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Review

Microneedles as a Promising Technology for Disease Monitoring and Drug Delivery: A Review

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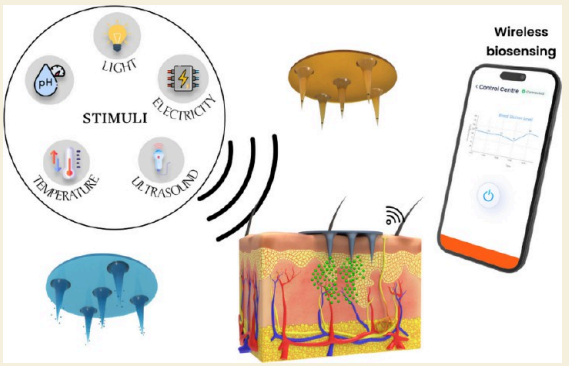
ABSTRACT: The delivery of molecules, such as DNA, RNA, peptides, and certain hydrophilic drugs, across the epidermal barrier poses a significant obstacle. Microneedle technology has emerged as a prominent area of focus in biomedical research because of its ability to deliver a wide range of biomolecules, vaccines, medicines, and other substances through the skin. Microneedles (MNs) form microchannels by disrupting the skin's structure, which compromises its barrier function, and facilitating the easy penetration of drugs into the skin. These devices enhance the administration of many therapeutic substances to the skin, enhancing their stability. Transcutaneous delivery of medications using a microneedle patch offers advantages over conventional drug administration methods. Microneedles containing active substances can be stimulated by different internal and external factors to result in the regulated release of the substances. To achieve efficient drug administration to the desired location, it is necessary to consider the design of needles with appropriate optimized characteristics. The choice of materials for developing and manufacturing these devices is vital in determining the pharmacodynamics and pharmacokinetics of drug delivery. This article provides the most recent update and overview of the numerous microneedle systems that utilize different activators to stimulate the release of active components from the microneedles. Further, it discusses the materials utilized for producing microneedles and the design strategies important in managing the release of drugs. An explanation of the commonly employed fabrication techniques in biomedical applications and electronics, particularly for integrated microneedle drug delivery systems, is discussed. To successfully implement microneedle technology in clinical settings, it is essential to comprehensively assess several factors, such as biocompatibility, drug stability, safety, and production cost. Finally, an in-depth review of these criteria and the difficulties and potential future direction of microneedles in delivering drugs and monitoring diseases is explored.



KEYWORDS: *microneedles, drug delivery, piezoelectric material, microneedle patch, disease monitoring, clinical trial, controlled release, therapeutics*

1. INTRODUCTION

Transdermal drug delivery is a significant method of delivering drugs that do not require invasive procedures and are commonly utilized in the field of biomedicine. In contrast to conventional treatment routes such as intravenous or oral techniques, transdermal drug delivery is pain-free, noninvasive, free from side effects, easily self-administered, and allows for regulated distribution of the medicine.[1] The method minimizes drug loss by bypassing first-pass metabolism and ensures gradual release into the bloodstream, resulting in reduced frequency of administration.[2]

Despite the benefits and progress made in transdermal drug delivery devices, the limited permeability of human skin restricts their use. The stratum corneum, which is the outermost layer of the epidermis, does not allow many drugs to pass through and enter the bloodstream in sufficient quantities. Therefore, numerous physical and chemical methods have been devised to augment the transportation of medicines across this barrier. Chemical approaches involve using chemical permeation enhancers (CPEs) to enhance the drug permeability. Many studies have been published on the use of CPEs to enhance permeability.[3] However, these reports indicate that CPEs are associated with safety concerns and potential pharmacological effects.[4,5]

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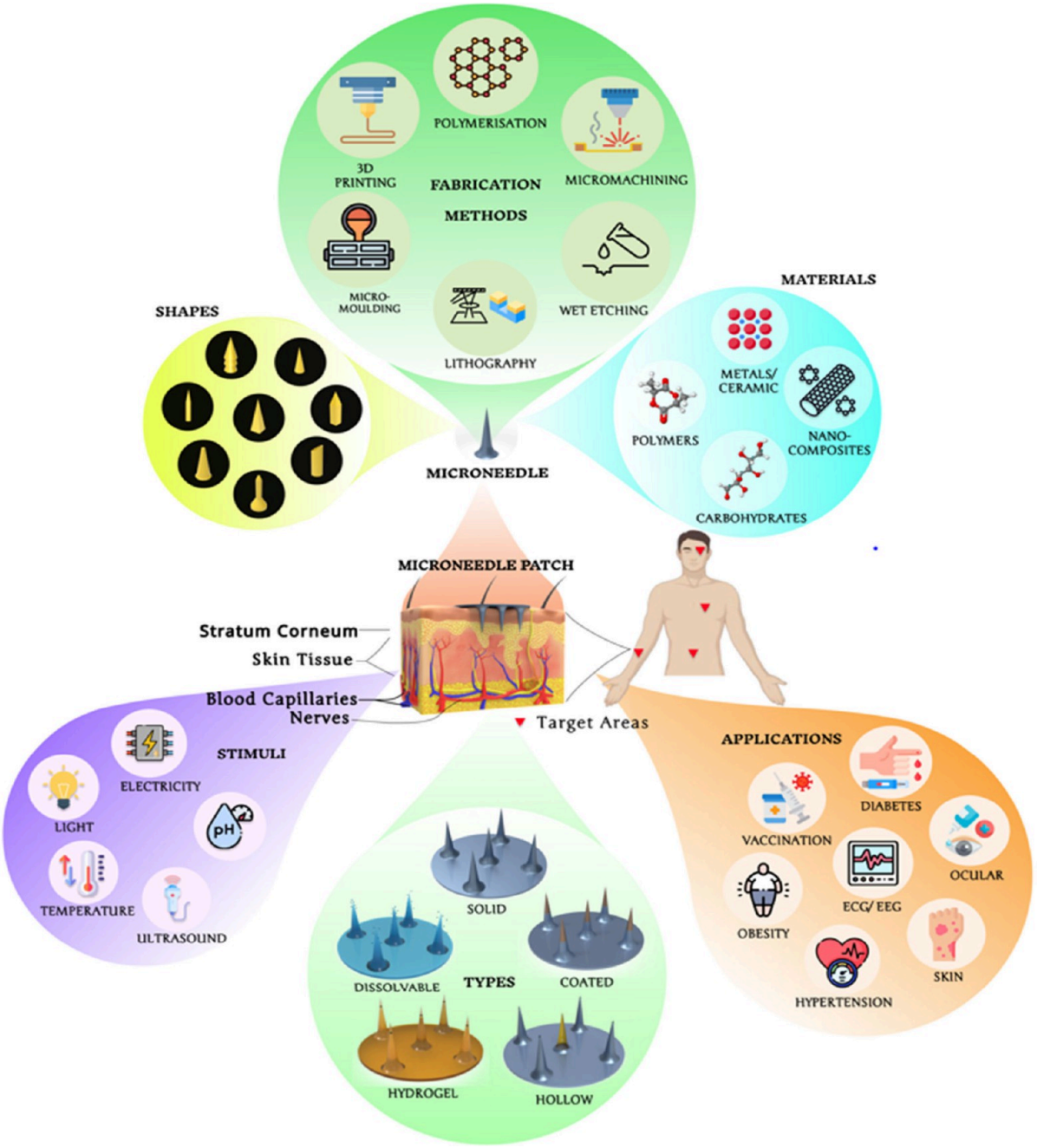

Figure 1. Schematic illustration depicting the numerous types of microneedles, the materials employed in their manufacture, the diverse forms and fabrication techniques utilized, the different stimuli that activate drug delivery as needed, and the wide range of uses for microneedle patches.

Currently, microneedle patches are the focal point of extensive study in the field of biomedical applications as drug-delivery devices (Figure 1).[6] Microneedle patches serve as protective barriers for damaged areas and therapeutic tools for treating injured organs or tissues. Additionally, they can function as monitoring devices that gather physiological information. There are two types of patches: active and passive patches. Active patches enable the controlled release of active substances into the body, while passive patches lack this ability. Active patches are propelled by external stimuli such as ultrasound, electromagnetic radiation, and other similar signals, which enable the deliberate and regulated discharge of payloads.[7]

This review will provide an overview of the fundamentals of microneedle technology, including diverse stimuli-responsive microneedles, choosing materials for microneedles, designing microneedles, and the numerous manufacturing processes involved. The biomedical application, which deals with integrating electronics with microneedle technology, is then highlighted. Lastly, the current state of clinical trials is examined in light of upcoming difficulties and possibilities.

2. TYPES OF MICRONEEDLES

Microneedle-based systems/patches have garnered significant interest for their minimally invasive approach and painless characteristics. Microneedles (MNs) are extremely small needles, typically ranging from 150 to 1500 μm in length

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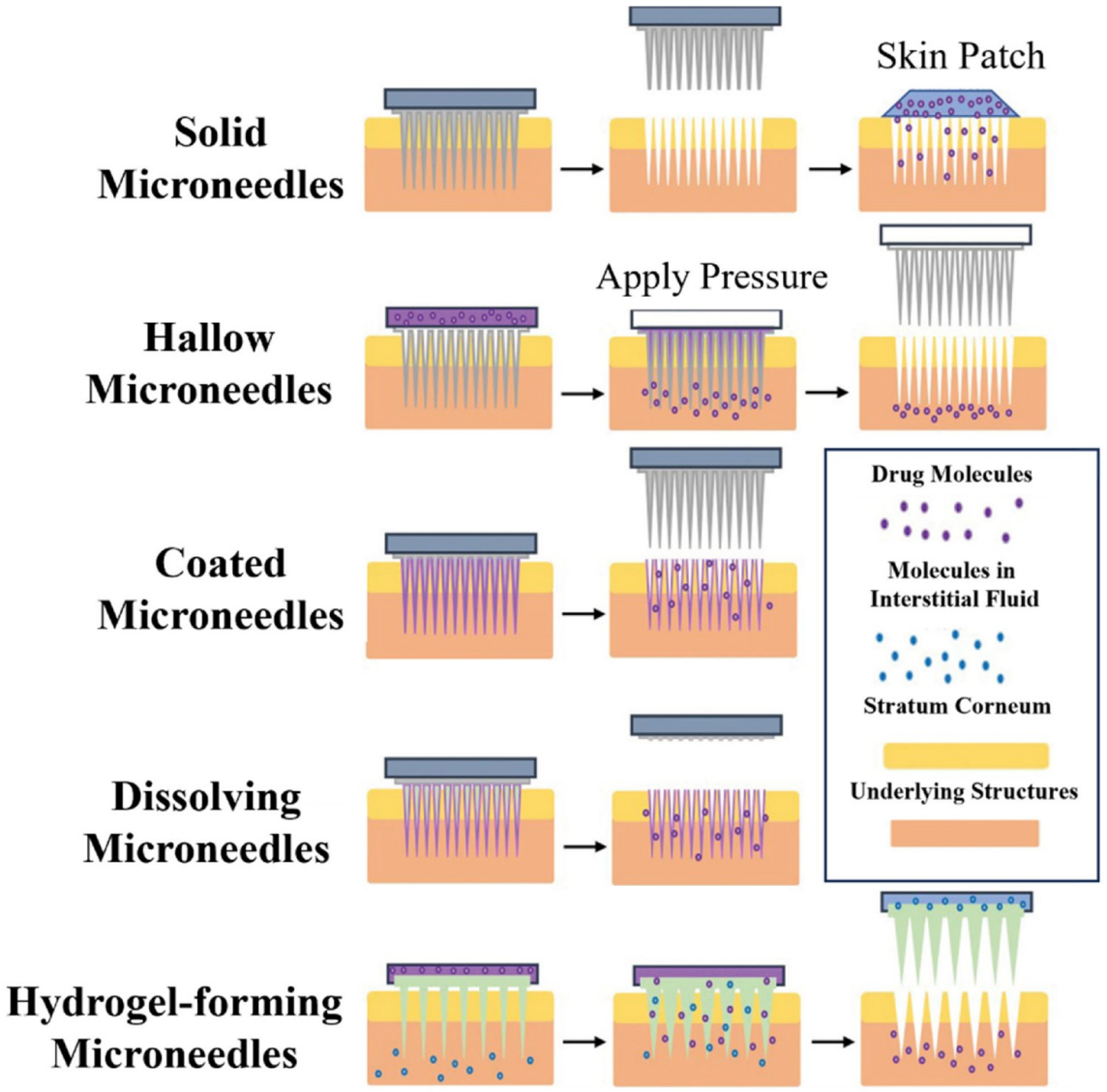

Figure 2. Different types of microneedles and their mode of action during drug delivery and ISF extraction. Adopted with permission under a Creative Commons CC BY-4.0 license from ref 14. Copyright 2020 The Authors.

and 50−250 μm in diameter. They are designed to pierce the outer layer of the skin, known as the stratum corneum, to deliver bioactive agents without contacting the blood vessels or neurons.[2] Various types of microneedles are used, including solid, hollow, coated, and dissolvable variants (Figure 2). Solid microneedles consist of metals like stainless steel, nickel, palladium, and titanium because of their favorable mechanical characteristics.[8,9] The purpose of solid microneedles is to pierce the skin to increase the delivery of drugs to the dermis, thereby improving their bioavailability and kinetic transport. The microneedles possess outstanding mechanical properties and include sharp tips, which enhance their ability to penetrate the skin. Additionally, they are easy to manufacture. Porcine skin was treated for hypokalaemia using microneedle rollers to give potassium chloride (KCl) through a specific microchannel pathway. The microneedle rollers exhibited a higher transdermal flow of KCl compared to passive diffusion.[10,11]

