Microneedles: A newer approach in NDDS in the management of Wound healing

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Abstract

Objective: Fundamental research is now being performed in the domain of chronic wound healing. There is major difficulty in getting medication to the site of wound and the wound healing process for diabetic patients which affects around 400 million people worldwide. There is a demand for the rise of painless method of delivering macro-molecular compounds. For this Microneedle patches are regarded as an effective and relatively new minimally invasive procedure involving superficial and controlled puncturing of the skin by rolling with miniature fine needles.

Methods: Microneedles (MN) are utilized to generate micro-punctures in the skin, causing controlled micro-injuries that do not harm the epidermis. These minor injuries result in slight surface-level bleeding and initiate a sequence of wound healing events. This sequence involves the release of different growth factors like platelet derived growth factor (PGF), transforming growth factor alpha and beta (TGF-α & TGF-β), connective tissue activating protein, connective tissue growth factor, and fibroblast growth factor (FGF). The devices based on microneedle with the loaded active medicines speed up wound healing and suppress bacterial infection. Various types of microneedles are developed such as solid, coated microneedles, hollow microneedles, dissolveable microneedles, hydrogel microneedles based on the type of drug delivery.

Significance: Thus, microneedle drug delivery systems could potentially combine the effectiveness of drug delivery associated with syringe injections with the comfort and convenience of a less invasive delivery method.

Conclusion: Finally, we have summed up the important approved microneedles products of the preceding discussions and forecasted their future evolution.

Keywords: PGF, TGF-α, TGF-β, FGF, hydrogels, stratum corneum.

1. INTRODUCTION

Skin is the largest sensory organ of the human body, and it is also the main barrier against harmful substances and micro-organisms to protect tissues and organs and maintain homeostasis[1]. People's life and health are seriously endangered by skin damage brought on by trauma, fire, dangerous chemicals, inherited illnesses, and systemic diseases. Hemostasis, inflammation, granulation, and remodelling are all part of the intricate and diverse process of wound healing, any link failure could impede healing. Biomaterials are made to interact with biological systems, allowing them to use their capacity for healing to promote the regeneration of tissues or organs [2]. In response to the increasing need for wound healing, skin biomaterials with exceptional bio-compatibility and regenerative capacity have been created.

