by the combination of Cu2+, Zn2+, and Qu ions. The results provided a theoretical basis for the development of biomaterial-based anti-hair loss therapy by demonstrating the efficacy of a treatment strategy for hair loss based on the systematic intervention targeting different pathophysiological links of AGA with the combination of organic drug and bioactive metal ions [68]. **Figure 6** schematically shows the MN structural design and its mechanism of action.

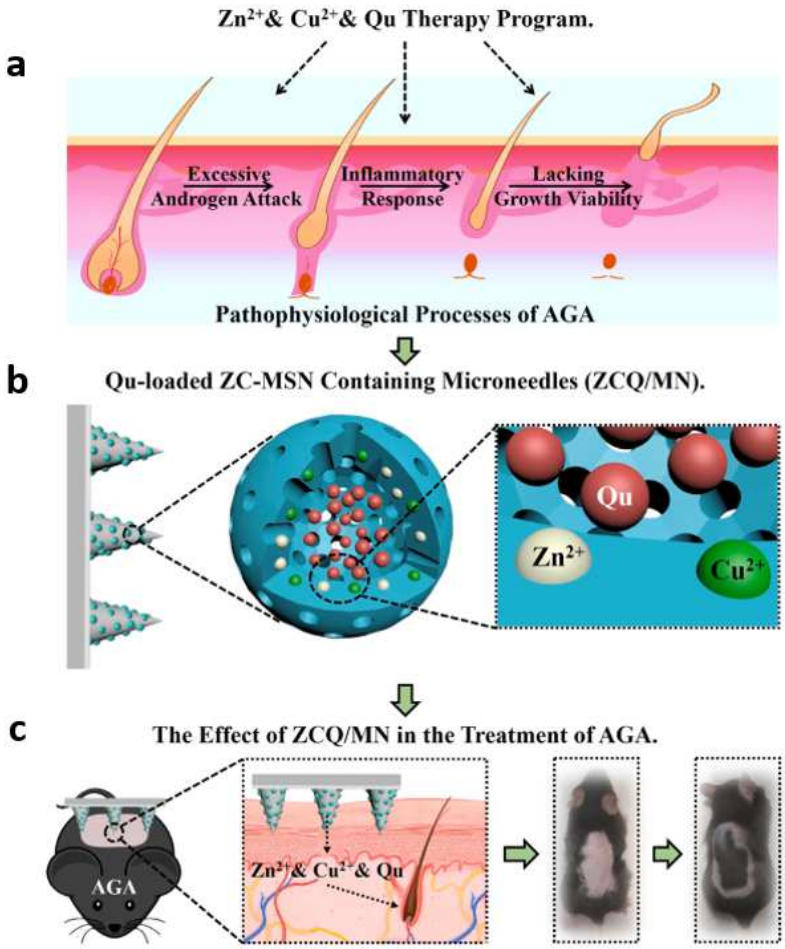


Figure 6. ZCQ/MN for AGA is shown schematically. (**a**) In individuals with AGA, Zn^{2+}, Cu^{2+}, and Quercetin (Qu) may comprehensively control the pathophysiological microenvironment of hair follicles. (**b**) A composite MN patch loaded with Qu (ZCQ/MN) and Zn/Cu dual-doped mesoporous silica nanoparticles was created. (**c**) To treat AGA, ZCQ/MN could release bioactive Zn^{2+}, Cu^{2+}, and Qu. Reprinted from [30] under open access license.

Despite recent developments in antibody immunotherapy to treat melanoma, the therapeutic impact is still limited by the tumor microenvironment's ineffective immune suppression and penetration. Additionally, immune-related side effects have often happened due to therapeutic drugs' off-target binding to normal cells following regular delivery. In this regard, the PD-L1 targeting peptide was designed by Li et al. and demonstrated both targeting recognition and self-assembly capability. Its affinity to PD-L1 was high compared to its intrinsic receptor, PD-1. In order to create multifunctional and integrated nanoscaled therapeutics, the PD-L1 targeting peptide was able to self-assemble into spherical micelles and effectively encapsulate immunologic adjuvants during the self-assembly process. This integrated nano drug was encapsulated within biodegradable MNs to develop a cascaded drug delivery system that could inhibit the PD-1/PD-L1 axis while changing the immunosuppressive tumor microenvironment. Importantly, the

method of employing MNs as a carrier to transport immune checkpoint inhibitors and immunologic adjuvants enhanced the retention time of therapies in the diseased lesion and maybe prevented the adverse consequences of systematic administration of cancer immunotherapeutics. Results showed that it might destroy tumors that were PD-L1 positive. Also, when used in conjunction with immunologic adjuvants and immune checkpoint inhibition, it can effectively hinder tumor growth *in-vivo* [31].