Coating the target substance onto the surface of solid microneedles produces coated microneedles. Typically, water-soluble compounds are selected for administration using coated microneedles. Upon insertion, the coated microneedles come into contact with the interstitial fluid, and the coating dissolves, releasing the desired substance. Coated microneedles facilitate the delivery of active molecules such as peptides, viruses, virus-like compounds, polymer particles, and DNA. Hollow microneedles facilitate the delivery of sizable macromolecules and substantial medication doses. Hollow microneedles are capable of regulating the delivery of macromolecules, such as proteins, mRNA, and vaccines, by controlling the flow of materials and dosage. Designing a hollow microneedle is a complex endeavor due to the potential for material leakage and structural disruption.[12]

Biocompatible and biodegradable materials, such as polysaccharides (Chitosan, gelatin, pectin) and polymers such as Poly(vinyl alcohol) (PVA), Polyvinylpyrrolidone (PVP), Poly l-Lactic Acid (PLLA), Poly(lactic-*co*-glycolic acid) (PLGA), are used to fabricate dissolvable microneedles which possess the benefits of the minimal danger of cross-contamination, simple preparation, and minimal generation of waste residues in comparison to other varieties of micro-

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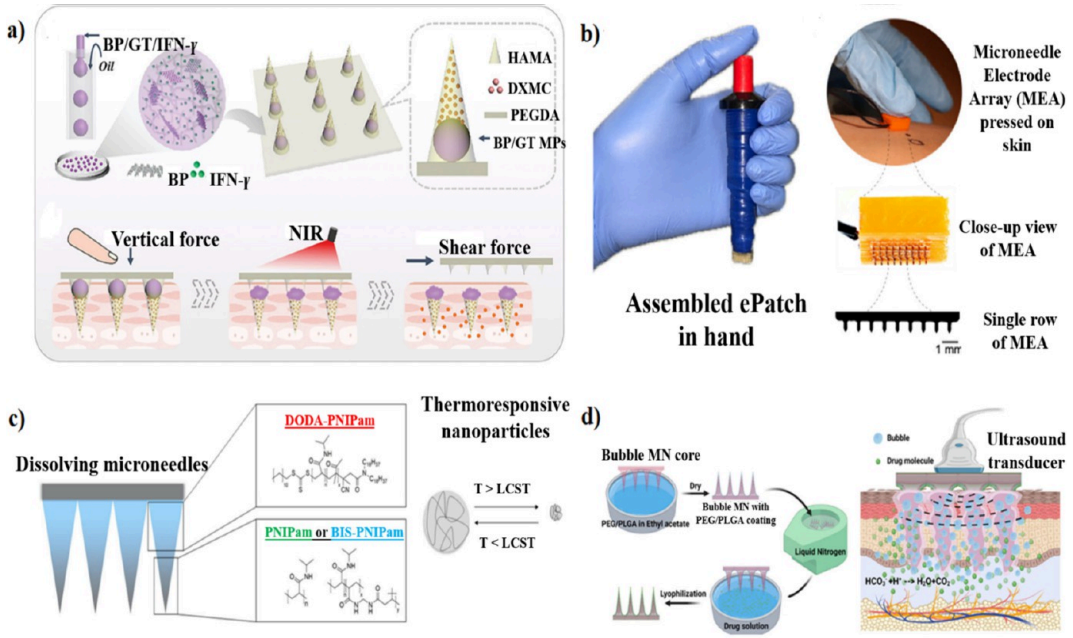

Figure 3. (a) Schematic of BP/GT MPs and MPs-MN patch. Adopted with permission from ref 30. Copyright 2021 Wiley. (b) Assembled ePatch applied on human subjects. Adopted with permission under Creative Commons CC BY-4.0 license from ref 42. Copyright 2024 The Authors. (c) Dissolving microneedles composed of thermoresponsive material. Adopted with permission under a Creative Commons CC-BY-4.0 license from ref 50. Copyright 2024 The Authors. (d) Schematic illustration of drug-coated bubble generating MNs. Adopted with permission from ref 49. Copyright 2021 The Author(s).

needles. It aids in overcoming the challenges of blockage and limited mechanical durability while expanding its range of uses.[8] Eum et al. reported the development of dissolvable microneedle implants that may be easily separated and dissolved. The microneedles made of polycaprolactone were filled with capsaicin to achieve continuous release of the drugs. The drug release rate was investigated using a pig skin model, and it was determined that the entire release happened within 15 days.[13]

Hydrogels are cross-linked hydrophilic polymer networks capable of absorbing water, resulting in swelling and responsiveness to diverse stimuli. Hydrogel microneedles can be utilized in various biomedical applications based on the selected material for hydrogel synthesis. Hydrogel microneedles do not leave residuals within the body, unlike dissolvable microneedles, and they are straightforward to make. The loading and release of cargo is simpler than other microneedle varieties owing to its semisolid composition.[14,15]

3. CLASSIFICATION OF STIMULI-RESPONSIVE MICRONEEDLES

In addition to the aforementioned microneedles, there are stimuli-responsive polymer microneedles that can be activated by external factors to release the desired drug. These MNs are developing technology for the continuous and controlled release of drugs on demand by relying on changes in the body or external stimulation. The MNs are designed to evenly and effectively encapsulate the active bioactive agents, thereby increasing the dose of the drug that can be loaded.

3.1. pH-Responsive MNs

The pH-responsive microneedles are a type of microneedles that react to variations in the pH of the surrounding environment.[16,17] These microneedles are commonly used to treat skin diseases or promote wound healing. The alteration in the skin pH resulting from a bacterial infection, whether it raises or decreases, triggers the liberation of the intended drugs, thus facilitating the healing process.[18,19] Researchers reported using stainless steel microneedles covered with a porous polymer sensitive to changes in pH. These microneedles were used to deliver a model drug, lidocaine. Sodium bicarbonate was included in the PLGA matrix as a pore-inducing substance during the production of microneedles to regulate medication release at an acidic pH of around 5.5. The drug release process was investigated in phosphate-buffered saline, where the polymer covering allowed the diffusion of protons at pH 5.5, releasing the medication through the pores.[20] Jia et al. stated that hydrogel microneedles were developed from silk fibroin and chitosan. These microneedles were designed to release insulin in a regulated manner. The hydrogel microneedles exhibited enhanced insulin release at a pH of 3.0, but the release was diminished beyond that point due to the hydrogel's swelling impact. Under acidic conditions with a pH of 3.0, hydrogen ions from the surrounding solution permeate into the polymer matrix, enlarging the pores for insulin release. Conversely, the microneedles began to expand when the pH was raised, causing the pores to close.[21] Maaden et al. showed the use of microneedles coated with antigens that can induce an immune response when activated by changes in pH. The drug ovalbumin was utilized as a representative model to investigate the pH-dependent release of the drug in human skin samples taken from outside the body, and these results were compared with findings from studies conducted on living organisms. The administration of the medication through antigen-coated microneedles resulted in an improved immune response by stimulating the release of CD4+ and CD8+ T-cells. The drug release efficacy of pH-responsive, antigen-coated microneedles surpassed that of the standard drug delivery approach.[22] Further, in another study, Huang et al. reported the development of microneedles made from a

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modified form of hyaluronic acid called HA-ADH@PpIX conjugate. These microneedles had a reservoir of iron (PA-Fe3+) at the tip. The microneedles are composed of acylhydrazone linkages, which, when exposed to an acidic pH environment, dissolve and release the therapeutic payload to eradicate cutaneous melanoma tumor cells.[23]

3.2. Photoresponsive MNs

Microneedles triggered by ultraviolet,[24] NIR (Near Infrared),[25] and visible light,[26] have been fabricated for cancer therapy. Microneedles consist of light-responsive components, such as light-responsive polymers, nanomaterials covered with photosensitive compounds, and certain low-melting point materials.[27,28] Liu et al. reported a study on dissolvable microneedles activated by Near-infrared (NIR) light for treating diabetes. The microneedles were filled with the drug Metformin and Bi (Bismuth) nanodots and covered with a thermally responsive lauric acid (LA) coating. Upon laser illumination, the microneedles demonstrated regulated drug release in an on−off manner.[29] Further, a microneedle patch that can be separated under controlled conditions when exposed to near-infrared (NIR) irradiation was developed to treat systemic lupus erythematosus (SLE). The microneedle patch composed of gelatin (GT) and black-phosphorus (BP) microspheres (MPs) was inserted into a methacrylate hyaluronic acid (HAMA) microneedle array (Figure 3a). The microneedle array patch was exposed to 808 nm light, causing the MNs to undergo a phase transition and transform into a liquid state, separating them from the patch.[30] Wang et al. reported the use of a self-powered microneedle patch for chemo-photothermal therapy in the treatment of skin cancer. The drug doxorubicin (DOX) and a photothermal agent, indocyanine green (ICG), were encapsulated within PATC polymer microparticles. Exposing the D/I@PATC polymer particles in the patch to light with a wavelength of 808 nm resulted in the absorption of energy by ICG, leading to the release of the drug doxorubicin. Upon cessation of exposure, the polymer microneedle patch begins a cooling process and reaggregates.[31]

3.3. Thermal Responsive MNs

Temperature-responsive microneedles release the target medication at the intended location in response to internal or external stimuli.[32,33] External temperature-sensing microneedles consist of low melting point materials, which release the active substance upon activation. Internal stimuli-responsive microneedles consist of thermoresponsive polymers that react to elevated phase-transition temperatures (Figure 3c).[34,35] Wu et al. published a study on a microneedle patch that responds to changes in temperature, specifically designed for treating diabetic foot ulcers. The bilayer microneedle patch comprised a layer of sodium alginate-*g*-poly(*N*-isopropylacrylamide) [SA-*g*-PNIPAM] containing sucrose octasulfate sodium salt, hyaluronic acid, and a layer of PCL/CS (polycaprolactone/chitosan) loaded with tetracycline hydrochloride and sucrose octasulfate sodium salt. PNIPAM is a thermoresponsive material with a crucial phase transition temperature of around 32 °C. The microneedle patch demonstrated precise and regulated release of tetracycline hydrochloride at 37 °C. The drug release rate efficiency was 20% higher at 37 °C than 24 °C.[36] A hydrogel microneedle patch made of gelatin and poly(*N*-isopropylacrylamide) [PNIPAm] was developed to administer insulin. The patch was affixed onto solid microneedles made of polylactic acid (PLA) and poly(vinyl alcohol) (PVA) to enhance the mechanical durability of the GP patch. The drug release parameters were evaluated using the model drug rhodamine-B. The regulated release of the drug was obtained due to the thermally driven reversible coiling characteristic of PNIPAm in the microneedle.[37]

3.4. Electroresponsive MNs

Electrotherapy is a significant method for administering drugs that rely on electricity. Both iontophoresis and electroporation techniques are employed to augment the transdermal delivery of medicine.[38] Extensive research has been conducted on the use of electrical stimulation as a means of drug delivery.[39] Several methods aid drug transportation, including piezoelectric effects, iontophoresis, electroporation, and triboelectric events. Y. Yang et al. described a piezoelectric nanogenerator (PENG) based transdermal medication delivery system that was self-powered and controlled. This system is designed to treat psoriasis-like skin conditions. The microneedles were coated with polypyrrole, a highly sensitive polymer capable of loading and releasing drugs through electrical stimulation. The microneedles administer medications upon receiving electrical stimulation from PENG.[40] Zhang et al. presented a novel wearable, self-sustaining microneedle (SepMN) system designed to treat infected wounds. This system combines antibacterial therapy with electrically induced tissue regeneration. The device utilizes conductive drugs derived from the synthesis of levofloxacin and carbon quantum dots, which offer antibacterial effectiveness and electrical conductivity. This microneedle patch was designed to administer antibiotics to the wound by providing electrical stimulation. Efficient energy harvesting from body movements was achieved by separating the triboelectric nanogenerator (TENG) from the microneedle patch. The system significantly enhanced cell migration, proliferation, and collagen deposition, reduced inflammation, and expedited wound healing in both *in vitro* and *in vivo* tests. These treatments achieved superior results by utilizing either electrical stimulation or drugs alone. This novel approach presents a new concept for the production of wearable wound healing devices that have the potential to be manufactured at a low cost.[41] Lu et al. included electroporation, a technique that used electric pulses to temporarily produce gaps in cell membranes, into the ePatch system. This integration aimed to improve the immunogenicity of drugs and vaccines by facilitating the intracellular transport of materials such as DNA and RNA. Conventional electroporators encounter difficulties due to their exorbitant price, large dimensions, intricate design, and the discomfort caused by nerve stimulation. The ePatch resolves these concerns by integrating a piezoelectric pulse, capable of producing high-voltage pulses without needing a power source, with a microneedle electrode array (MEA) (Figure 3b). The microneedles of the MEA specifically target the outer layers of the skin, concentrating the electric field on the epidermis and superficial dermis. This ensured that deeper nerves were not affected, resulting in pain reduction. This design enables the direct transfer of genetic information to antigen-presenting cells (APCs) in the epidermis, improving the effectiveness of vaccines while bypassing the complications associated with viral vectors and lipid nanoparticles (LNPs).[42] Bok et al. conducted a study where they developed and produced a portable ion power supply for delivering drugs to the skin. The study aimed to compare the effects of the microneedle therapy system (MTS) method and iontophoresis on drug delivery. Iontophoresis, a