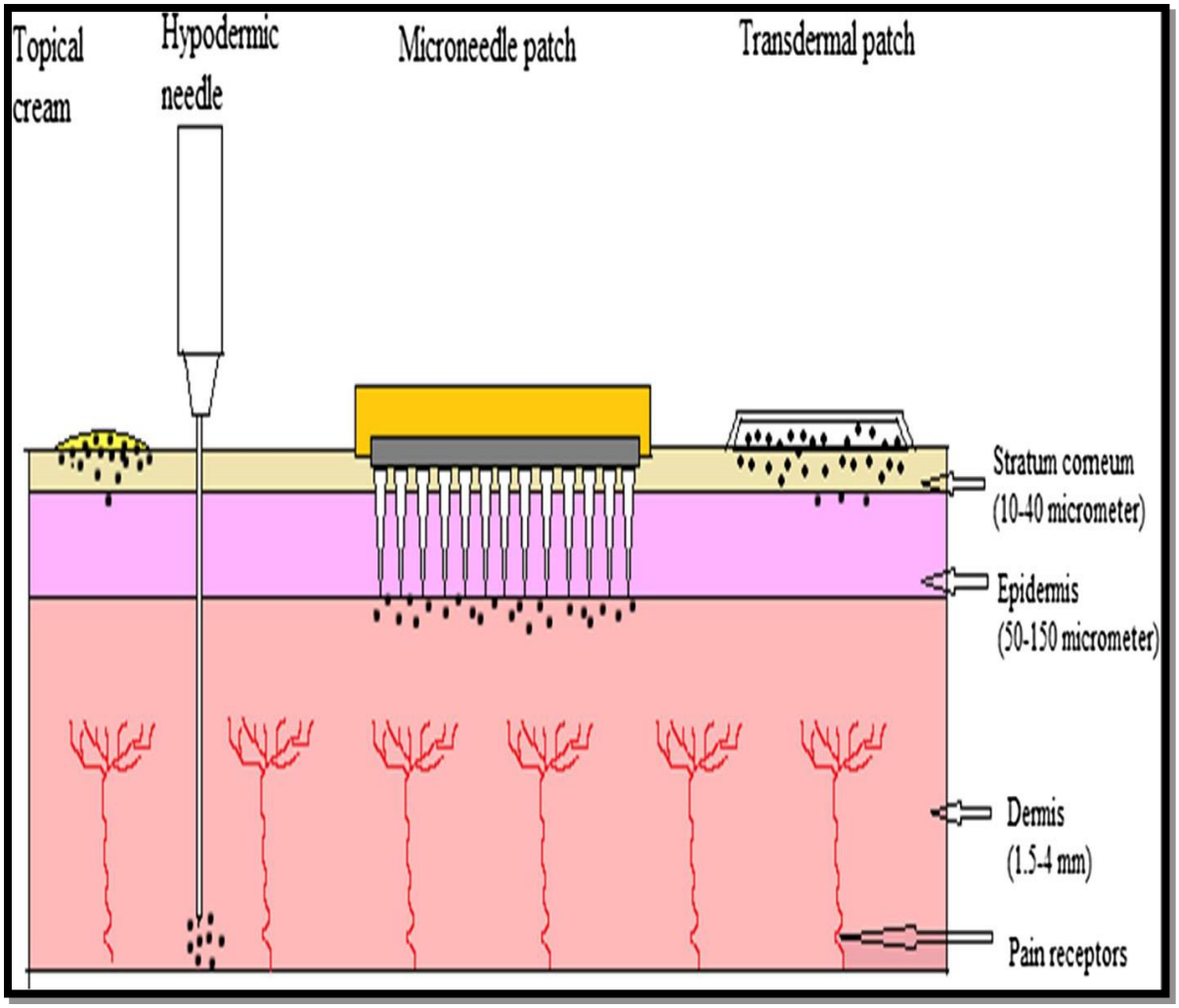
When it comes to administering medication topically, hypodermic needles and lotions are most frequently employed. Due to the pain they cause, needles are less well-liked by patients, and topical creams have a lower bioavailability. For drug delivery via the topical route, skin acts as the main barrier. Stratum corneum, middle epidermis, and dermis (deepest layer), make up the 3 primary layers of skin. Only specific molecules, such as medications with low molecular weight and lipophilic natures, can pass through the stratum corneum layer, which functions as a significant barrier. The comparatively low permeability of the layer creates numerous challenges for topical formulation creation. Different topical or transdermal administration techniques (Table 1.) have been researched to increase medication permeation such as topical gel, transdermal patches, and microneedles [3,4]. The drug delivery through various administration techniques have been shown in Figure 1. This article extensively focusses on Microneedles (MN) a newer approach in drug delivery system.

Table 1. Comparison of Topical cream, Transdermal patch, Hypodermic needle, Microneedle [28]

	Topical cream	**Transdermal patch**	**Hypodermic needle**	**Microneedle (MN)**
Description	Topical medication: Emulsions/ Ointments/ Paste.	Transdermal patches are applied to the skin and deliver medication through its surface.	A hypodermic needle is a hollow instrument frequently utilized alongside a syringe to introduce substances into the body.	Microneedles (MNs) refer to tiny needles of micron scale that are applied to the skin, establishing minuscule routes for transportation and thus improving the administration of medicinal compounds.
Onset of action	Slow	Slow	Fast	Fast
Pain	Pain-free	Pain-free	Painful	Pain-free
Bioavailability	Poor	Inadequate	Adequate	Adequate
Patient compliance	Low	Better	Low	Better

Self administration	Able to be done	Able to be done	Not able to be done	Able to be done
Mechanism of delivery	Penetration via skin pores.	The drug needs to traverse the stratum corneum barrier, leading to limited diffusion for larger molecules.	The drug is directly inserted into the dermis.	Precise and controlled skin puncturing is achieved by rolling miniature fine needles across the surface, reaching the stratum corneum. This allows direct placement of the drug into the epidermis or dermis, resulting in improved permeability.

Figure 1. Drug delivery by Topical cream, Transdermal patch, Hypodermic needle, Microneedle (MN) [5]



Microneedling, a recently developed minimally invasive method, entails the controlled and shallow puncturing of the skin using small fine needles. This technique has rapidly gained widespread recognition and approval due to its ease, affordability, safety, and efficacy, demanding only limited training. While it was initially employed as a means of fostering collagen and revitalizing facial skin, it has now extended its applications to serve as a vehicle for administering therapeutic medications and vaccines through the skin [6].

