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Fabrication of porous polymeric microneedles: a concise overview

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Recent advancements in microneedle (MN) technology have increasingly focused on porous polymeric microneedles (PPMNs), which are, among various types of MN, emerging as a promising platform for diverse biomedical applications, including transdermal drug delivery, interstitial fluid (ISF) extraction, and biosensing. This growing interest stems from their distinctive internal architecture, characterized by continuous nano- or micro-scale pores that enable the efficient transport of drugs and biofluids, primarily through capillary action. The optimal selection of polymeric materials, combined with appropriate fabrication techniques, plays a critical role in enhancing the functional performance of PPMNs while ensuring sufficient mechanical strength. This concise review summarizes recent research progress in the fabrication methods of PPMNs, emphasizing the interplay between polymer(s) choice, manufacturing technique, intended biomedical application, and the resulting structural and functional properties of the microneedles. It also addresses key challenges in the fabrication field and discusses future development.

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Introduction

By definition, the microneedle (MN) system consists of integrally formed micron-scale needles on a patch substrate.[1–3] These tiny needles, which are 25 to 2000 μm long,[4,5] can go through the outerlayer of skin to effectively transport a plethora of diverse bioactive materials while avoiding skin injury.[1,5,6] This system neatly integrates the benefits of skin injection with the safety of a transdermal patch.[1] Because of their promising clinical results, tissue tolerability, patient acceptance, and capacity to self-administer, MN systems offer easy-to-use tool for controlled transdermal drug release in a variety of settings.[1]

MNs are usually fabricated from metal, silicon, glass, ceramic,[7,8] or polymer (*e.g.*, carbohydrates and hydrogels).[9] These materials have been used to fabricate microneedles for diverse purposes, based on their mechanical and degrading qualities.[9] Silicon, ceramics, and metals have stiffness values over 10 GPa and are nondegradable under typical circumstances.[9] Metal MNs are cost-effective to produce and exhibit superior mechanical and physical properties; yet, they are nondegradable and not flexible.[10] There are currently six main categories of MNs: solid, coated, dissolving, hollow, hydrogel,[11–15] and porous.[11,13,16] Porous microneedles (PMNs) are channel-based devices[1] made up of arrays with a network of linked channels or pores capable of delivering medications[17–19] or capturing biological fluids *via* the epidermis or other tissues. Furthermore, PMNs facilitate therapeutic monitoring[11] or biosensing applications by periodically and selectively capturing (when functionalized) and detecting biological molecules[11,17] *via* capillary action[11,18,19] (Fig. 1). They are also attracting interest for their capacity to encapsulate larger volumes of fluid and for providing superior isotropic fluid directionality compared to hollow MNs, enabling both fluid injection and extraction at significantly greater volumes.[20] PMNs are usually fabricated using inorganic substances, biocompatible metals, or polymers.[11,19,21]

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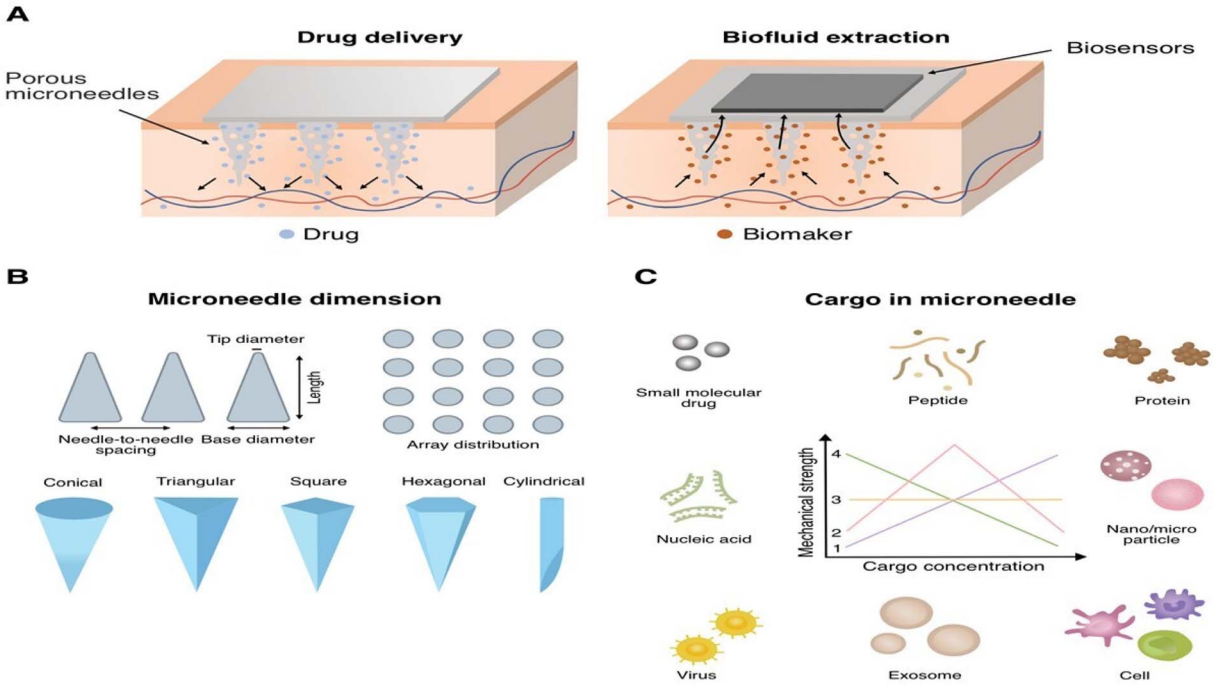