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Table 1. Materials Used in the Manufacturing of Different Microneedles

sl no.	material	target drug/vaccine	type of microneedle	disease	ref
1	Polylactic acid	Insulin	Hollow	Diabetes	70
2	Hyaluronic acid	Methotrexate	Dissolvable	Psoriasis	71
3	Light-sensitive resin (BIO) with PZT transducer	Sodium fluorescein (model drug)	Hollow		72
4	PVP	tetracycline		Postoperative wound infection	73
5	PVA	Bevacizumab	Dissolvable and Hydrogel	Cancer	74
6	Modified Silk fibroin	Insulin	Dissolvable	Diabetes	75
7	Metallic glass	Fluoroscent sulforhodamine	Coated Solid Hollow	Model drug delivery	76
8	Poly(ethylene glycol) diacrylate [PEGDA]	Glucose and Lactic acid bisensor		Glucose and Lactic acid monitoring Biosensor	77
9	Polylactic acid	Insulin	Solid	Diabetes	78
10	CMC-Trehalose	Human growth hormone (hGH)	Dissolvable		79
11	Methoxyethylene-maleic Anhydride Copolymer	Amphotericin-B		Antifungal	80
12	Hyaluronate-PLGA NPs	Antigen ovalbumin-TLR3 ligand poly(I:C) adjuvant	Dissolvable	Humoral and Cellular immune response	81
13	Hyaluronic acid-collagen tripeptide (HA-CTP)	CRISPR-Cas9	Dissolvable	Inflammatory skin disorder (ISD)	82
14	Hyaluronic acid, PVP and PLGA	lysozyme	Dissolvable	Dermal disease	83
15	PCL, SHA, PVP and PVA	Artemether Lumefantrine	Dissolvable	Malaria	84
16	γ-PGA-PCL	γ-PGA	Dissolvable	Atopic dermatitis-like skin lesions	85
17	PVA/PVP	Doxorubicin	Dissolvable	Skin tumor	86
18	PVA/PCL	metformin	Dissolvable	Diabetes	87

technique that improves the permeation of drugs through the skin by applying an electric current, was employed to address the challenges faced by conventional facial masks in delivering drugs effectively, which is hindered by barrier lipids. Iontophoresis utilizes the formation of tiny openings and the application of an electric field to generate ionic repulsion, which aids in the transdermal administration of drugs. The analysis of drug absorption was conducted using fluorescence images and rhodamine B, revealing enhanced skin penetration of ionic drugs through the electric facial mask system that was designed. The effectiveness of the system was assessed in terms of skin moisture levels and the range of absorption. This evaluation was supplemented by electrical field simulations, which helped determine how water is absorbed through the flow of current and the distribution of potential differences in the skin. A portable electric facial mask prototype with a power supply supported by the ear was developed, demonstrating improved effectiveness in delivering drugs using iontophoresis.[43]

3.5. Ultrasound-Responsive MNs

Ultrasound stimulation of microneedles can initiate and accelerate drug delivery through the skin. Sonophoresis, a technique that utilizes ultrasound to exert mechanical force, is a painless process that operates regardless of the electrical properties of the medicine being used.[44,45] The ultrasonic-responsive patch comprises elements that specifically react to either low-frequency (<100 kHz) or high-frequency ultrasound (>100 kHz and MHz range). A study revealed the use of a microneedle made from sodium hyaluronate to deliver ultrasound-responsive nanoparticles for addressing skin problems. The soluble microneedles administer zinc porphyrin-based metal−organic framework and zinc oxide (ZnTCPP@ZnO) nanoparticles. The nanoparticles generate reactive oxygen species, which result in the eradication of bacteria. The successful loading of ZnTCPP@ZnO nanoparticles into the microneedles is demonstrated by the darkening of the microneedles in the fluorescence images. In this case, the microneedles are capable of dissolving, and the behavior of the needles is not directly affected by ultrasound stimulation.[46] M. Bok et al. developed a multifunctional hyaluronic acid microneedle system that utilizes ultrasonication and iontophoresis to rapidly distribute hyaluronic acid and rhodamine B locally. The drug release was facilitated by utilizing ultrasound results, while the AC iontophoresis technique enhanced the permeation of ionized substances into the skin. The efficiency of the microneedles was enhanced through the utilization of a combination of ultrasound and iontophoresis.[47] The sonophoretic enhanced microneedle array utilizes hollow microneedles and low-frequency ultrasound (∼20 kHz) to facilitate the deeper penetration of big molecular substances into the dermis. B. Chen et al. conducted a study on the transportation of calcein and Bovine serum albumin in pig skin and observed enhancements in drug delivery. The hollow needles utilized had a height of 100 μm and a base diameter of 80 μm, produced on a silicon substrate. The favorable effects of ultrasound on medication delivery acceleration were attributed to the thermal and acoustic cavitation phenomena.[48] Microneedles that generate bubbles are used to create microbubbles in the fluid between the skin cells, either by using electrolysis or chemical processes to enable the loading of hydrophobic and hydrophilic drugs (Figure 3d). Ultrasound enhances the ability of microneedles to penetrate the skin. Ultrasound stimulation can be utilized to initiate drug delivery, activate the drug after it has been delivered, and enhance the depth and speed of drug delivery.[49]

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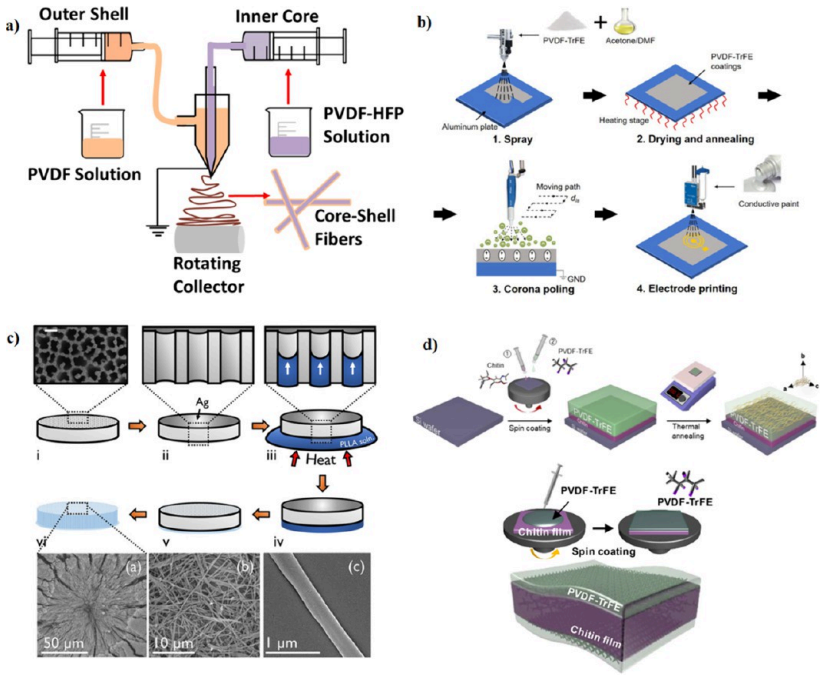

Figure 4. (a) Schematic representation of coaxial electrospinning process. Adopted with permission under Creative Commons CC-BY-4.0 license from ref 92. Copyright 2020 The Author(s). (b) In situ fabrication and processing of PVDF-TrFE by corona poling. Adopted with permission under Creative Commons CC-BY-4.0 from ref 93. Copyright 2021 The Authors. (c) Template wetting process for PLLA nanowire formation. Adopted with permission under Creative Commons CC-BY-4.0 from ref 98. Copyright 2017 The Author(s). (d) Epitaxial growth of PVDF-TrFE on chitin. Adopted with permission under a Creative Commons CC-BY-4.0 license from ref 99. Copyright 2020 The Author(s).

4. MATERIAL SELECTION FOR MICRONEEDLES

The materials used to develop the microneedles should possess biocompatibility and biodegradability, depending on the intended use. It should have sufficient mechanical strength to penetrate the skin without causing any adverse effects. Different types of materials, ranging from metals to polymers, are utilized to fabricate microneedles (Table 1). Among several types of materials, the primary ones include inorganic materials, polymers, and metals.[51]

There is a strong emphasis on polymeric microneedles in biomedical research because of their advantageous characteristics, including large drug-loading capacities, low-cost manufacturing, and exceptional biocompatibility. Researchers have shown increased interest in drug-delivery systems based on piezoelectric polymers and nanomaterials to target drug delivery. These materials can convert mechanical energy into electrical energy and vice versa. Piezoelectric materials are utilized for the precise administration of drugs to specific organs or cells, which will be further discussed in this review.[52,53]

4.1. Inorganic Materials

Inorganic materials include glass, silicon, and ceramic, which are used for fabricating solid microneedles. Due to its versatility in achieving various forms and sizes, silicon is the preferred material for fabricating microneedles. The initial documented microneedle was composed of silicon. The material's limited biocompatibility hinders its extensive use in biomedicine.[54] Because glass is brittle, it is not commonly used for microneedles. Ceramic materials such as alumina, zirconia, and calcium sulfate-based ones are commonly employed in producing microneedles. Biodegradable bioceramic materials are utilized to manufacture microneedles due to their exceptional mechanical durability and precise drug-release characteristics.[55] Microneedles are produced utilizing ceramic materials through the micromolding technique. Alumina, with the chemical formula Al_2O_3, is the primary ceramic substance that has been extensively researched for the production of microneedles. Alumina exhibits excellent chemical resistance and porosity, making it suitable for applications involving controlled-release formulations. Calcium sulfate dihydrate and calcium phosphate dihydrate are utilized as materials for microneedles because of their exceptional mechanical qualities and drug-loading capacities. Ormocer, a composite material consisting of organic and inorganic components, is also utilized in the manufacturing of microneedles. The hybrid material can adjust its qualities by altering the concentration of its constituents and the synthetic methods employed.[54,56]

4.2. Polymer Materials

Polymers are the favored materials for making microneedles because they are inexpensive, can expand and dissolve, are compatible with living organisms, and may be broken down naturally. They are extensively utilized in the fabrication of dissolvable and hydrogel-based microneedles. Additional microneedles, including solid, hollow, and coated variations, have also been reported using polymer materials. Polymers such as poly L-lactic acid (PLLA),[57,58] poly lactic-*co*-glycolic acid (PLGA),[59,60] poly(methyl methacrylate) (PMMA),[61] polyvinyl pyrrolidine (PVP),[62] poly(vinyl alcohol) (PVA),[63,64] polycaprolactone (PCL),[65,66] carboxymethyl cellulose (CMC),[67] polyethylene glycol (PEG)[68] have been identified as the most frequently used polymers for fabricating microneedles. Certain polymers exhibit low rigidity and the ability to withstand the insertion of microneedles securely. Therefore, materials with superior mechanical strength are integrated to address this issue.[55,51]

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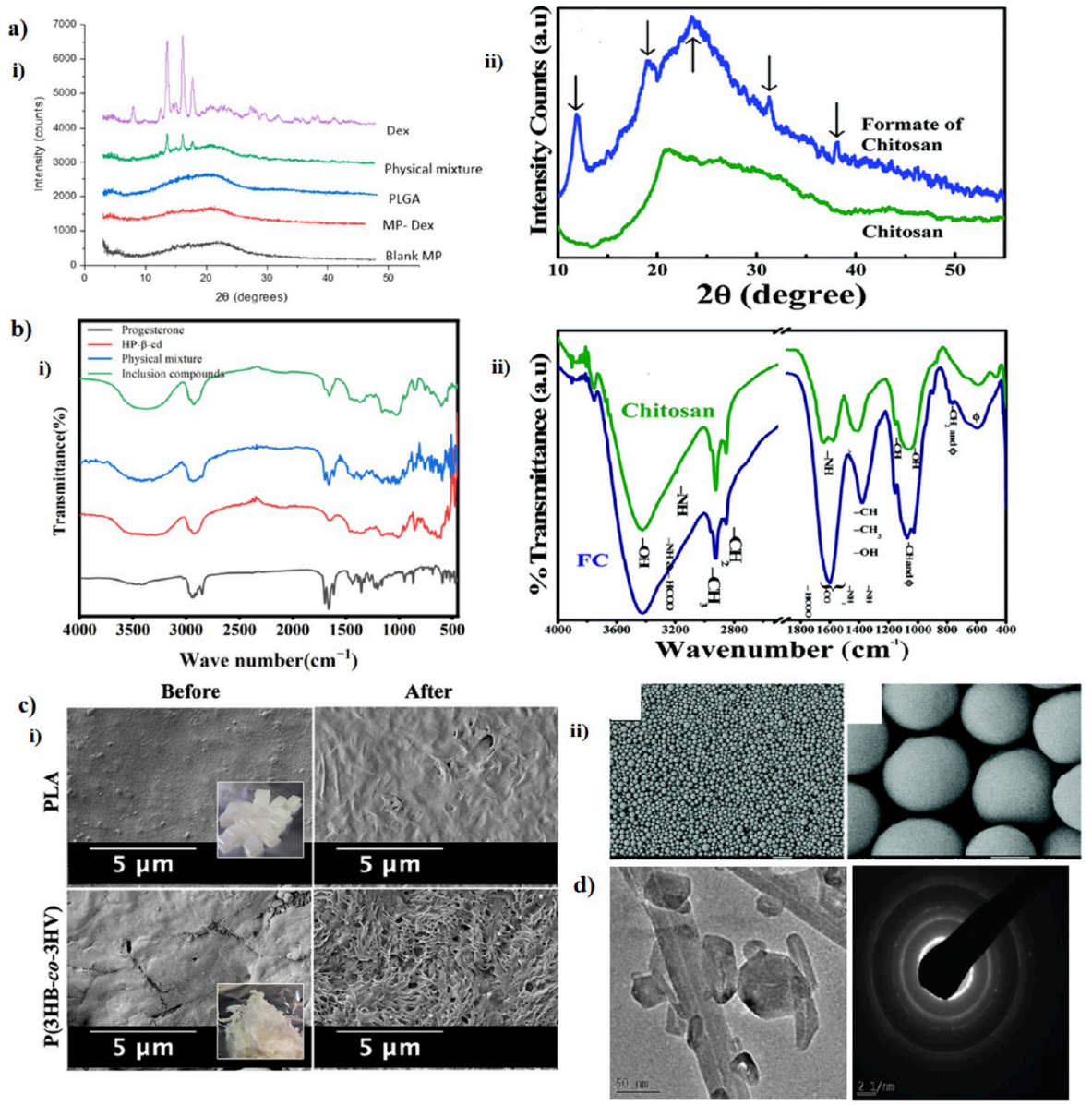