But not until the 1990s, with vast improvement in techniques in the micro-fabrication industry, microneedles were developed with more precise structure and better functionality [7].

The origin of the microneedling concept can be traced to 1995, when Orentreich introduced the idea of dermal needling through subcision for scar healing. This concept was further developed independently in 1997 by plastic surgeon Camirand, who employed tattoo guns without ink to relieve tension from post-surgical scars [6,8,9].

In 1998, an innovative strategy for enhancing the transdermal delivery of drugs, which significantly boosted the movement of molecules through the skin, was introduced [7, 10]. Microneedles, produced by fabricating arrays of micron-sized needles through silicon etching, demonstrated the ability to greatly enhance calcein permeability by over 1000 times upon insertion into the skin. This revelation suggested substantial room for improvement in microneedle applications, sparking heightened interest among researchers in exploring this field. A few years later, Matriano et al. documented that a particular commercially available micro-projection array patch (Macroflux@), coated with ovalbumin (OVA) at doses of 1 and 5 μg, led to immune responses up to 50 times greater than those observed with equivalent cutaneous or intra-muscular doses [7, 11].

In this review, we highlight the constantly evolving research and developments in microneedle development and formulation techniques, instruments used, and its various applications.

2. MECHANISM OF DRUG DELIVERY BY MICRONEEDLE (MN)

MN comprise two parts: invasive and supporting components. The invasive component is an array formed by hundreds of needles with length from 25 to 2000 microns [12]. The diffusion mechanism is used to deliver the drug via topical route. The skin is momentarily damaged during the drug delivery process using microneedles. In order to deliver the drug to produce necessary therapeutic response, a microneedle device is made by arranging several microneedles in arrays on a tiny patch (similar to transdermal patch). By cutting through the stratum corneum, it avoids the barrier layer, the drug is directly injected in epidermis or dermis layer, then it enters the systemic circulation and reaches the site of action, to produce therapeutic response [13,14,15].

Microneedles produce tiny punctures in the skin, causing controlled injury that doesn't harm the outermost layer. These small injuries cause minimal bleeding and trigger a healing process, releasing growth factors like platelet-derived growth factor (PGF), transforming growth factors alpha and beta (TGF-α and TGF-β), connective tissue activating protein, connective tissue growth factor, and fibroblast growth factor (FGF)[6, 16].

3. DIMENSIONS OF MICRONEEDLES

MN are micron sized needles that can be formulated from various materials with height ranges from 25-2000 μm. MNs topically applied to develop micron-sized transport pathways that promote improved drug delivery. MNs were first introduced in 1976, but they could not be produced until the first application of micro - electromechanical (MEMS) in 1998 [17]. Needle length of up to 1500 μm is sufficient to release the drug as thickness matches with the epidermis. Larger length and thicker needles can go deeper into the dermis that could damage the nerves and cause pain [18]. Mostly they are 150–1500 microns long, 50–250 microns wide, and have 1–25 microns tip thickness and can be of cylindrical, triangular, pointed, pentagonal, octagonal shapes.

4. TYPES OF MICRONEEDLES

Depending upon the transportation method MN are of following types .

- **Solid microneedles (SM):** To promote drug delivery to dermal layer and to increase the bio-availability and kinetic transport across skin, this type of microneedle is designed to penetrate the top layer of skin [19,20]. The SM is preferred for the delivery of vaccines over i.m injections as it lasts longer and creates stronger immune response [21]. When compared to HM, SM are simpler to produce, have better mechanical qualities, and have sharper edges [22]

- **Coated microneedles (CM):** In CMNs, a coating of drug solution is applied to the surface of the needle. The drug solution or drug dispersion layer envelops the microneedles. Following this, the drug dissolves from the layer, facilitating rapid delivery. The quantity of loaded drug relies on coating thickness and needle size, typically minimal. Li and colleagues applied diverse formulations and drugs to individual microneedles, enabling simultaneous co-delivery of multiple agents with distinct properties, encompassing both water-soluble and water-insoluble dyes [23,24,25,26,27,28].