Fig. 1 (A) Microneedle structures and the delivery mechanisms, and microneedle structures and the sampling mechanisms. (B) Microneedle dimensions. Reproduced from[26]. (C) Cargos including the small molecular drug, peptide, protein, nucleic acid, nanoparticle, microparticle, virus, exosome, and cell could be loaded in microneedle for delivery. The cargo in microneedle maybe linear increase,[1] first increase and then decrease,[2] not affect,[3] or linear decrease[4] the mechanical strength of microneedle in response to the increase of cargo concentration. Reproduced with permission from[15] [Copyright© 2023, Elsevier].

Over the past twenty years, great progress has been made in developing MN-based drug delivery systems.[3] Among the various types of MNs, polymeric MNs have garnered significant interest in drug delivery research due to limitations associated with other materials—such as high cost of raw materials, complex fabrication techniques, fragility, limited biocompatibility, low drug-loading capacity, and the risk of MN facture in the skin upon insertion.[22] Polymeric porous microneedles (PPMNs), in particular, have drawn substantial attention for their unique features, as they are fabricated using biocompatible and biodegradable polymers, which can be customized to control the release profile of the encapsulated active compounds.[23] Fig. 2 depicts the research trends for each type of PPMN over the last two decades (2001–2024) based on data from the Web of Science (~109 articles), excluding review articles (**https://www.webofscience.com/wos/woscc/basic-search**).

The use of PPMNs for transdermal drug delivery (TDD) offers several advantages. First, the minimally invasive nature of PPMNs can considerably reduce pain and discomfort experienced by patients during application, making them more patient-friendly. Additionally, the ability to engineer the MN geometry and porosity allows for tailored drug release profiles, enabling both burst and sustained release, depending on the specific therapeutic needs.[24,25] Furthermore, PPMNs exhibit greater flexibility in applications compared to other MN types due to their distinctive drug-loading method, which enables the separation of the MN preparation process from the drug loading process, therefore minimizing drug loss and inactivation during preparation, especially for large-molecule drugs like vaccines, and improving mass production of MNs. Moreover, PPMNs offer excellent detection capabilities because of their large specific surface area and their flexibility to be integrated with other detection platforms, making detection easier and faster. This type is an adaptable and useful choice when designing and manufacturing wearable products and point-of-care (POC) testing devices.[11]

In this review paper, we considered recent studies involving the fabrication of PPMNs. These strategies were discussed in detail, together with examples, challenges, limitations, and factors to be considered.