Figure 5. (a) XRD patterns: (i) dexamethasone-loaded microparticles encapsulated in dissolving MN array. Adopted with permission under a Creative Commons CC-BY-4.0 license from ref 110. Copyright 2023 The Authors(s). (ii) Chitosan and chitosan formate. Adopted with permission under a Creative Commons attribution 3.0 unported license from ref 104. Copyright 2017 Royal Society of Chemistry. (b) FTIR spectra: (i) MNs containing inclusion complexes loaded with progesterone. Adopted with permission under a Creative Commons CC-BY-4.0 license from ref 111. Copyright 2023 The Author(s). (ii) Chitosan and chitosan formate. Adopted with permission under a Creative Commons attribution 3.0 unported license from ref 104. Copyright 2017 Royal Society of Chemistry. (c) SEM images: (i) PLA and P(3HB-*co*-3HV) polymer surface morphology before and after melting/cooling. Adopted with permission from ref 112. Copyright 2020 American Chemical Society. (ii) DS@PEG−PLGA microcapsules. Adopted with permission from ref 108. Copyright 2019 Royal Society of Chemistry. (d) (i) TEM images and (ii) diffraction pattern of MWCNTs dispersed in ethanol after a sonication time of 4 h. Adopted with permission under a Creative Commons CC-BY-4.0 license from ref 109. Copyright 2018 The Authors.

4.3. Metallic Materials

Metallic materials, including palladium, titanium, stainless steel, nickel, and alloys, have long been utilized to fabricate microneedles. Metals exhibit excellent biocompatibility and possess great mechanical qualities, including exceptional fracture resistance. The initial metallic microneedle reported was made of stainless steel and had Young's modulus of 180 GPa. In addition to stainless steel, titanium microneedles have been developed and employed as transdermal drug delivery systems. Certain metal microneedles have been found to elicit inflammatory reactions, and the production of these materials is likewise an intricate procedure.[53]

4.4. Carbohydrates

Microneedles are produced using carbohydrates because they have excellent biocompatibility and biodegradability. The varied structure and numerous inherent characteristics of these materials impact the mechanical robustness and penetrability of microneedles. Hyaluronic acid, cellulose, methylcellulose, sugars, and other polymers are combined or utilized individually to produce microneedles. Sugars such as

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maltose, trehalose, mannitol, and sucrose are employed to produce microneedles to administer biomolecules.[69]

Piezoelectric polymers have numerous advantages over their inorganic equivalents, such as flexibility, cost-effectiveness, lightweightness, low dielectric constant, and ease of processing. Their level of optical transparency and efficiency in electromechanical coupling can be altered by adjusting the processing parameters. Several polymer families exhibit piezoelectric activity, including polyamides, polyureas, fluoropolymers, polysaccharides, polyesters, and polypeptides. Among biopolymers, collagen, silk, and cellulose also exhibit piezoelectric characteristics.[88]

Piezopolymers can be classified into three categories: bulk polymers, piezocomposites, and cellular polymer films. Piezoelectricity in bulk polymers is attributed to the intrinsic molecular dipoles inside their structure. Piezocomposites consist of inorganic elements enclosed within a polymeric matrix. These materials benefit from combining the superior piezoelectric capability of inorganic materials with the mechanical flexibility of polymers. Cellular polymer films have the advantage of exhibiting polymers with superior piezoelectric properties and reduced thickness.[89] Three interrelated operations that significantly impact the properties of piezoelectric polymers during processing are annealing, drawing, and poling.

Annealing is a heat treatment process used to enhance the crystallinity of polymers. In a study, PVDF composite was processed by thermal annealing in hot water. The β-phase content was enhanced by thermal treatment, leading to increased piezoelectricity, and also faster removal of ionic liquid was observed with reduced porosity.[90] Men et al. studied the effect of annealing temperature on the physical and mechanical properties of PVDF microporous membranes. The annealing temperature of 145 °C for 6 h showed enhanced crystallinity with lamellae separation and formation of micropores during stretching.[91] The effect of different parameters such as annealing and poling is widely studied using PVP, PVDF, and its copolymers (Figure 4a and b).[92,93] The effect of processing parameters on the carbon fiber-reinforced polylactic acid was reported by Arjun et al. Improvement in the tensile strength of composite fiber treated at 95 °C for 120 min was observed.[94] The synthesis of PLGA−PEG [poly(lactide-*co*-glycolide)-poly(ethylene glycol)] induced by swelling during the recrystallization annealing process was reported by J. Dai et al. The increased crystallinity of the prepared PLGA−PEG was confirmed by XRD analysis of the material before and after the swelling process. The SEM images of the material showed enhanced porosity after swelling.[95] Drawing is a process of stretching polymer material. The drawing can be performed at ambient conditions but is done at higher temperatures, usually near the melting point of the polymer. The lengthening of the polymer generates the alignment of chains along the drawing axis, leading to a large degree of anisotropy. Apart from the orientation of dipoles, the parallel alignment of polymer chains is also an important criterion for exhibiting piezoelectricity in polymers such as PLLA, PHV, collagen, and cellulose.[88] Drawing also induces phase transformation and increases the crystallinity of polymers.[96] Poling is a strategy where the dipoles of a material are aligned in a particular direction. The alignment of dipoles is induced by applying a strong electric field. The most effective ways to improve the piezoelectric response of a material are poling procedures and optimized parameters. Different poling techniques are employed for materials to improve piezoelectric performance.[97]

Further, various strategies are used to enhance the piezoelectric performance of materials. Copolymerization is one technique used to improve the electromechanical character of polymeric materials. Fillers are also a well-known method for improving the piezoelectric response. Fillers such as PZT, $BaTiO_3$, and ZnO are widely used, and this addition of fillers is mainly demonstrated in the case of PVDF.[100] Modification of processing methods also improves the piezo behavior of the material. Drawing in combination with annealing improves the crystallinity of amorphous materials. Using nanostructuring processes such as electrospinning and template wetting also improves the piezoelectric performance of polymers (Figure 3 c and d).[88,101,98,99]

The piezoelectric materials are characterized by various techniques, including electromechanical and structural characterizations. The electromechanical characterization includes Piezoresponse Force Microscopy (PFM), Laser Interferometry, and Piezometry. PFM is based on the contact mode AFM setup, where alternating voltage is applied between the tip and cantilever, which are conductive.[102] There are various material characterization techniques, such as X-ray diffraction (XRD), for analyzing the crystal phases (Figure 5a),[103,104] Fourier Transmission Infrared Spectroscopy (FTIR) (Figure 5b),[104,105] to identify crystal phases of polymers, Differential Scanning Calorimetry (DSC) to determine the thermal behavior,[106] Polarized Optical Microscopy (POM) to observe orientation in polymers, Scanning Electron Microscopy (SEM) (Figure 5c)[37,107,108] and Transmission Electron Microscopy (TEM) (Figure 5d)[109] for surface morphology study of materials are used.

5. DESIGN OF MICRONEEDLE STRUCTURE

When developing microneedles, various parameters must be considered, including needle length, spacing, tip angle, tip diameter, needle shape, and aspect ratio. Multiple research studies have verified that microneedles necessitate a specific length to effectively penetrate the layers of the skin.[113] The penetration depth of microneedles can be varied by adjusting the distance between microneedles. Research studies have shown that increasing the distance between needles aids in an increase in application force, leading to higher penetration.[114,113] During the insertion of microneedles, there is a chance of needle fracture if the diameter of the tip and base of microneedles are not considered. The diameter of the tip of the needle affects the contact area between the needle and the skin. Microneedles with a tip diameter of less than 15 μm aid in controlled skin piercing to a required depth. Howells et al. reported the fabrication of a hollow microneedle array by a wet etch process and investigated the administration of insulin and hyaluronic acid using hollow microneedles. The microneedles with a height greater than 66 μm and a breadth less than 460 μm demonstrated effective skin penetration. Hyaluronic acid was loaded into microneedles measuring 300 μm height, whereas insulin was loaded into needles measuring 600 μm height.[115] In addition, the role of skin penetration is also influenced by the tip angle. An optimal tip angle for successful microneedle insertion without causing any damage is 30° or less.[116,117] The aspect ratio, which is the ratio of the length of the needle to its base diameter, is a significant characteristic that influences the mechanical properties of the microneedles. The microneedles, which have a higher aspect ratio, lead to a

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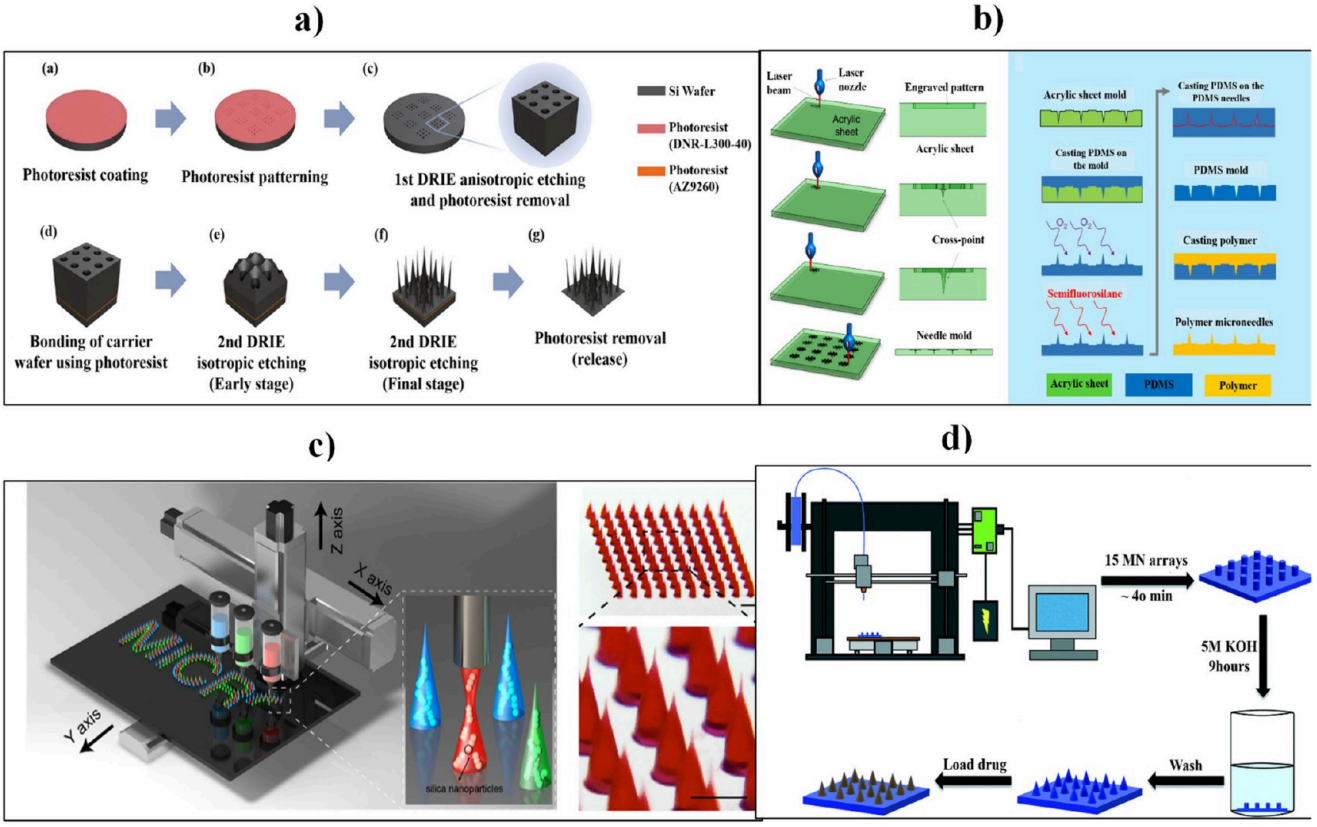

Figure 6. (a) Fabrication of microneedle array by photolithography combined with deep reactive ion etching. Adopted with permission under a Creative Commons CC-BY-4.0 license from ref 142. Copyright 2021 The Author(s). (b) Laser ablation: (i) CO_2 laser cutting for acrylic mold fabrication by crossover lines (COL) technique and (ii) PDMS mold fabrication using acrylic mold. Adopted with permission under a Creative Commons CC-BY-4.0 license from ref 143. Copyright 2018 The Author(s). (c) Microneedles via direct ink drawing. Adopted with permission from ref 144. Copyright 2023 American Chemical Society. (d) 3D-printed microneedles. Adopted with permission from ref 145. Copyright 2018 Royal Society of Chemistry.