- **Hollow microneedles (HM):** Hollow microneedles can deliver liquids, rather than requiring dry formulations, and allow relatively high doses to be administered. The HM has a hollow, empty core or chamber that is used to inject or store drug fluid [28]. The HM has a greater drug loading capacity than the SM [29]. For HMW (high molecular weight) compounds HM has the ability to deliver medicament into the viable epidermis or dermis layer [30]. It is appropriate to use HM with liquid vaccine formulations as it modulates the drug release over time [31].

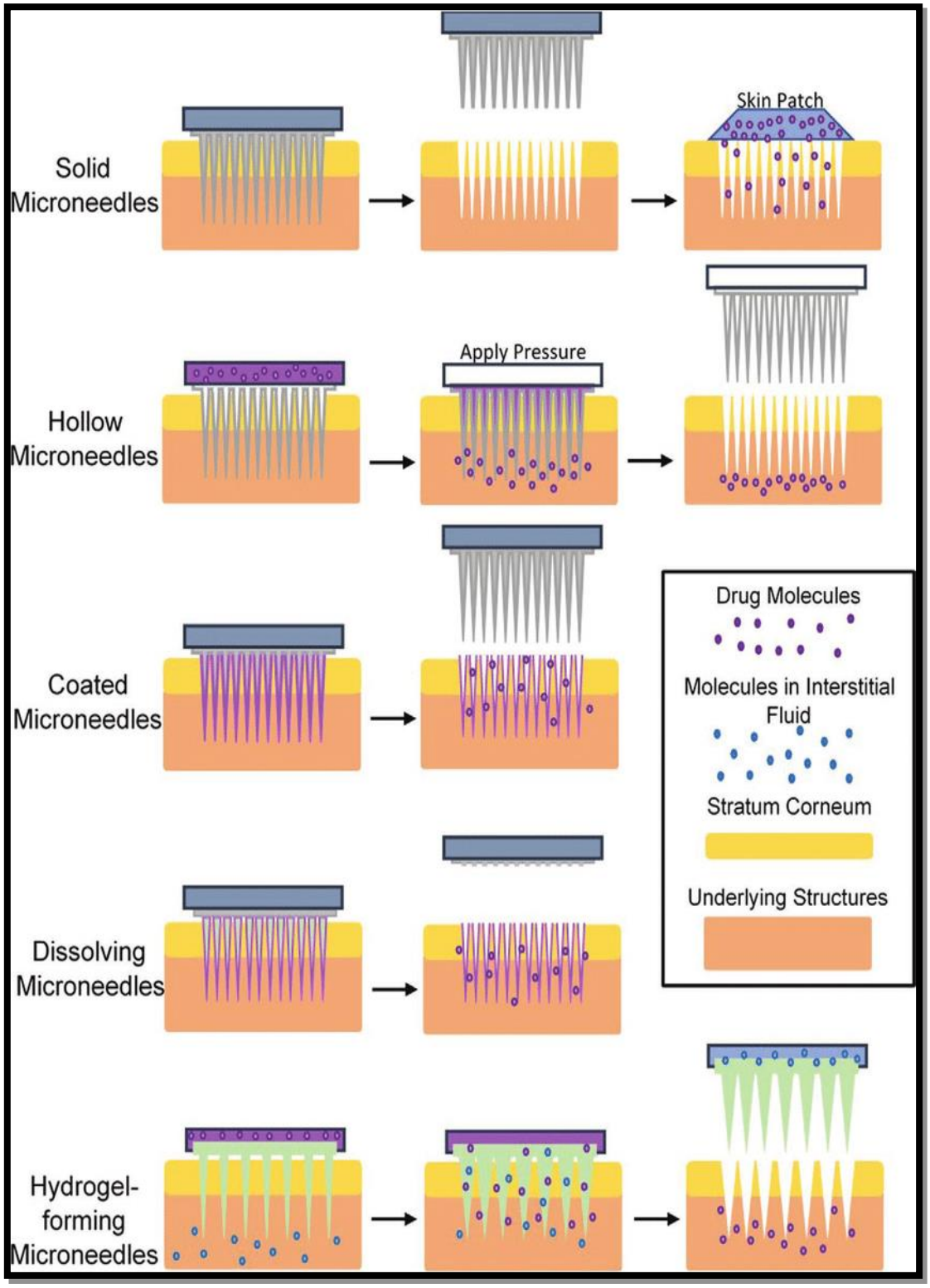
- **Dissolveable microneedles (DM):** Biodegradable polymers play a crucial role in the creation of dissolving microneedles, where medication is securely enclosed within the polymer structure. Upon insertion into the skin, these microneedles dissolve, releasing the medication they contain. Unlike other scenarios, these microneedles don't require removal after insertion, simplifying the application process to a single step. The polymer, responsible for controlling the gradual release of the medication, naturally breaks down within the skin. This approach is particularly advantageous for long-term therapy due to its biocompatibility and the polymer's ability to