Consideration and insights on the formulation aspects of PPMNs

The formulation and composition of MNs depend on the type of MN and its intended use. For example, drug-loaded PPMN comprises a polymer, drug (*e.g.*, protein, vaccine, or nanocarrier), and other excipients such as solvent, plasticizer, and/or permeability enhancer.[22] To further enhance a drug's solubility in the polymer or in water, PPMNs may also contain a copolymer or cosolvent in their formulation. Moreover, PPMNs can be formulated using advanced materials to obtain stimuli-responsive systems that respond to both internal and external stimuli.[22]

In general, PPMN fabrication involves two main steps. First, polymer blends are prepared, with or without various other

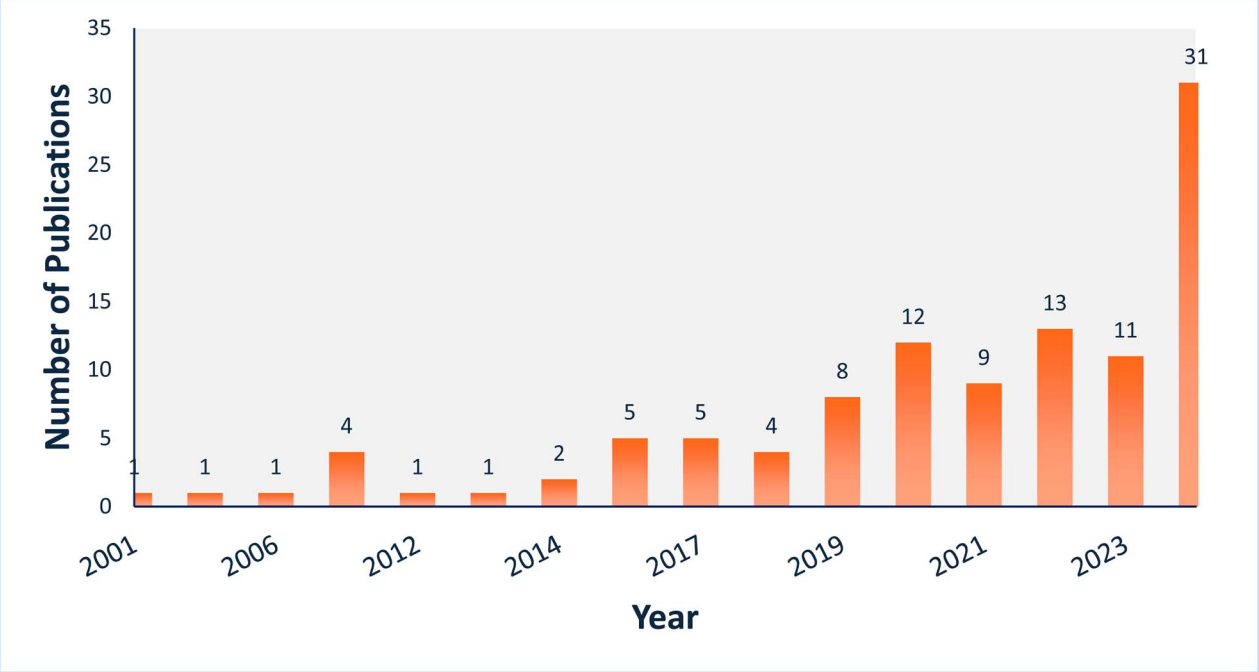

Fig. 2 The graph depicts the published papers on porous microneedles (search words: porous, polymer, microneedle, excluding the review articles) per year in last two decades, based on Web of Science (https://www.webofscience.com/) on 5 January 2025.

excipients. Then, a pore-forming step is performed to obtain the interconnected porous architecture. Therefore, there are three main focal points in the preparation of PPMNs.

1-Polymers

Over the past decade, polymers have been extensively researched and developed as microneedle materials for a range of biomedical applications, particularly transdermal drug delivery (TDD) and biofluid extraction.[26] Polymeric materials have sparked attention in the medical field due to their ease of manufacture, low cost, and beneficial biological and mechanical properties.[27] Polymers offer multiple advantages, including biodegradability, favorable biocompatibility, adjustable molecular weight and hydrophilicity,[28] nontoxicity and inexpensive[29] as well as straightforward fabrication processes.[28]