reduced application force. Consequently, the needle structure is compromised, resulting in diminished efficacy in drug delivery to the intended location.[118,119] Further, the microneedle's geometry is a crucial factor that impacts its mechanical characteristics, stress distribution, and drug loading.[120] De Martino et al. explored how the shape of microneedles' base affects the ability of drugs to permeate the skin and penetrate it. They investigated the efficacy of skin penetration for four distinct needle shapes: circular, square, triangular, and star-shaped. The star base microneedles exhibited a penetration effectiveness of 60%, surpassing that of other designs. Furthermore, the drug release kinetics were found to be improved when the number of vertices in the shape of the microneedles increased (specifically, star-shaped microneedles).[121]

The geometry of microneedles determines the penetration depth through the dermis layer of the skin.[122,123] Skin insertion studies of polylactic acid microneedles fabricated by the microhot-embossing method were reported by Chang et al. The study demonstrated that tapered cone-shaped microneedles may penetrate the skin efficiently with reduced insertion effort. Increased insertion force was noted for beveled, cone, and pyramid-shaped microneedles that compromised the stratum corneum layer of the epidermis. The insertion force diminished for microneedles with base diameters under 200 μm as the depth of skin increased.[124] Kochhar et al. studied the effect of microneedle geometry and supporting substrate on microneedle array penetration into the excised skin of a rat model. The penetration depth was observed to be affected by the needle-to-needle distance in the array. Microneedle arrays with larger needle-to-needle spacing displayed deeper penetration than arrays with less spacing between the needles.[125] Solid microneedles with varying tip diameters were tested for penetration depth and force. The results indicated that *In vitro* penetration tests on the human abdominal skin showed that microneedles with tip diameters less than 15 μm are essential for proper deep insertion.[126] Studies involving patients demonstrated that microneedle geometry significantly influences patient comfort. Eighteen (18) distinct designs of microneedle patches were developed by altering various geometrical parameters and evaluated on human subjects for the delivery of contraceptive hormones. Of the 18 prototypes, MN-3 and MN-18, including needle lengths of 800 and 1000 μm, were capable of administering the maximum drug dosages of approximately 5 mg and 4 mg, respectively. The drug delivery efficiency reached 87% in MN-3 and 65% in MN-18, with no pain or pain levels comparable to a pinprick. All 18 microneedle patch designs exhibited excellent tolerance, mild to moderate erythema, and no bleeding or adverse effects. The interstitial distance among the microneedles in the patch exhibited no discernible impact on the drug delivery efficiency for 800 μm long needles. The drug dose delivery efficiency was influenced by needle spacing alone in the case of long microneedles measuring 1000 μm or

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more.[127] A comparison study was undertaken to evaluate the intensity of discomfort associated with microneedle and hypodermic needle insertion. The researchers developed microneedles with diverse geometries and discovered that the length and density of the microneedles influence pain severity in human volunteers. The discomfort associated with microneedle insertion was minimal or minor in comparison to that of hypodermic needle insertion.[128]

6. DIFFERENT MANUFACTURING STRATEGIES

Multiple methodologies exist for the production of microneedles using several materials. Microneedles can be fabricated either by using a mold or by direct manufacturing methods to meet the demands of large-scale production.

6.1. Microelectromechanical System (MEMS)

This technique fabricates hollow and solid microneedles and prepares molds for dissolving microneedles (Figure 6a). It involves three processes, namely deposition, patterning, and etching. During the deposition process, a thin layer of material, typically ranging from nanometer to micrometer thickness, is deposited through physical or chemical vapor deposition. During the patterning process, the two-dimensional pattern of the material from the mask is transferred onto the substrate coated with photoresist. Ultimately, the patterned substrate undergoes etching through the utilization of etchants. The undesirable material is eliminated from the surface of the substrate, resulting in the fabrication of the final functional microneedle. There are two recognized types of etching processes: dry and wet etching. Wet etching involves removing undesired material by submerging it in a liquid etchant. The isotropic approach involves the etchant uniformly corroding the material from all directions simultaneously. These etchants corrode various materials, including oxides, nitrides, gold, silicon, aluminum, and others. Anisotropic etchants selectively corrode materials at varying speeds and in different orientations. Anisotropic etchants are employed to process silicon wafers and produce precisely regulated geometries. Dry etching is a process that treats materials using inert or reactive gases at low temperatures.[129,130]

6.2. Micromolding

Micromolding is the predominant method employed for the production of microneedles. The process entails using a negative mold containing hollow spaces for loading material. Subsequently, the material undergoes a cooling and curing process, followed by the removal of the mold. This approach can be used to process materials such as polymers, hydrogels, and ceramics.[131] Various curing and shape-forming techniques are employed depending on the characteristics of the materials. This technique has benefits such as being easily replicated, straightforward, and cost-effective. This technology allows for the step-by-step input of loads and materials into the microneedles and composites. Different mold-filling methods, such as centrifugation, vacuum, infiltration, spin coating, imprinting, atomized spray, etc., are employed to address the challenges associated with filling the mold cavities. Demolding hydrogels poses a challenge due to the potential risk of damaging the microneedles. This approach cannot produce intricate structures, such as hollow structures and structures with barbs. Furthermore, this technology cannot process materials such as metals, glass, and silicone.[132]

6.3. Injection Molding

Injection molding is a cost-effective and often employed technique for the large-scale manufacturing of microneedles. The injection machine introduces a blend of polymer and metal into the cavities of the mold.[133] Injection molding offers exceptional consistency, precise metering, and enhanced injection flow rates. The approach is plagued by the disadvantages of expensive equipment, challenging control over small shot size, and labor-intensive nature.[120] This technique enables the production of microneedles on flexible surfaces by solidifying liquid ingredients on a mold.[134] Yu et al. investigated how different processing parameters impact the filling fraction of a microneedle array made of polylactic acid. The filling fraction of microneedles increased with higher packing pressure.[135]

6.4. Laser Cutting

The manufacture of metal microneedles involves using 3D laser cutting and laser ablation techniques, which are employed with either positive or negative molds. Laser cutting is the process of using an infrared laser and computer-aided design software to create solid microneedle arrays. This technique can successfully attain the intended form, structure, and size of microneedles. This approach is advantageous since it allows for the fabrication of two-dimensional arrays of metallic microneedles as well as a single array of microneedles with different geometries.[136] Anbazhagan et al. fabricated a solid polymer microneedle patch made of PDMS utilizing a CO_2 laser and molding technique. Two-needle geometries, specifically conical and pyramidal shapes, were manufactured using laser cutting techniques. This integrated approach is well-suited for the high-volume manufacturing of microneedles.[137]

Laser ablation involves the formation of solid metal arrays through the use of light pulses that cause a particular shape to protrude on a metal plate. If the laser radiation is sufficiently intense, continuous-wave lasers can also be employed for material bulging.[138] Laser ablation can be applied to any metal to achieve the desired shape. This technique is particularly advantageous for the rapid production of microneedles. Nevertheless, the temperature impact resulting from the radiation can create issues in the composition and mechanical integrity of the manufactured microneedles. Additionally, it can result in the formation of cracks and reduced fatigue resistance in the produced microneedles. This approach could be better for the large-scale manufacturing of microneedles, and the equipment utilized may be more cost-effective.[139,120] An alternative method for fabricating microneedles with a high aspect ratio, without the necessity for a cleanroom, has been reported (Figure 6b). An acrylic mold was used to build the microneedles, while CO_2 laser cutting equipment was employed to produce conical microneedles.[140]

6.5. Drawing Lithography

Lithographic drawing is a method that produces microneedles measuring in millimeters in height. This method employs the glass transition temperature of polymeric materials for producing microneedles (as shown in Figure 6c). The glass transition refers to the dynamic transformation of the amorphous portion of a polymer material from a solid to a liquid state. Through the manipulation of 2D viscous polymer materials, microneedles are formed using drawing techniques to create 3D structures. These microneedles are then exposed to various forces such as gravity, centrifugal force, thermal field, magnetic field, and electric field, which take advantage of the

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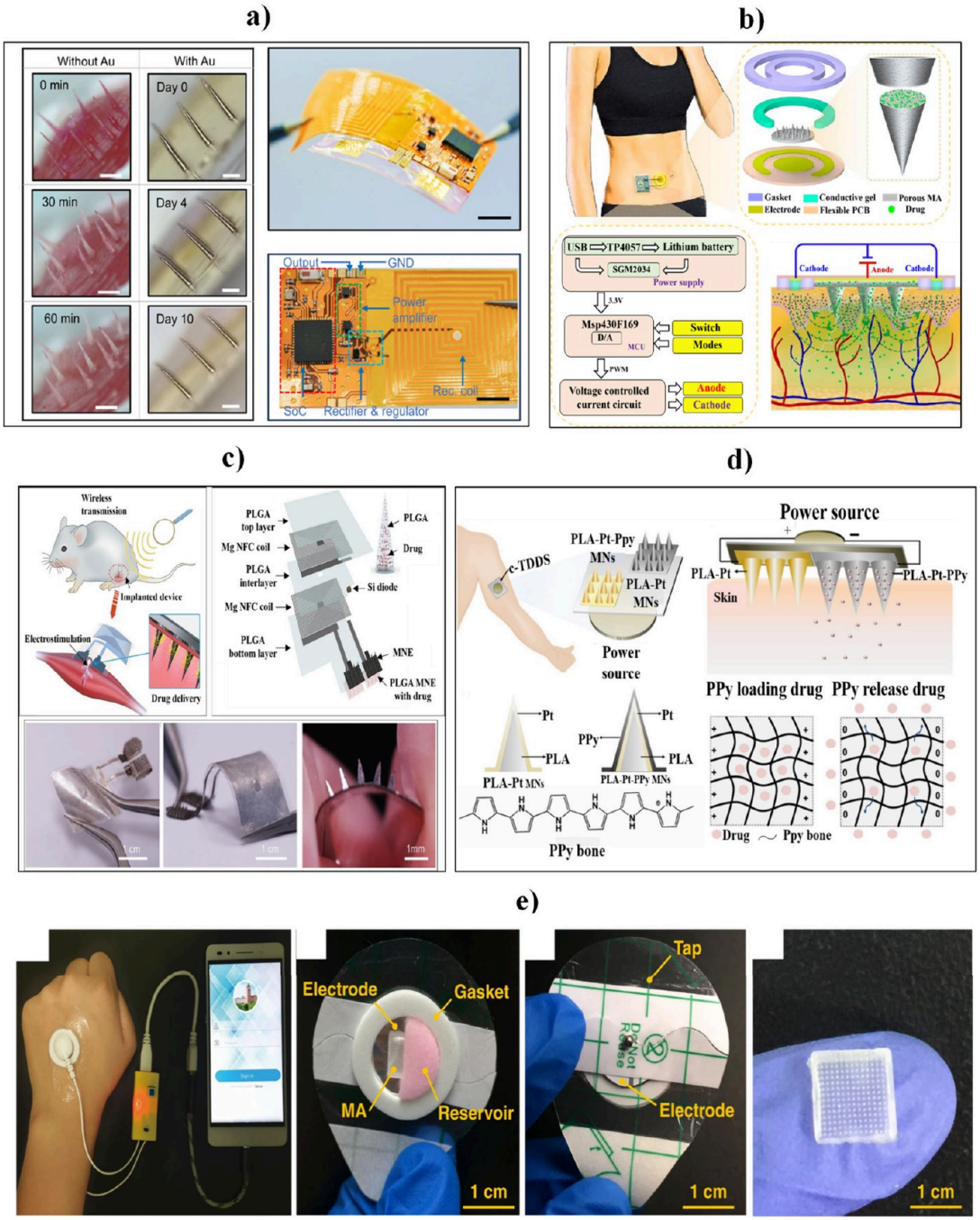

Figure 7. Microneedle-based devices for drug delivery. (a) (i) Optical image of microneedle without and with gold coating after various periods in artificial tissue. Gold needles can be seen to be intact. (ii) Image of the wireless flexible patch. (iii) Top view of the wireless patch with electronics visible. Adopted with permission under a Creative Commons CC-BY-4.0 license from ref 150. Copyright 2024 The Author(s). (b) An iontophoresis-driven microneedle patch for active delivery of charged macromolecular drugs. Adopted with permission from ref 151. Copyright 2020 Acta Materialia Inc. (c) An implantable and bioresorbable microneedle device that provides wireless electrostimulation and sustained drug delivery for tissue regeneration. Adopted with permission from ref 154. Copyright 2022 American Chemical Society. (d) Illustration of conductive microneedle patch using polylactic acid−platinum−polypyrrole (PLA-Pt-PPy) for controlled transdermal drug delivery for atopic dermatitis. Adopted with permission from ref 39. Copyright 2022 American Chemical Society. (e) Images of smartphone-powered microneedle patch that uses iontophoresis to deliver drugs through microholes created by the microneedle patch. Adopted with permission under a Creative Commons CC-BY-4.0 license from ref 155. Copyright 2020 The Authors.

material's properties.[141] The drawing lithography process uses the tensile and elongating capabilities of viscous fluids. The process involves the interaction and elongation of polymer droplets with high viscosity, resulting in the formation of microneedle structures. The produced microneedles will exhibit low mechanical strength and lack the ability to adjust their shape precisely.[133,141]

6.6. 3D Printing-Based Techniques

Using 3D printing techniques, it is possible to develop microneedles with intricate 3D structures (Figure 6d). It