dissolve within the skin, leading to improved patient adherence [32,36]. However, the development of dissolving microneedles faces challenges in ensuring effective distribution of medication through the needles [33, 36]. Niu et al. demonstrated that utilizing a hollow microneedle array for intradermal delivery results in a sustained release of medication within the skin, with the potential for rapid transit through draining lymph nodes [34,36]. Notably, the application of hollow microneedle arrays garnered significant support when it was found to elicit a much stronger immune response compared to the traditional intramuscular injection method [35,36].

- **Hydrogel microneedles:** It represent a novel approach in the field of microneedle technology. These microneedles are crafted using highly absorbent polymers with exceptional swelling properties. The inherent hydrophilic nature of these polymers enables them to absorb significant volumes of water, expanding within their intricate three-dimensional polymer structure. Upon insertion into the skin, they respond to the presence of interstitial fluid by undergoing controlled swelling. This swelling effect gives rise to microchannels between the medication patch and the capillary system. Primarily employed to create controlled skin barrier disruption, these microneedles also function as a modulating barrier due to their swelling behavior. Their versatility extends to their customizable size and shape. A notable feature is their rapid sterilization potential and ease of removal from the skin, ensuring minimal harm [36, 38].

  To lessen the gastrointestinal side effect connected with oral metformin administration, Migdadi et al. investigated hydrogel-forming microneedles. Results showed that using specially designed microneedles improved the drug's permeation and bioavailability. The mechanism of drug delivery through various types of microneedles have been shown in Figure 2. [38].

Figure 2. Mechanism of drug delivery through various types of microneedles [37]



5. MATERIALS USED CREATION OF MICRONEEDLES (MN)

All microneedles are created using a variety of materials (Table 2) which includes silicon, stainless steel, sugar, and polymers. Each form of MN has distinct qualities, benefits, drawbacks, uses, and types of materials [39-48].

Table 2. Materials used in creation of Microneedles [28]

MN Type	Advantages	Disadvantages	Manufacturing Method	MN Type Fit
Silicon	Adaptable and capable of being shaped into preferred forms and dimensions.	The process of creating it takes a significant amount of time and comes with a higher price tag. There is a potential for the skin to experience ruptures.	The technique of dry-etching silicon material, Uniform etching in all directions, Specific wet etching in a preferred direction, Segmenting a silicon base through dicing followed by chemical etching, Laser-based removal in a three-dimensional manner.	SM HM CM
Metal	Demonstrates favorable biocompatibility and satisfactory mechanical characteristics. Possesses strength and resists breakage effectively.	Initial investment is substantial. Additional processes needed after manufacturing. Has the potential to trigger allergic responses.	Techniques involving laser-based cutting, wet chemical etching, and electroplating with metals.	SM HM
Ceramic	It demonstrates resistance to both chemical and compressive forces.	Its tensile strength is minimal.	The processes of ceramic micro-molding and sintering lithography.	SM HM
Polymer	Remarkable biocompatibility. Minimal toxicity and economical.	Exhibit limited strength.	Photolithography processes utilized.	SM HM CM DM

6. APPROVED MICRONEEDLE (MN) PRODUCTS

The derma roller was the first item with microneedles. There are numerous microneedle items on the market that can be used for both medicinal and aesthetic purposes [49,50]. Below table (Table 3) lists out some the of microneedles which are in use. Microneedle items are sold by numerous businesses in Japan, the US, Europe, and Germany [51-53].