Although MNs have made it possible to distribute drugs through the skin painlessly, their effectiveness has been restricted by slow drug diffusion and often need external stimuli. Lopez-Ramirez et al. proposed an autonomous and degradable active MN delivery platform that uses magnesium microparticles embedded inside the MN patch as the built-in engine to deliver deeper and faster intradermal payloads. The magnesium particles interact with the body fluid, resulting in the explosive-like quick formation of H2 bubbles required to break skin barriers and improve payload transportation. *In-vitro*, the release kinetics of active MNs were assessed by quantifying the quantity of IgG antibody (as a model medication) that passed through phantom tissue and a pigskin barrier. Experiments *in-vivo* using a B16F10 mouse melanoma model indicated that active administration of anti-CTLA-4 (a checkpoint inhibitor medication) resulted in a considerably improved immune response and much-prolonged life. **Figure 7** illustrates these composite MNs and their release profile behavior. A combinational quick burst reaction and gradual, sustained release are possible because of the spatially defined zones of active and passive MNs. Autonomous dynamic MN administration has enormous potential for a variety of therapeutic applications because of its adaptability, efficacy, and potential for vastly improved outcomes, simplicity, and affordability [32].

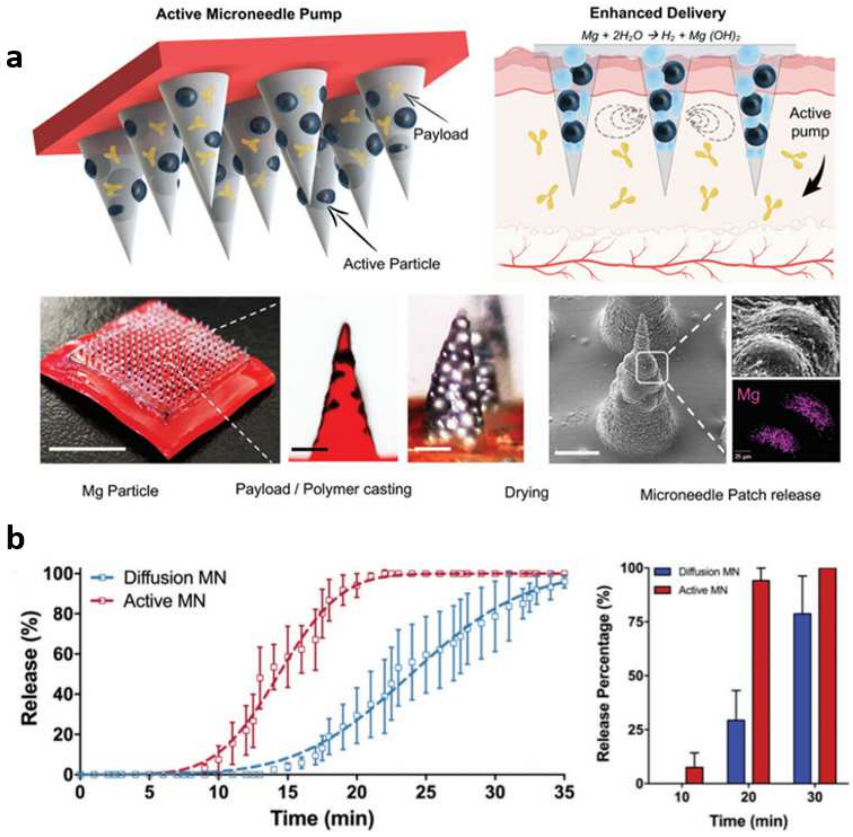


Figure 7. (**a**) The active MN patch composition and integrated magnesium particles work as pumps in contact with body fluid, enhancing drug release. Also, a digital image of a patch of 15 by 15 MN array, optical fluorescence microscopy photographs of a single active MN tip that is loaded with magnesium particles, and an EDX analysis of the Mg content of the active MN tip were respectively depicted, (**b**) The release kinetics of corresponding IgG delivery of both passive and active MNs at pH 6.0. MNs that are both passive (PVP and IgG-HRP) and active (PVP, IgG-HRP, and Mg particles); n = 5. Reprinted from [32] under open access license.

5. Conclusion and outlook

Utilizing MN devices has sparked hopes for the transdermal delivery of therapeutic agents. These wearable devices allow for painless administration, avoiding hypodermic needles and eliminating the requirement for a trained technician during administration. They have made great strides in many other fields over the years, including immunobiological drug delivery in various infectious diseases, tissue regeneration, treating and identifying diseases like cancer, dermatology, cosmetology, and many more. Polymeric MN patches, combined with nanocomposite materials, significantly improve their physical properties and penetration capability. Also, this combination provides a multifunctional drug delivery platform that could be administrated locally. Considering the existence of inherent limitations in the area of transdermal MN-based delivery, further investigations should address these issues.

Authors' contributions

F. A. The original draft, Writing & Critical revision; A. M. Conception and design of the study, Original draft, Writing & Critical revision; R. Z. Conception and design of the study, Writing & Critical revision.

Declaration of competing interest

The authors declare no competing interest.

Funding

This paper received no external funding.

Data availability

Not applicable.

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