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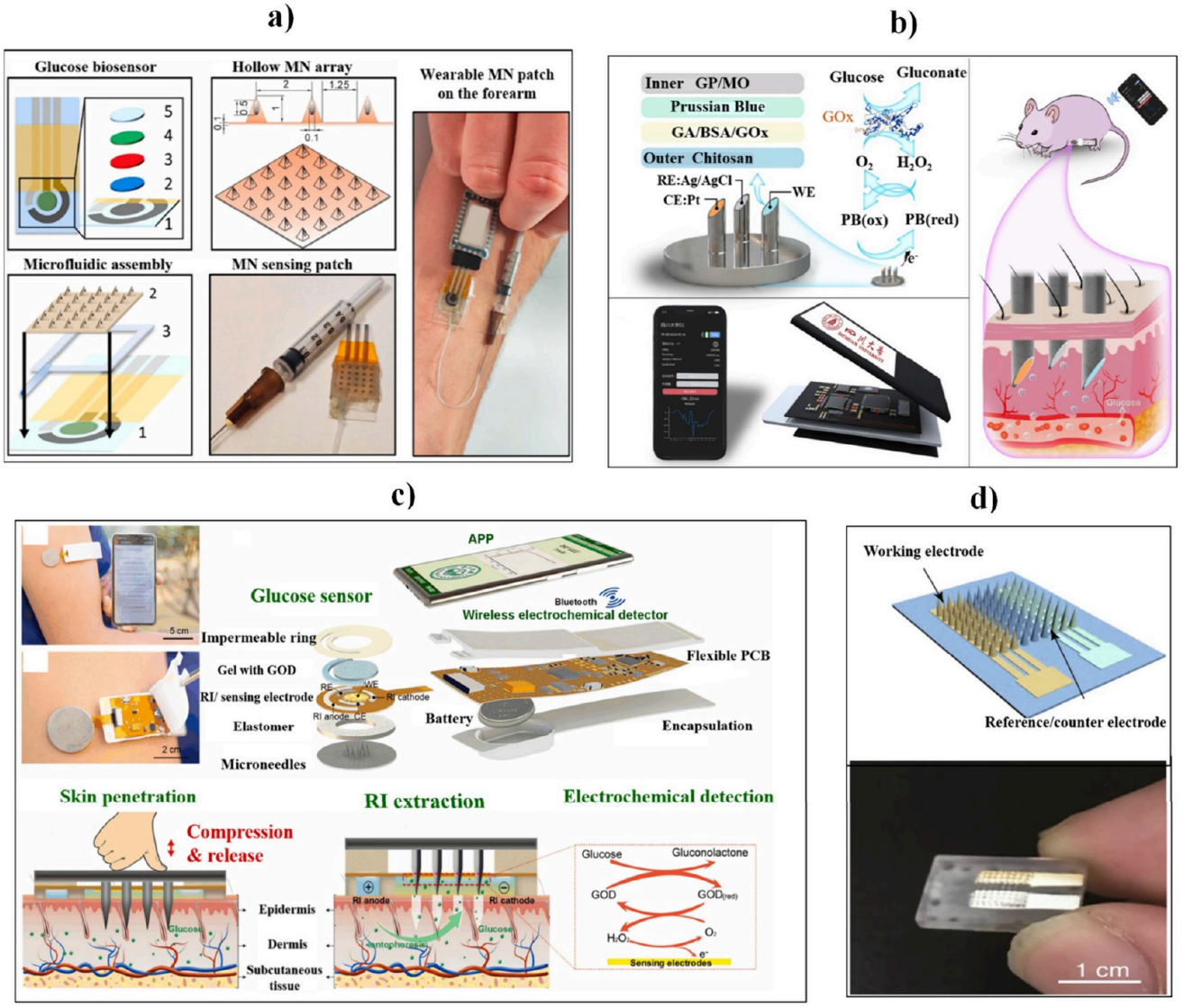

Figure 8. Microneedle based devices for disease diagnosis. (a) Wearable hollow microneedle patch for monitoring glucose in interstitial fluid. Adopted with permission from ref 156. Copyright 2021 Wiley. (b) Three-electrode wearable microneedle continuous glucose monitoring system. Adopted with permission from ref 157. Copyright 2024 Elsevier. (c) Touch-activated microneedle glucose sensor using reverse iontophoresis. Adopted with permission from ref 158. Copyright 2022 Elsevier. (d) 3D printed microneedle device for continuous glucose monitoring: (i) illustration and (ii) camera image. Adopted with permission under a Creative Commons CC-BY-4.0 license from ref 159. Copyright 2021 The Author(s).

encompasses many techniques such as stereolithography (SLA), two-photon polymerization (TPP), liquid crystal display (LCD), projection-based printing (PBP), continuous liquid interface production (CLIP), selected laser sintering (SLS), selected laser melting (SLM), and others. The fabrication of metal microneedles involves the employment of two methods: selected laser sintering and selected laser melting.[133]

Stereolithography is the predominant technique employed for fabricating microneedles, owing to its exceptional precision and high-resolution capabilities, resulting in superior surface quality. The process utilizes a photopolymerization approach, where laser radiation is used to illuminate a liquid photopolymer resin and trigger a polymerization reaction. Subsequently, the microneedles undergo a thorough cleansing in an alcohol solution to eliminate any remaining unreacted resin. They are then exposed to ultraviolet (UV) light for curing, resulting in the production of the ultimate microneedle arrays. Nevertheless, the approach is laborious, expensive, and has a restricted selection of printable materials.[136] Tang et al. investigated the influence of various 3D-printing parameters on the efficacy of the transdermal drug delivery method. The study was conducted to investigate the impact of temperature, extrusion width, nozzle orifice diameter, infill width, and layer thickness on the fabrication of milliprojections using poly(lactic acid). The print's surface smoothness was improved by reducing the nozzle diameter and increasing the spacing between the milliprojections while maintaining the same level of precision.[146] 3D bioprinted microneedles have grabbed the attention of researchers due to their increased permeation, efficacy, and safety.[147] 3D-printed microneedles have been used in regenerative medicine and tissue engineering applications to deliver viable cell cargo. These microneedles

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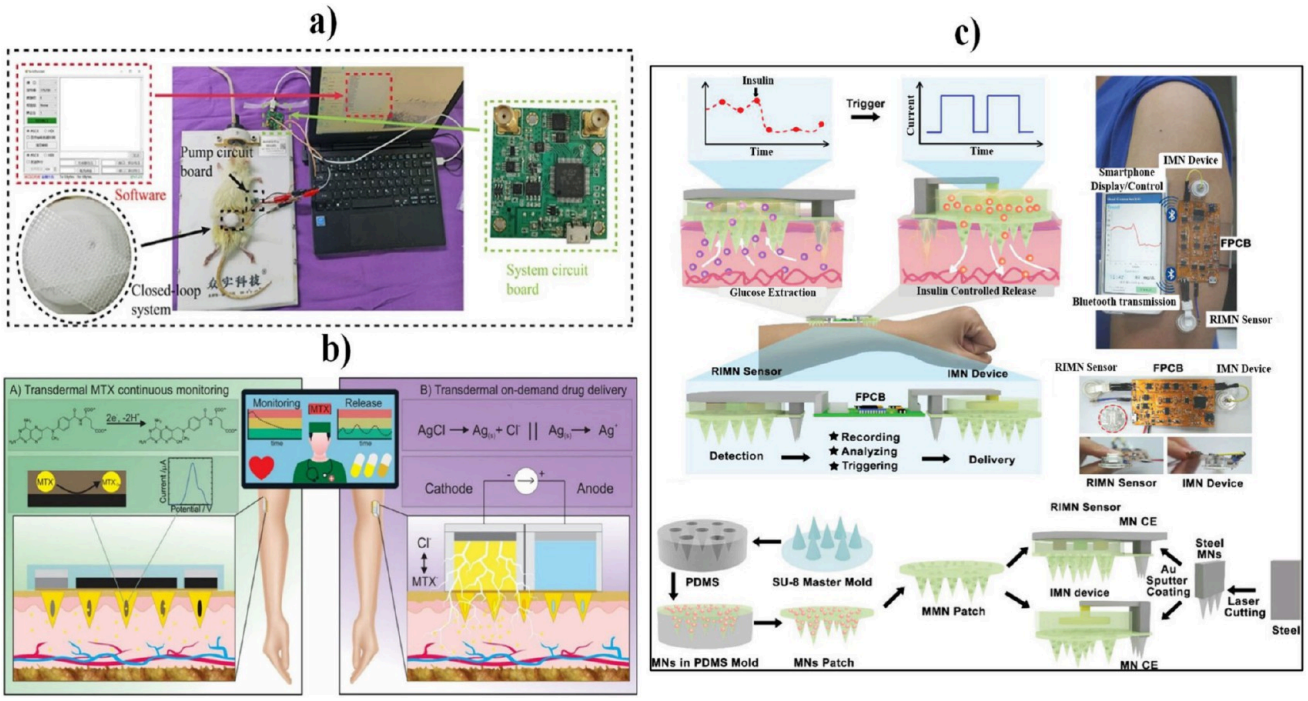

Figure 9. Microneedle-based dual-function devices (both drug delivery and disease monitoring). (a) (j) Closed-loop system that senses glucose and automatically delivers insulin, Adopted with permission from ref 70. Copyright 2023 American Chemical Society. (b) Wearable microneedle patch for continuous electrochemical monitoring and delivery of methotrexate through ISF. Adopted with permission from ref 160. Copyright 2023 American Chemical Society. (c) A fully integrated wearable closed-loop system (IWCS) based on a mini-invasive microneedle platform is developed for in situ diabetic sensing and treatment. Adopted with permission under a Creative Commons CC-BY-4.0 license from ref 161. Copyright 2021 The Authors.

can safeguard the bioactive agent and help in controlled delivery.[148]

7. INTEGRATION OF MICRONEEDLES WITH BIOMEDICAL DEVICES

Microneedles can be integrated into electronic devices to make biomedical devices capable of acquiring various biological information and performing drug delivery (Figure 7, 8, and 9). The different kinds of stimulation that were previously discussed can be used for triggering drug delivery. Light can be used to activate microneedle drug delivery. Wu et al. reported the creation of a microneedle patch filled with biologics to treat Psoriasis, which uses light to activate microneedle drug delivery.[149] The patch utilizes hyaluronic acid−based needles enhanced with MXene additive, known for its high photothermal conversion efficiency. The photothermal conversion is initiated by the exposure to near-infrared light. This results in the quick melting of the needle and subsequent release of the enclosed medicine. Wang et al. reported a microneedle patch filled with drugs. The patch is coated with a biocompatible metallic material, allowing for electrically triggered regulation of drug release. The patch employs a needle coated with a tiny layer of gold, approximately 150 nm in thickness, to enclose and safeguard the medicine. To initiate drug delivery, a low voltage direct current (2.5 V) is supplied to the needle, causing the gold layer to break down and the poly(lactide-*co*-glycolide) (PLGA) microneedle to dissolve, resulting in the release of the medication. The MN patch is affixed to a flexible PCB, enabling wireless energy harvesting and control (Figure 7a).[150] Y. Yang et al. demonstrated polypyrrole as a highly sensitive polymer that can load and release drugs under electrical stimulation. Polypyrrole-coated microneedles that release drugs on electrical stimulation were used for treating psoriasis and atopic dermatitis (Figure 7b).[151,40] Y. Yang et al. described developing a self-powered transcutaneous electrical stimulation system with a microneedle base. This system was designed to enhance the pharmacodynamics of epidermal growth factor.[152] Zhang et al. reported a wearable self-sustaining microneedle system utilizing conductive drugs to heal infected wounds. The researchers integrated triboelectric nanogenerators with drug-loaded microneedles. Electrical stimulation enhances the movement, growth, and accumulation of collagen in cells.[153]

Iontophoresis can be used to deliver some drugs by the action of an electrical field on charged drug molecules (Figure 7c and d).[154,39] A microneedle patch can also function as a biosensor for continuously monitoring certain biomarkers, temperature, pH levels, and other related factors. Microneedles offer a less intrusive route for accessing Interstitial Fluid (ISF). Samant et al. have described creating a minimally invasive technique using microneedles to sample ISF from the skin. The team employed a microneedle patch and gentle suction to collect interstitial fluid (ISF) samples. The acquired samples were compared to corresponding blood plasma samples. It was observed that the nonclotting nature of ISF enables the ongoing monitoring of biomarkers in a minimally intrusive manner.[162] Lee et al. exhibited the electrochemical efficacy of the amalgamation of graphene and a gold mesh, which has potential applications in monitoring diabetes through sweat analysis. The combination of a gold mesh and gold-doped graphene creates a very effective electrochemical contact that facilitates the reliable transmission of electrical impulses. They enhanced a patch by incorporating a graphene electrochemical sensor, supplementary sensors, and polymeric microneedles for

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drug administration. The patch employs thermal activation to facilitate medication delivery.[163] Microneedles have also been used to directly provide electrical stimulation to promote tissue regeneration and healing (Figure 7e).[155]

Y. Wu et al. reported the development of an aptamer-based microneedle array capable of sensing biomarkers that do not undergo redox reactions (Figure 8a).[156] Researchers have demonstrated the capability of microneedles to accurately measure glucose levels in ISF. A hollow or solid microneedle array can be employed to access ISF, from which the glucose levels can be estimated electrochemically (Figure 8b and c).[158−164] Liu et al. presented the ability to continuously monitor interstitial glucose levels by utilizing an integrated microneedle device fabricated by 3D printing. The device accurately measured subcutaneous glucose levels in both normal and diabetic mice. The identified values were also precisely associated with measurements collected from a commercially available blood glucose meter. The device consists of a working electrode coated with gold (Au) and a reference electrode coated with gold (Au) or silver/silver chloride (Ag/AgCl). The microneedles have a height of approximately 0.5 mm, a base diameter of 0.1 mm, and are spaced 0.4 mm apart. The needle is coated with immobilized glucose oxidase, which catalyzes biochemical reactions with glucose to produce H_2O_2. The device utilizes the oxidation or reduction of H_2O_2 to carry out glucose measurement. Experimental results have shown that a voltage range of 0.3 V to 1 V can produce accurate measurement signals (Figure 8d).[159]

Gao et al. designed a versatile array of microneedle electrodes that simultaneously detect glucose, uric acid, and cholesterol. The microneedle electrode array biosensor exhibited exceptional sensing capabilities, encompassing a broad linear range.[165] Luo et al. devised a sophisticated wearable system that uses ultrasound technology to detect glucose levels and administer insulin automatically. The administration of drugs is accomplished by utilizing hollow needles made of PLA (polylactic acid) and a piezoelectric-based ultrasonic pump. The device is equipped with two distinct sets of needles, one set for detecting and the other set for administering drugs. The system operates on a 5 V DC input power and employs an internal DC-AC converter to generate a 100 V voltage and drive the ultrasonic transducer at a frequency of 100 kHz (Figure 9a).[70] Many teams have demonstrated integration of biosensing and drug delivery into a single wearable patch. These closed-loop systems are capable of closely monitoring parameters such as blood glucose and pH and delivering drugs in response to the measured values (Figure 9b)[160] Such microneedle patches are equipped with a set of microneedles capable of performing electrochemical measurements and another set capable of delivering the drug (Figure 9c).[161,166]

8. APPLICATIONS

Researchers, scientists, and industry players are all very interested in MNs. Numerous research has shown that MN has the potential and capacity to be administered in various domains. These include administering drugs and vaccines, diagnosing illnesses, and applying cosmetics. Encapsulated proteins, antibodies, antigens, and other biotechnological active components are the best options for transdermal distribution by microneedles. This section summarizes the primary applications of MNs researched so far.