Polymers are known to have the ability to withstand large bending forces without being fractured.[26] Although they possess lower tensile strength than metals or silicon; yet, they are tougher than most other materials used for MN fabrication.[30,31] Fabricating MNs from polymeric materials offers substantial benefits in terms of structure controllability,[1] biocompatibility, biodegradability, solubility, the ability to accommodate both small and large molecules, extended drug release characteristics, mechanical properties, as well as functionality modulation *via* physicochemical modifications.[12] In addition, polymer biocompatibility and biodegradability ensure that even if the needle breaks, it naturally degrades inside the body,[32,33] which is immensely important in the case of PPMNs. Polymers are also preferred for their cost-effectiveness, hygiene, and safety, in addition to their swelling and dissolving capabilities. The *in vivo* enzymatic degradation of a polymer yields harmless products. Therefore, the likehood of infection within the body is reduced.[34] In addition, the polymeric nature of PPMNs allows for the incorporation of various functional groups that can enhance drug specificity and targeting capabilities. This approach can potentially improve the therapeutic efficacy of the delivered drugs while minimizing off-target effects.[1] More importantly, PMNs can be fabricated without complicated micromachining processes, equipment, or the requirement for a clean room environment.[26] However, it is important to note that biodegradable polymers may have different particle size distributions and pharmacokinetics that are difficult to recreate due to unanticipated hydrolytic or enzymatic degradation of the drug carrier.[35] Additionally, if made of nonbiodegradable materials, PPMNs array debris stays beneath the skin after shattering, potentially causing discomfort and inflammation.[28]

Polymers like polylactic acid (PLA), poly(lactic-*co*-glycolic) acid (PLGA), cellulose acetate (CA), polyglycolic acid (PGA), poly (glycidyl methacrylate), polydimethylsiloxane (PDMS), polyethersulfone (PES), and polysulfone (PSF) have all been utilized in the fabrication of PPMNs.[19]

2-Fabrication methods

The fabrication process is a key aspect of developing PPMNs. The choice of fabrication method depends on various factors, including the manufacturing material, access to specific technologies, and the intended application.[27] The fabrication approach allows for precise control of the MN geometry, dimensions, and porosity, enabling the tailored design of the drug delivery system to meet specific therapeutic requirements.

The geometry of porous microarray structures is an important consideration in the design of MN-based drug delivery systems because the porosity and surface area can considerably affect the loading capacity, drug release kinetics, and mechanical properties of the MNs.[36] However, advances in manufacturing techniques have enabled the production of more complex MN geometries.[27]

A range of techniques have been developed for the fabrication of PPMNs. Micromolding,[21] leaching, phase separation, hot embossing, freeze-drying, ultrasonic welding,[11] two-photon polymerization (TPP),[20] wet etching,[21] and emulsion and bolding are the main fabrication processes to achieve porous MNs.[26] The current methods for producing PPMNs, which are complicated and only applicable to limited types of materials,[26] are introduced here.

I-Micromolding. The micromolding technique is a fabrication method in which microscale structures or parts are created by casting polymeric or other materials into molds with submicron-level precision. The process starts with preparing molds with the desired needle shape and size using photolithography, a technique that employs light to transfer a pattern onto a photosensitive material. The mold is then filled with a polymer substance, which is subsequently cured to produce the MNs. Once formed, MNs can be loaded with a drug or a vaccine[12,37] (Fig. 3). In addition, using mild processing conditions, molds can be filled with solid polymer microparticles instead of a polymer melt to create microstructures with multiple materials or complex geometries.[38] Micromolds are often made of PDMS because it is durable, optically transparent, inexpensive, and moldable.[38] However, the metal molds used for conventional processing don't work for the high aspect ratios of complex structures. Furthermore, the high temperatures and pressures of traditional processing are inappropriate for the replication processes essential to construct multiple component structures or intricate geometries.[38]

This technology has been developed to fabricate microstructures that are cheap and simple to process, and the potential for mass production using injection molding, embossing, and other methods.[38]

Notwithstanding the numerous advantages of polymer molding, traditional micromolding fails to fabricate sophisticated microdevices or ones that include several materials. Microstructures with high aspect ratios or complicated geometries are difficult to manufacture using injection molding or embossing molds techniques, as the high viscosity of the thermoplastic polymer melt often causes premature cooling before filling the mold cavity.[38]

Centrifugation micromolding and vacuum micromolding are the most commonly employed technologies to introduce the needle solution or suspension into the microholes of male molds for MN preparation. Yet, centrifugation micromolding may lead to separation of the polymer matrix and microparticles due to the higher-density microparticles settling into the mold microholes during centrifugation. Furthermore, asynchronous centrifugation creates an inhomogeneous distribution of needle compositions, resulting in needle fracture because of the poor mechanical properties of the microparticles. On the other hand, the vacuum micromolding technique may be an improved option to centrifugation micromolding, since it uses a moderate pressure gradient to allow synchronous settling of needle components into the microholes of the mold, potentially enhancing MNs' formability.[39]