Table 3. Some Approved Microneedles (MN) products [28,62,63,64]

Product name	Company	Description of product	Uses
Dermaroller	Dermaroller Germany, White Lotus	A cylindrical roller containing solid or metal microneedles, ranging from 0.2 to 2.5mm in length.	Enhance skin texture and address issues like scars and hyper-pigmentation.
C-8 (Cosmetic type)	Dermaroller Series by Anastassakis K.	Microneedles measuring 0.13mm (or 130 micrometers) in length.	Utilized to improve the permeation of topical substances.
CIT-8 (Collagen Induction Therapy	Dermaroller Series by Anastassakis K.	A needle measuring 0.5mm (or 500 micrometers) in length.	Applied in collagen induction and the process of skin remodeling.
MF-8 type	Dermaroller Series by Anastassakis K.	A needle with a length of 1.5mm (or 1500 micrometers).	Addressing scars.
MS-4	Dermaroller Series by Anastassakis K.	A compact cylinder measuring 1 cm in length and 2 cm in diameter, featuring four circular arrays of needles with a length of 1.5mm each.	Applied to treat facial acne and scars.
Micro-Hyala	CosMed transdermal drug delivery	A patch of dissolving microneedles containing hyaluronic acid.	Intended for the treatment of wrinkles.
LiteClear	Nanomed skincare	Solid silicon microneedles are employed as a preliminary step, followed by the topical application of the drug.	For the purpose of addressing acne and skin imperfections.
Soluvia	Sanofi Pasteur Europe	Hollow microneedles connected to a syringe.	Immunization against influenza.
H-patch	Valeritas	A compact adhesive device (patch) is utilized.	Administer drugs into the subcutaneous tissue.
Micro-structured transdermal system	3M	HM	Conveys biologics and other diminutive compounds to the intended destination.

7. ADVANCES AND RESEARCH IN MICRONEEDLES (MN)

A. Black Phosphorus-Loaded Microneedles (MN) as Responsive Oxygen Delivery carriers for wound healing

Separable, responsive microneedles (MNs) for wound healing that are filled with black phosphorus (BP) and have the ability to give oxygen under control. Such MNs consist of a backing layer made of polyvinyl acetate (PVA) and tips made of gelatin methacryloyl (GelMA) that are filled with haemoglobin and BP quantum dots (BP QDs) (Hb). After the MNs are applied to the skin, the backing layer quickly dissolves, leaving the noncytotoxic, biocompatible GelMA tips inside the skin. This takes use of PVA's quick dissolvability. Following near-infrared ray irradiation, the local temperature of the skin will rise due to the outstanding photothermal impact of BP QDs and the reversible oxygen binding
capability of Hb, resulting in the responsive oxygen release. Notably, treating the cutaneous wounds of a type I diabetic rat model has highlighted the useful performance of such MNs, suggesting the prospective value in wound healing and other associated scientific disciplines [54].

B. Wound healing potential of anti-bacterial MN loaded with green tea (extracts)

In this work, the effectiveness of an antibacterial microneedle made of hyaluronic acid (HA) and green tea extract (GT) for the effective delivery of GT is assessed. These microneedles have the potential to replace traditional sustained medication release with an approach that is more patient-friendly. In this study, transdermal drug delivery systems were made utilising a fabrication procedure that produced GT/HA microneedles with a maximum area of less than 50 mm2 and antibacterial characteristics. It was done using Fourier transform infrared (FTIR) spectrometry to look for any potential changes that might occur to the microneedles when combined with GT. By changing the HA composition, the degradation rate of GT in GT/HA microneedles was easily regulated. The release qualities were measured in order to ascertain the impacts of various GT ratios in the HA microneedles [55].

C. Anti-bacterial and Angiogenic chitosan MN array patch to promote wound healing

A patch with a biomass chitosan microneedle array (CSMNA) and smart responsive drug delivery system for accelerating wound healing.Chitosan has a number of exceptional qualities, including a built-in antibacterial capability, and is frequently used to treat wounds. Additionally, the microstructure of microneedles allows for efficient medication administration to the target location while preventing overly strong skin and patch adherence. Furthermore, the CSMNA micropores have been employed to trap vascular endothelial growth factor (VEGF) within a temperature-sensitive hydrogel. Consequently, the controlled release of medications can be achieved by harnessing the temperature elevation triggered by the inflammatory reaction at the wound site [56].

It has been shown that the biomass CSMNA patch can encourage collagen deposition, angiogenesis, inflammation inhibition, and tissue regeneration during wound healing. Therefore, this adaptable CSMNA patch may be useful in clinical settings to promote wound healing [57].