8.1. Drug Delivery

Diabetes is a prevalent and significant chronic ailment worldwide that necessitates careful and diligent management. Administering appropriate dosages of insulin to individuals with diabetes is crucial for reducing the health hazards associated with high blood glucose levels. Luo et al. described a microneedle patch that delivers insulin in response to changes in pH, specifically targeting glucose levels. The pH-sensitive nanoparticle (SNP) comprised of poly(ethylene glycol)-*b*-PHMEMA (mPEG-*b*-PHMEMA) was used to encapsulate insulin. Acidic circumstances facilitate the release of insulin from the microneedles by gluconic acid generation. The *in vivo* trials conducted with SNP(I) demonstrated the expedited responsiveness of the microneedles in regulating blood glucose levels.[167] Zong et al. described using a microneedle patch containing phenylboronic acid (MA-HA-PBA@Gins and MA-HA@Gins) to deliver insulin. The microneedle patch is composed of hyaluronic acid, which is a substance that is compatible with living organisms. The covalent linkage between insulin and phenylboronic acid was achieved by utilizing the o-diol group contained in the substance. The MA-HA-PBA@Gins MN patch exhibited a more consistent and predictable drug release profile than the MA-HA@Gins patch. The insulin release from the MA-HA-PBA@Gins MN patch was contingent upon glucose levels. As a result of the strong attraction between phenylboronic acid and the hydroxyl group of glucose, the Gins were freed, causing insulin to be released into the bloodstream. Without glucose, the presence of PBA keeps the Gins in the patch, inhibiting insulin delivery. Therefore, MA-HA-PBA@Gins confirmed the regulated release of insulin.[168]

Fu et al. reported the existence of a soluble glucose-responsive microneedle patch (SGRM). The study utilized mesoporous silica nanoparticles carrying insulin as reservoirs for insulin storage. Additionally, a ZnO-PBA conjugate was employed as a gatekeeper to prevent any insulin leakage. Mesoporous silica nanoparticles encapsulating G-MSN@insulin@ZnO-PBA-1 and G-MSN@insulin@ZnO-PBA-2 were incorporated into hyaluronic acid microneedles to deliver drugs under hyperglycemic conditions. The microneedle patch, which contains G-MSN@insulin@ZnO-PBA-2, indicated the precise and regulated release of insulin in response to elevated blood glucose levels. *In vivo* experiments confirmed that the patch effectively controlled blood glucose levels in diabetic rats.[169] Chen et al. reported the development of temperature-independent PVA hydrogels (hydrogel-1 and hydrogel-2) for regulated medication delivery for diabetes. The Hydrogel-2, which includes an MN patch, demonstrated precise and regulated release of insulin in response to glucose levels in the bloodstream.[170] The authors, Qi et al., published a study on the development of electroresponsive microneedles that can be used for the delivery of insulin. These microneedles can be reversed and respond to electrical stimuli. Thiolated silk fibroin (TSF) was employed in the production of microneedles, while graphene was utilized to enhance their conductivity. Thiolated silk fibroin possesses a sulfhydryl group that can be cleaved and reformed reversibly upon electrification. The microneedle patch was administered to the abdomen region of the bullfrog rat to evaluate its potential for inducing swelling, as depicted in Figure 5a. Introducing graphene into the microneedles (TSF/GR@MN) enhances the sensitivity of TSF to electrification, resulting in better control over the release rate of insulin.[171]

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Rini et al. evaluated the continuous microneedle-based drug delivery via a wearable hollow microneedle patch during a 72-h period. Blood samples for measurements of insulin aspart and blood glucose in serum were obtained at predetermined intervals during dosing visits to evaluate insulin absorption kinetics and glycemic response. Microneedle-based insulin delivery has enhanced the pharmacokinetic uptake and good blood glucose control compared to subcutaneous injections.[172] Kochba et al. have studied the pharmacokinetic and safety profile of intradermal (ID) insulin delivery using an MJ needle and compared it with the subcutaneous (SC) insulin delivery in patients with type 2 diabetes. Intradermal delivery of insulin displayed a shorter Tmax and Cmax level and lower interpatient variability than SC injections. ID injection of insulin showed a good safety profile with reduced late hypoglycemic events compared with SC injection.[173] Gupta et al. reported a comparative analysis of insulin administration using a catheter and microneedle on human subjects. Insulin delivery using hollow microneedles reduced plasma glucose levels while reaching a peak insulin concentration in half the time compared to the subcutaneous route.[174] Further, Wang et al. studied the insulin delivery using microneedles with two-stage glucose-sensitive controlled release. The FITC-insulin-loaded CS-PBA composite hydrogels were suspended in glucose PBS solutions of varying concentrations. The 100 μL of supernatant from the test samples were analyzed at regular time intervals. The results of *in vitro* studies revealed that rapid insulin release occurred within 0−1h and slowed down thereafter. The *in vivo* analysis using diabetic-induced SD rat models revealed that the particle mixed hydrogel (PVA/PVP composites) were more effective in controlling blood glucose levels than sustained-release microneedles. Also, the particle-mixed hydrogels have shown increased insulin load with enhanced drug usage.[175] Glucose-responsive insulin release was studied using a semi-IPN hydrogel microneedle array patch. High performance liquid chromatography (HPLC) was employed to study the *in vitro* release of insulin in response to changing glucose concentration. MeOH-treated semi-IPN hydrogels showed insulin secretion in response to increased levels of glucose. The fluorescence images of FITC-insulin-loaded and rhodamine B labeled semi-IPN hydrogels confirmed the uniform distribution of insulin and hydrogel throughout the needle area.[176]

8.2. Delivery of Biomolecules

Li et al. reported the development of a microneedle patch with antihypertensive properties designed to lower blood pressure. The microneedle patch was fabricated utilizing a centrifugation casting technique and a PDMS mold. The treatment of hypertension was using microneedles made of sodium carboxymethylcellulose, which contained particles of sodium nitroprusside (SNP) and sodium thiosulfate (ST). The concurrent administration of medicines (SNP-ST) not only effectively decreased blood pressure but also mitigated the danger of inflammation induced by SNP in isolation.[177] Chen et al. presented a 3D-printed ultrasonic microneedle array (USMA) designed for transdermal medication administration. The hollow microneedle array was created using a non-conductive GR resin, and two substances (methylene blue and bovine serum albumin) were employed as model drugs. The USMA functioned at a frequency of 110 kHz and had an intensity of 2 W/cm^2. The findings of *in vitro* drug delivery experiments have demonstrated that ultrasound activation leads to faster delivery, regardless of the molecular weight of the material. Additionally, this method ensures uniform dispersion of the drug.[178] Abiandu and Ita have developed robust microneedles for the delivery of potassium chloride (KCl) to address hypokalemia. The development of micro-channels for KCl diffusion and sustained release was confirmed by the Franz diffusion test and confocal microscopic characterizations.[10] Electrospinning allows the synthesis of various functional materials that can be used in different biomedical applications.[179,180] In addition to its numerous advantages, this method is also constrained by limitations like irregular fiber deposition, challenges in combining different capabilities, and the utilization of toxic solvents during the process. Recently, researchers have developed sophisticated electrospinning methods to integrate biomolecules and living cells into the nano/microfibers produced by this process.[181,182] A PLGA nanofiber membrane (called DEPA) was used to attach the dissolving microneedles to the skin's surface in a study rather than an adhesive patch. The microneedles were manufactured on a pillar array. The results of this micro-needle's implantation in pig skin demonstrate that it solves the issues with dissolving microneedles based on flat patches, including restricted penetration and reduced drug efficiency.[183] A biphasic scaffold for delivering antimicrobial drugs to treat bacterial biofilms integrated with dissolvable microneedle arrays was reported.[184] For the sustained release of antimicrobial agents like $AgNO_3$, $Ga(NO_3)_3$, and vancomycin were incorporated in the nanofibre mats through coaxial electrospinning technique.

8.3. Wound Healing and Wound Dressing

The clinical effectiveness of several treatment variables for treating chronic wounds has been hindered by their inefficient delivery to the wound area.[185] Zhang et al. have created a wearable, self-powered microneedle system that combines antimicrobial treatment with electrically stimulated tissue repair. This innovation addresses the urgent requirement for advanced wound therapy solutions, especially for infected wounds, and shows great potential for improving wound healing outcomes. This innovative technology has the potential to effectively control infected wounds by delivering electrical stimulation and antibacterial medicines directly to the location of the wound simultaneously.[41] Abednejad et al. described a wound dressing material composed of a bilayer structure of polyvinylidene fluoride and hyaluronic acid. Therapeutic substances known as active pharmaceutical ingredients (API-IL) were incorporated into bilayer material using dual-function ionic liquids. The API-ILs have demonstrated effective anti-inflammatory properties and enhanced and regulated drug delivery characteristics.[186] Acne is a prevalent issue globally. It induces psychological distress in adolescents and results in a lasting mark on the skin. Propionibacterium acne is the primary causative agent of acne. Xiang et al. described a microneedle patch that is activated by ultrasound to treat acne infections. The microneedle patches were filled using a combination of zinc porphyrin (ZnTCPP) based metal−organic framework and ZnO, using sodium hyaluronate as the basis material. The inclusion of ZnTCPP and ZnO in the composite enhanced the electron transfer efficiency of the patch by augmenting charge transfer and diminishing the activation energy of adsorbed O_2. Ultrasound activation of ZnTCPP-ZnO increases the production of reactive oxygen species (ROS), decreasing skin infection.[46]

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8.4. Vaccine Delivery

Vaccination is a highly effective strategy for protecting people from infectious diseases. Despite the significant effectiveness of vaccination in previous years, the mortality rate caused by infections is currently rising at a concerning rate. Microneedle-based delivery of vaccines through the skin barrier, such as live attenuated vaccines, inactive vaccines, pathogen component vaccines, RNA vaccines, protein vaccines, toxoid vaccines, etc., has emerged as an alternative to standard vaccine delivery methods, addressing the challenges encountered in the process.[187] Electroporation's capacity to enhance the intracellular transportation of genetic material, such as DNA and RNA, offers a promising strategy for improving the immunogenicity of vaccines and treatments. The utilization of both a piezoelectric pulser and a microneedle electrode array (MEA) allows for the targeted administration of electric pulses to the outermost layers of the skin. This approach minimizes discomfort and negative consequences while optimizing the effectiveness of delivering vaccines to antigen-presenting cells. This enhances the global accessibility and comfort of crucial medical operations.[188] M. A Boks et al. described the controlled release of model vaccine OVA257−264 peptides combined with agonistic anti-CD40 antibodies in ceramic nanoporous microneedle arrays. The insertion of microneedles into the human skin explant model demonstrated that the developed microneedle array can serve as an efficient instrument for stimulating T-cell response.[189] A study was conducted to assess the effectiveness of a portable ion power supply in improving the distribution of drugs via the skin and transforming skincare methods. This research aimed to use iontophoresis to overcome the difficulties caused by lipid barriers in conventional facial masks. The goal was to enable effective drug penetration into the skin, resulting in improved therapeutic results.[190]

8.5. Cancer Therapy

Cancer poses significant challenges in medical treatment due to its high mortality rate and propensity for recurrence. Microneedle patches have attracted considerable interest in the treatment of superficial cancer due to their ability to deliver medication directly to the affected area and their minimally invasive nature.[191−193] A study reported the use of a microneedle patch to administer PROTAC for the treatment of breast cancer. MPEG-poly(β-amino ester) (MPEG-PAE), a micelle that is sensitive to changes in pH, was employed to encapsulate a PROTAC compound that degrades estrogen receptor alpha (ERα). This encapsulated compound was then put into a microneedle patch capable of biodegrading. The microneedle patch demonstrated a consistent and extended release of the medication into tumors, with a degradation rate of 87%.[194]