II-Leaching. The porous architecture of PPMNs can be produced using the leaching method. In this common technique, a water-soluble porogen (a substance that creates pores), such as salts (*e.g.*, sodium chloride), sugars (*e.g.*, sucrose), or

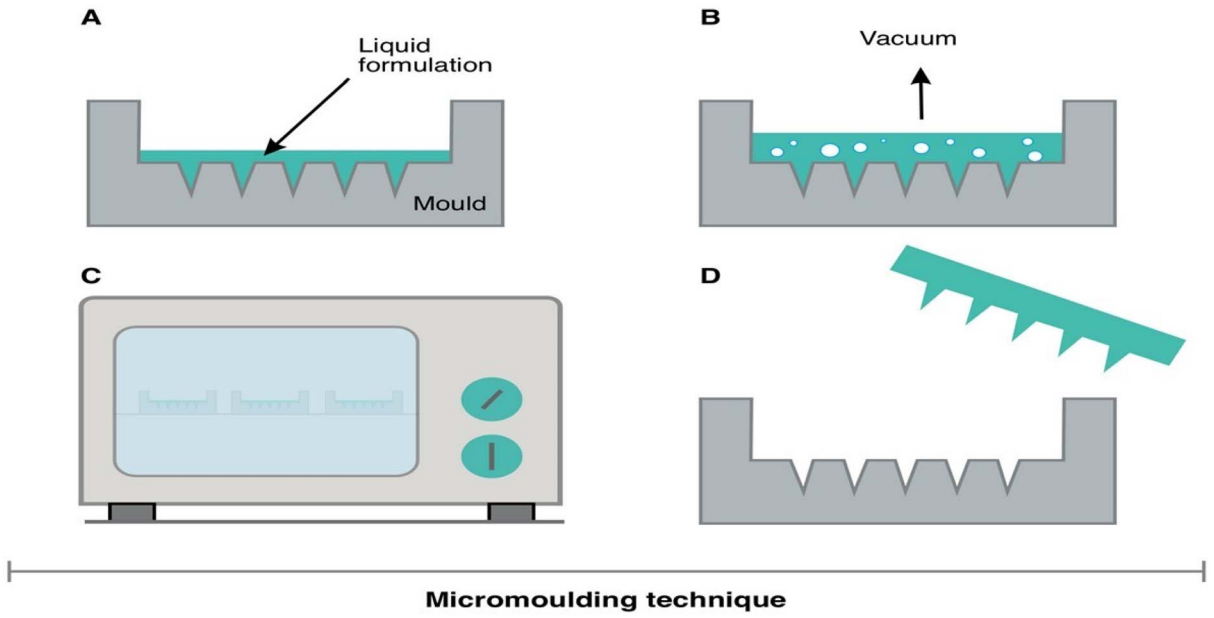

Fig. 3 Polymeric microneedle production with micromolding (A) pouring the liquid polymeric formulation mixture, (B) vacuum degasification, (C) drying and (D) removal of MNs from the mould [Reproduced from[37] under a Creative Commons CC BY 4.0 license].

other soluble particles, is mixed with a polymeric material. The blend is then cast into molds with specific properties and dimensions to obtain the desired PPMN shape. Following MN formation, the porogen is forced to leach out selectively by dissolving it in a suitable solvent, resulting in a porous network inside the polymeric matrix[40,41] (Fig. 4). During porogen leaching, different porosities and pore sizes are produced by elution of the pore-forming agent, which is achieved by adjusting the proportion, type,[18] concentration, and particle size of the porogen.[40,41] However, because organic solvents are used during the preparation process, biocompatibility issues due to organic solvent residues must be considered.[18]

III-Phase separation. Phase separation is a widely used technique for producing polymeric membranes for diverse applications in gas separation, water treatment, the biochemical industry, and the pharmaceutical sector.[42] Phase inversion is a versatile and facile technique for fabricating PPMNs from different polymers, with porosity as high as 90%. This strategy can be used to fabricate PPMNs from a wide range of polymers.[26,43] A variety of approaches can be employed for phase inversion, including:

(i) Thermal-induced phase separation (TIPS): TIPS is an effective method for producing porous membranes.[44] Phase separation can be induced by the removal of thermal energy. This involves dissolving the polymer in a solvent at an elevated temperature and then cooling the solution to induce phase separation, resulting in the formation of a porous structure. The diluent is removed *via* extraction, evaporation, or freeze-drying to obtain the porous membrane.[45] In TIPS, thermodynamic properties, such as those employed in phase diagrams, can greatly affect the pore size and porosity.[44]

(ii) Nonsolvent-induced phase separation (NIPS): The NIPS technique can be applied using three distinct approaches: air-casting of a polymer solution, precipitation from a vapor phase, and immersion precipitation.[45] In the first approach of air-casting, the polymer is first dissolved in a mixture of a volatile solvent and a nonvolatile nonsolvent. As the volatile solvent evaporates, phase separation is induced.[45] During vapor phase-precipitation, nonsolvent vapor infiltrates the polymer solution, promoting phase separation and solidification of the polymer matrix.[42,45] During the immersion precipitation process, the homogeneous polymer solution is cast into a film or molded into an MN shape, briefly exposed to air, and then immersed in a bath of a nonsolvent medium to form the membrane or polymer matrix solution. The nonsolvent causes the polymer to precipitate and solidify, forming a porous structure[26,42] (Fig. 5).

IV-Hot embossing. Hot embossing is a straightforward technique for fusing polymeric powders into the MN's body, enabling the fused powder to form interconnecting pores. A cavity array mold is initially fabricated by laser-drilling aluminum sheets. Then a polymer powder is subsequently positioned on the aluminum mold and gradually compressed using an upper heating block with significant high force (up to 800 Newton). The top heating block is set and maintained at a temperature that is marginally higher than the melting point of the polymer, whereas the bottom block is set to a temperature below the melting point. Consequently, a structure with a gradient porosity higher than 20% is formed[18,26] (Fig. 6). Although the fabrication process is simple and cost-effective,

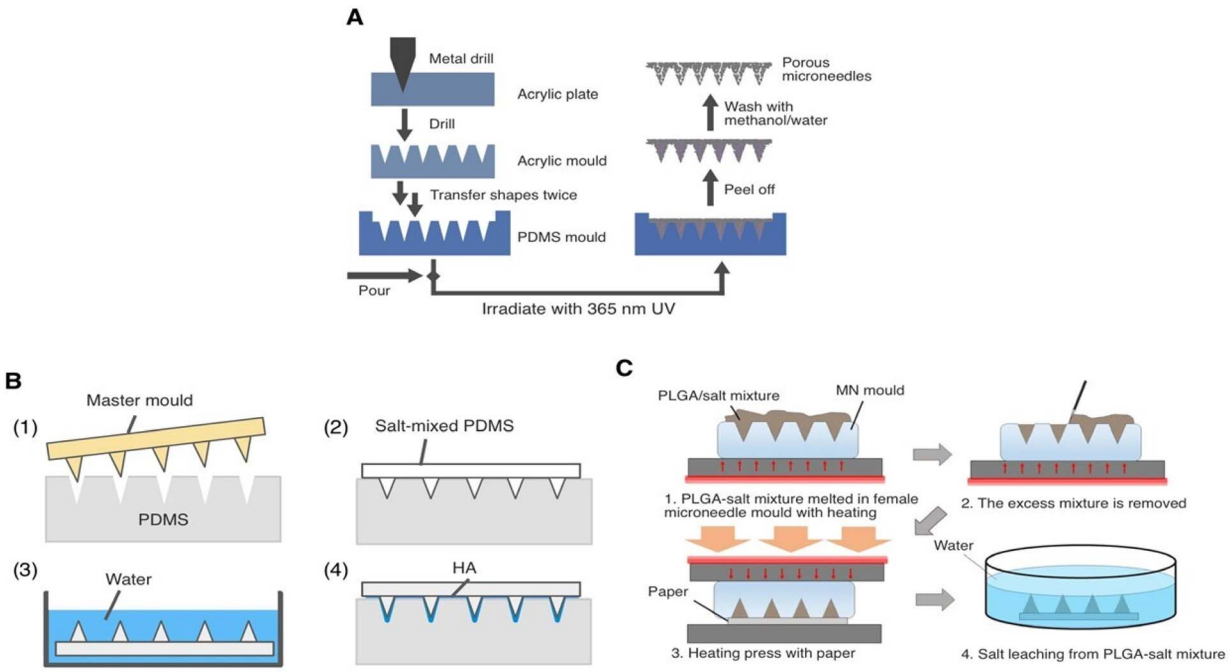

Fig. 4 (A–C) Illustration of porogen leaching process to produce porous microneedles: a polydimethylsiloxane (PDMS) blended with salt eliminated by deionized (DI) water after curing reproduced with permission; c poly (lactic-*co*-glycolic acid) (PLGA)-mixed salt removed by DI water after PLGA solidification [Reproduced from[26] under a Creative Commons CC BY 4.0 license].