D. Zn-MOF encapsulated anti-bacterial and degradable MN Array to promote wound healing

In this, a Zn-MOF encapsulated array of metha-crylated hyaluronic acid (MeHA) microneedles (MNs) is made using a moulding technique to be degradable, ductile, and wound-friendly. Such MNs array exhibits good antibacterial activity as well as significant biocompatibility due to the ability of the zinc ion produced from the Zn-MOF to cause damage against the bacteria capsule and oxidative stress. Additionally, the photo-crosslinked MeHA degradable MNs array has the superior ability to constantly and steadily release the loaded active ingredients while preventing secondary wound damage. Additionally, the hydrolysis of MeHA produces low molecular weight hyaluronic acid (HA), which supports tissue regeneration. It has been shown that these characteristics allow the Zn-MOF encased degradable MNs array to significantly accelerate epithelial regeneration and neo-vascularization. The combination of MOFs and degradable MNs array result promoted wound healing [58].

E. Multi-functional magnesium organic framework-based MN patch for increasing Diabetic wound healing potential

We create a microneedle patch based on a magnesium organic framework (abbreviated MN-MOF-GO-Ag) that can achieve transdermal administration and combination therapy for diabetic wound healing. In order to slowly release Mg2+ and gallic acid into the deep layer of the dermis, multifunctional magnesium organic frameworks (Mg-MOFs) are combined with poly(glutamic acid) (PGA) hydrogel and inserted into the tips of MN-MOF-GO-Ag. Cell migration and endothelial tubulogenesis are induced by the released Mg2+, while antioxidation is encouraged by gallic acid, a ROS scavenger. Additionally, the backing layer of MN-MOF-GO-Ag is constructed from graphene oxide-silver nanocomposites (GO-Ag) and -PGA hydrogel, providing additional good antibacterial benefits for quickening the healing of wounds. The full-thickness cutaneous wounds of a diabetic mouse model are used to illustrate the therapeutic effects of MN-MOF-GO-Ag on wound healing. The substantial wound healing improvement is attained with mice treated with MN-MOF-GO-Ag [59].

F. Chinese herb MN patch for wound healing

The herbal extracts *Premna microphylla* and *Centella asiatica* are combined with the microstructure of the MN. A novel Chinese herb microneedle (CHMN) patch for the treatment of wounds is discussed. Such a route is made of sap that has been traditionally removed from herbal leaves by kneading, and it is then solidified in a well-designed mould using plant ash that has been produced during the brine-induced process of making tofu. Premna microphylla leaves are abundant in pectin and other amino acids, which allows the CHMN to have the medical effects of heat clearing, detoxicating, detumescence, and hemostatic. Additionally, the CHMN has the potential to promote the expression of relevant growth factor genes in fibroblasts and exhibit excellent performance in anti-oxidant, anti-inflammatory, and anti-bacterial activity due to the superb pharmaceutical activity of Asiatic acid extracted from *Centella asiatica*. We have shown that the generated CHMN was dramatically effective as anti-bacterial, suppress inflammation, collagen deposition, angiogenesis, and tissue reconstruction

during the wound closure by taking use of the pure herbal components. These findings suggest that the growth and promotion of traditional Chinese medicine in contemporary culture will be facilitated by the incorporation of traditional Chinese herbs with cutting-edge technologies [60].

G. Lamprey-teeth-inspired anti-bacterial sericin MNs for infected wound healing

Limited wound healing and a high risk of inflammation provide obstacles to the therapeutic potential of wound infections brought on by bacteria. Due to their ability to effectively penetrate the epidermis and deliver medications, microneedles have been developed for the treatment of wounds. Regular microneedles, on the other hand, are typically made of inert polymers that primarily serve as a support but infrequently participate in the following physiological processes. As a result, they are unable to offer directed traction to "reduce" the wound area. Here, we created orientated antibacterial sericin microneedles with dual-functionalized needles to enable penetration and directing traction, drawing inspiration from lamprey teeth. Sericin, a product of silkworm cocoons, was used to create microneedle tips, greatly enhancing skin restoration through angiogenesis and hair follicle regeneration. Additionally, a high level of bacterial suppression was added to the OASM by integrating zinc oxide nanoparticles as an antibacterial module. It is thought that the interaction of these systems may be able to successfully treat infected wounds, indicating its potential for practical application [61].

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