Microneedle-assisted photodynamic therapy (PDT) and photothermal therapy (PTT) have emerged as promising treatment strategies for various disease conditions. Both are light-dependent therapeutic methods for treating diseases with enhanced selectivity, noninvasiveness, and fewer/no side effects. PDT uses a photosensitizer to convert photon energy to reactive oxygen species (ROS), and PTT involves photothermal material to convert photon energy to thermal energy.[195,196] Song et al. developed a photosensitizer immunotherapy integrated microneedle to prevent metastasis and tumor recurrence. Dissolvable gelatin microneedles (MN) containing organic PSs (N3−4F) nanoparticles (NPs) as photosensitive materials were used for breast cancer therapy. NPs@MN were irradiated with NIR-II for rapid release of NPs at the tumor site for causing immunogenic cell death and to induce dendritic cell (DC) maturation. An increase in temperature up to 55 °C was observed at the tumor site after irradiation with NIR-II.[197] Moreira et al. reported polyvinyl pyrrolidine (PVP) microneedles coated with doxorubicin (Dox) and gold nanorods (AuMSS) for cancer therapy. The combination of chemo and photothermal therapy (PTT) facilitates in the faster diffusion of gold nanorods to the target site and is followed by an increase in the sensibility of the tumor cells toward the doxorubicin.[192] Immunotherapy combined with microneedle technology is a new approach for delivering drugs in cancer treatment. Immunotherapy employs the body's immune system to fight against tumor cells by therapeutic agents such as checkpoint inhibitors, adoptive cellular therapy, or vaccines.[198] Weng et al. reported a microneedle-based antitumor drug delivery system to improve the tumor-killing ability of T lymphocytes. The combination of photothermal therapy and immunotherapy was employed to prevent immune escape by utilizing photothermal material gold nanorods (AuNR)-polyethylene glycol (PEG) and an immune checkpoint blocker anti-PD-1 polypeptide. Poly methyl vinyl ether maleic anhydride copolymer (PMVE-MA) microneedles were loaded with AuNR and anti-PD-1. Laser irradiation of loaded dissolving microneedles led to the photothermal ablation of tumor cells and, thereby, cell death.[199] Joo et al. fabricated a dissolving self-locking microneedle patch, a 3D printing technique for treating melanoma. They have used SD-208, a transforming growth factor-β (TGF- β) inhibitor and anti-PD-L1 to improve the efficiency of immunotherapy against melanoma. Hyaluronic acid (HA) microneedles loaded with cargo to be delivered displayed good immunomodulatory effects in treating melanoma.[200]

8.6. Disease Monitoring

Continuous evaluation of specific biomarkers in the interstitial fluid (ISF) is essential for the effective management of chronic diseases and for modifying treatment accordingly. Most of the components present in the ISF originate from the blood plasma and thus act as biomarkers for many disorders. Microneedles are successfully utilized for the collection of ISF for biomarker evaluation. Solid microneedles cannot be used for ISF extraction directly; instead are integrated with other mechanisms due to their solid nature.[201,202] Hollow microneedles for ISF extraction are favored for biomarker detection due to their expedited sampling process compared to hydrogel microneedles.[203,204] However, the major issue with hollow microneedles is channel blockage due to entrapped dermal tissue.[205] Hydrogels are 3D polymeric networks with good biocompatibility. Hydrogels are 3D polymeric networks with good biocompatibility. Hydrogel microneedle patches are widely used in ISF extraction due to their good skin insertion capabilities and swelling nature.[206,207] Razzaghi et al. developed a microneedle array (MNA) for pH and glucose biomarkers. The poly(ethylene glycol) diacrylate (PEGDA) based hydrogel MNAs exhibited faster swelling and ISF extraction capabilities.[208] The fabrication of PVA/PVP hydrogel microneedle patches for ISF extraction to monitor blood glucose levels was reported by Xu et al. A 10 × 10 array of needles, varying in length, base width, and tip form, was evaluated for fluid extraction. They found that microneedles

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with pyramidal tips can absorb a greater volume of interstitial fluid than those with conical tips.[209] Further, Park et al. developed hydrogel microneedles for the early detection of colorectal cancer. The microneedle body was composed of polycaprolactone (PCL), and alginate hydrogel with GPC-1 antibodies coated onto it. The patch consisted of 100 needles with 300 μm in diameter and a height of 750 μm. The GPC-1 antibody-coated hydrogel microneedles could absorb more tumor-specific exosomes.[210] Fonseca et al. fabricated a swellable cross-linked gelatin methacryloyl (c-GelMA) microneedles for urea detection. The array consisted of 15 × 15 needles of pyramidal shape with a height of 550 μm. *Ex-vivo* skin insertion studies using human abdominal skin showed that the microneedle patch can extract 3.0 + 0.7 mg of ISF for analysis.[211] In another study, Zheng et al. developed a multiplexed electrochemical detecting microneedle system for the monitoring of kidney disease. In the ISF, multiple renal biomarkers including phosphate, uric acid, creatinine, and urea were evaluated for the early identification of kidney disease. The microneedle coupled electrochemical sensor array (MNESA) consists of hyaluronic acid and methacrylate-modified hyaluronic acid. The MNESA exhibited elevated detection specificity with reduced cross-reactivity to other biomarkers found in the ISF.[212]

8.7. AI-ML in Drug Delivery and Disease Monitoring

Artificial intelligence (AI)-driven intelligent drug delivery systems can automatically modify prescription dosage, reducing the dangers of drug dependence and adverse consequences in patients.[213,214] By improving treatment effectiveness and appealing to the specific demands of each patient, personalized medicine is becoming more useful in managing pain. Integrating artificial intelligence and machine learning models can envisage chronic pain levels and reduce personal assessment vulnerability.[215] The integration of machine learning algorithms facilitates new opportunities for the creation and enhancement of MN patches.[216] Zhang et al. used a machine learning algorithm to discover a manganese thiophosphite-based superoxide dismutase mimic for treating androgenetic alopecia (AGA).[217] Machine learning can improve the development process of a microneedle patch by analyzing the drug release pattern prior to fabrication. The preliminary evaluation can facilitate both *in vitro* and *in vivo* analyses by minimizing time, resources, and costs.[218] Yuan et al. compared four machine learning models for assessing drug permeation through the skin in *in vitro*drug release studies. They reported that drug permeation, microneedle surface area, and drug loading played a crucial role in models.[219] Multiple research teams have documented the application of machine learning (ML) algorithms to forecast biomarker levels in the body at specific time intervals.[220] Bhat et al. reported a machine learning-based blood glucose monitoring system. The integration of machine learning with the biosensor facilitated effective dietary planning for diabetes management.[221]

9. CLINICAL TRIALS

Several MN devices have recently transitioned to clinical trials, with some integrated into commercial products. Clinical trials are steadily rising due to enhanced cooperation among pharmaceutical companies, universities, and research organizations.[222] The predominant focus of clinical studies lies in utilizing hollow microneedles for various therapeutic applications, including diagnostics, cancer treatment, osteoporosis management, diabetes treatment, local anesthesia, pain relief, cosmetics, and ocular injection.[223] Micronjet devices used for intradermal delivery of influenza vaccine were developed by NanoPass Technologies. It consisted of four silicon hollow microneedles of 600 μm long (NCT00558649).[224] The inactivated polio vaccine was delivered to newborns to assess the immunogenicity of the material using Micronjet600 (NCT01813604). A clinical study reported using hollow microneedles to deliver insulin to children and teenagers with type-1 diabetes. These are borosilicate glass microneedles with a tip diameter of 60−80 μm and displayed reduced insertional pain compared to the subcutaneous catheter.[225] Another group researched the administration of a hepatitis B vaccine (NCT02621112). During the phase-II experiment, it was noted that the treatment group exhibited a greater level of protection compared to the control group.[226] To minimize pain, a clinical trial used a microneedle device to provide the pain-relieving medication lidocaine before the peripheral venous cannulation process (NCT05108714).[227] The MicronJet600 gadget addressed periorbital wrinkles by employing microneedles containing a dermal filler composed of hyaluronic acid (NCT02497846). Clinical trials were conducted by Becton-Dickinson (NCT01061216 and NCT01557907) and NanoPass businesses (NCT00602914) using hollow injector systems to investigate the pharmacokinetics of insulin transdermal delivery.[223] A preliminary clinical study involving 100 individuals was carried out to administer an inactivated influenza vaccine using dissolvable microneedles (NCT02438423). The immunization elicited a comparable immunogenic response to intramuscular injections of the identical dosage. Doxorubicin liposomal injections have been employed in cancer therapy for an extended period, although numerous patients have had toxicity affecting multiple organs.[228] Several studies have shown the diminished negative impacts of doxorubicin when administered through a microneedle transdermal drug patch for cancer treatment.[64]

Multiple clinical trials are underway to assess the efficacy and safety of doxorubicin. SkinJet, Inc. has created a microneedle patch to administer doxorubicin to treat basal cell carcinoma. This patch is being tested in a phase-I clinical trial with the registration number NCT03646188. A study was conducted on using microneedles carrying tuberculin to treat tuberculosis (NCT04552015). The microneedle patch, Therapass RMD-6.5A, made of hyaluronic acid and consisting of 76 conical microneedles of 650 μm in length, was utilized to treat psoriasis. The microneedles were filled with the medication calcipotriol betamethasone dipropionate. The clinical trial identifier for this treatment is NCT02955576.[229] The microneedle patch M207, also known as QtrptaTM, loaded with Zolmitriptan for treating migraines, was utilized. The device comprised a reusable applicator and a patch coated with the drug on titanium microneedles.[230] Zosana Pharma has developed a parathyroid hormone patch that utilizes the M207 delivery method. This patch is currently undergoing phase-I clinical trials with the registration number NCT02478879. A phase-II clinical trial is now underway for the treatment of Osteoporosis using a patch containing Abaloparatide (NCT01674621). Clinical trials are also being conducted on microneedle patches that do not include active substances. These patches enhance the penetration of active substances via the skin prior to their delivery (NCT01257763).[231] To treat facial conditions, devices from Dermapen (NCT03472235 and NCT05108272) and SkinPen

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Precision System (NCT03803059 and NCT05071274) were registered for clinical trials. Radiofrequency microneedles from various companies were registered for clinical trials (NCT03380845, NCT03573076, NCT03426098, and NCT03507036). Radiofrequency from 3 kHz to 300 GHz induced the growth of elastic fibers, collagen remodeling, and dermal coagulation in the skin.[232] A microneedle patch developed by the CellF system (NCT03612570) for hyperplasia was proven effective in removing sebaceous hyperplasia.[233]

10. CHALLENGES AND FUTURE PERSPECTIVES

Microneedle patches have become a favorable technology for delivering therapeutic molecules via the skin in transdermal drug delivery. These patches are composed of microscopic needles filled with specific bioactive substances to be delivered to specific locations. Due to their outstanding efficacy as a vehicle for delivering drugs in long-lasting treatments and as monitoring platforms for different illness situations, they have been a focal point in biomedical research. Microneedle-based medication delivery devices are manufactured using organic and inorganic materials. Polymeric materials are widely used to produce microneedle patches due to their excellent biocompatibility, biodegradability, and mechanical strength. Stimuli-responsive microneedle patches provide a continuous and regulated/on-demand administration of medications to the desired location. Different external and internal stimuli can activate the immediate release of the active substance without causing any side effects or pain. These gadgets are hindered by the disadvantages of being easily moved and having elevated expenses. The recurrent insertion of microneedle patches into the same region of the skin presents a challenge in the form of skin allergy and inflammation.

Additionally, it is important to consider the enduring stability and integrity of the payload contained within the microneedle. The geometric characteristics of microneedles are crucial in determining the efficacy of medication administration via the skin. The geometry must be designed to allow for the optimal loading of medicines into the needles and guarantee their complete delivery to the intended target site. Despite extensive study, numerous registered patents, and clinical trials, some unresolved concerns persist with microneedle patches, including their mobility, material safety, and biocompatibility. Different microfabrication techniques have been utilized to create microneedle patches. The communication and drug delivery modules must have accurate control and rapid response capabilities to deliver on-demand medicine. However, there is a need to fulfill the demand for a microfabrication technology that can meet the requirements of drug release rate, duration, drug dosages, and long-term stability. The precision of MN sensor measurements directly influences drug distribution, necessitating high detection accuracy and meticulous monitoring of drug dosage to ensure clinical pharmaceutical safety. Potential developments in microneedle technology may result in the development of a diverse array of portable and assembled monitoring devices utilizing MN technology. With the evolution of Internet and artificial intelligence technologies, MNs-based closed-loop systems can now serve as smart devices. They can monitor patients' health markers in real-time, dynamically, and in the long run. The utilization of microneedle-based technology can enhance illness prevention, diagnosis, and control while augmenting patient pleasure in their health on a global scale.

11. CONCLUSIONS

The effectiveness of drug administration using microneedle patches mostly relies on successful penetration of the epidermal barrier. In recent decades, significant studies have been dedicated to creating and developing microneedle patches to deliver drugs and monitor different biomarkers within the body. The field of biomedical research has seen a surge of interest in developing and producing a medication release mechanism that can be activated or regulated as needed. This article provides an overview of the many methods used to create microneedles, the various types of microneedles, and the materials utilized in their fabrication, specifically focusing on their applications in biomedicine. The improvements in microneedle-based controlled release systems across several areas are potentially revolutionizing medicine delivery and various disease detection and monitoring systems.

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Notes

The authors declare no competing financial interest.

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