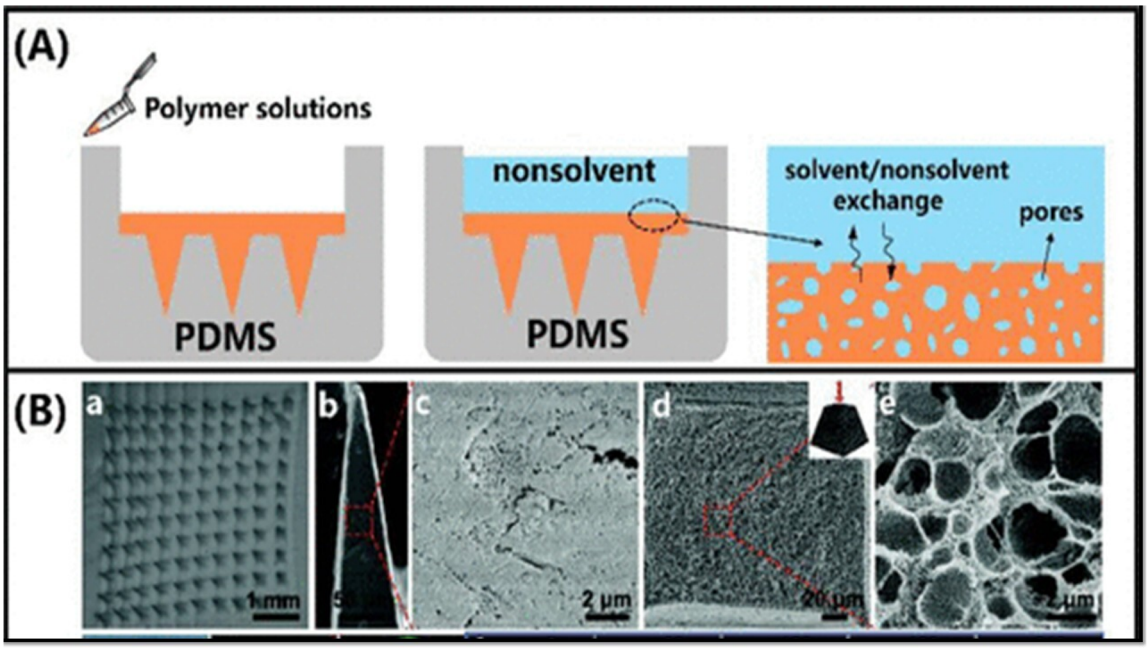

Fig. 5 Process and pictures of PPMNs prepared by the nonsolvent induced phase separation method. (A): The process of preparing PPMNs by nonsolvent induced phase separation. (B): Structural characterization of porous microneedles made of CA (a–e): optical microscopy images of the microneedle arrays (a) and surface (b–c) and cross-sectional (d and e) SEM images of microneedles at different magnifications. Reproduced with permission from[11] [Copyright© 2023, ACS].

achieving perfect control over the temperature, pressure, and duration is challenging.[16,18]

To improve the mechanical strength of the produced MN, hot embossing is usually combined with a coating.[18] Hot embossing is simple and can be introduced in industrialization. Nevertheless, it is challenging to precisely control the temperature, pressure, and time during the process. The high embossing temperature may limit its application because it can affect the pharmacological activity of protein peptides, vaccines, gene therapy pharmaceuticals, nano-formulations, *etc.*[46]

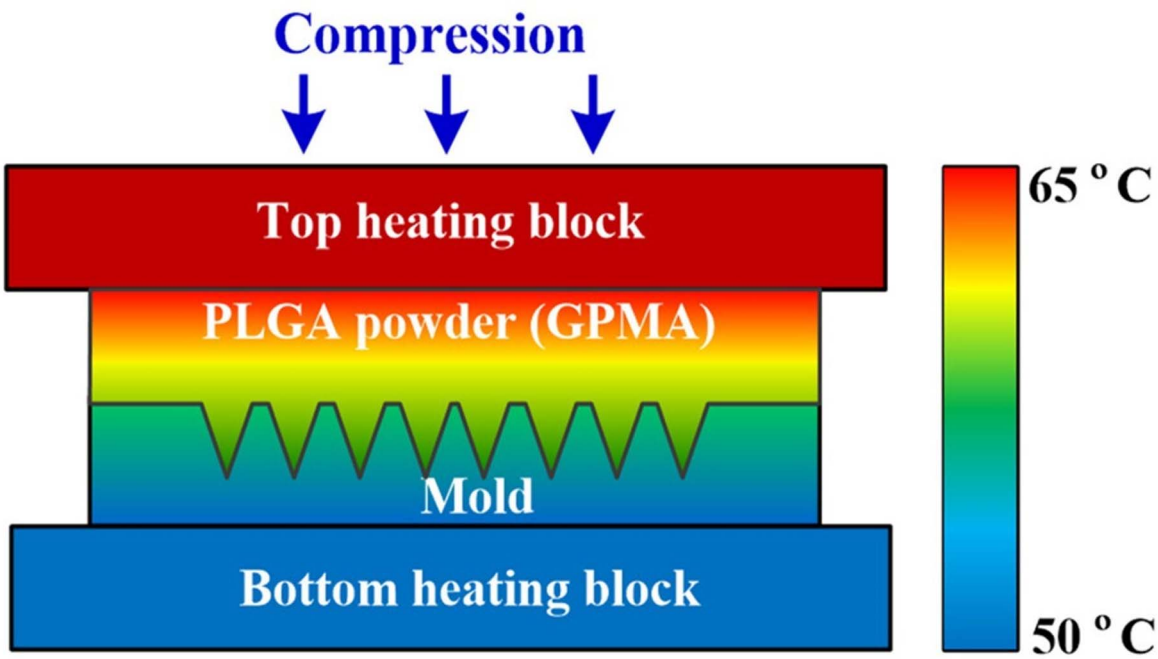

Fig. 6 Schematic illustration of modified hot embossing process setup for the GMPA fabrication. Reproduced with permission from[16] [Copyright ©2019, Elsevier].

V-Freeze-drying (lyophilization). While freeze-drying is a common method for fabrication of large biomolecular drugs, it is rarely used to produce MNs. The primary concept of freeze-drying relies on low-temperature ice crystal sublimation, a process in which water in the material is converted into water vapor by directly sublimating ice particles under high vacuum conditions, resulting in the final drying of the product. This process allows for the fabrication of MNs without destroying heat-sensitive compounds, such as protein peptides at high temperatures[47] (Fig. 7). Once dried, the exceptionally low water content can offer reliable stability and an extended shelf life.[48]

Freeze-drying is a scalable fabrication process in which the process parameters can be adjusted and product quality can be controlled, making it highly suitable for large-scale industrial production.[49] However, it is often reported to be unsuitable because it results in mechanically weak, porous structures caused by water sublimation from a stiff, frozen structure. Therefore, the MN patch production process requires considerable development of specialized formulation and manufacturing processes for each type of medication, particularly vaccines, to preserve stability during manufacture and storage.[46] The use of freeze-drying technology to prepare MNs can potentially improve the transdermal delivery of biotechnology formulations, advancing clinical research and commercialization of MNs in drug delivery.[49]

VI-Emulsion and bonding. The emulsion technique produces biodegradable microspheres that can be placed into an MN mold to form porous structures.[50] The emulsion and bonding technique for fabricating PPMNs involves preparing the emulsion by mixing the polymer and solvents. This emulsion consists of a dispersed phase (the polymer solution) and a continuous phase (usually a nonsolvent) to produce micrometer-sized droplets. If necessary, another emulsification step may be added to create a double emulsion. The emulsion or the double emulsion is then subjected to evaporation to obtain microspheres, which are isolated *via* filtration to yield microparticles with the desired size. This step is followed by casting and pushing processes, which are repeated until the mold is filled with microspheres that solidify into structured shapes resembling MNs. During this stage, the conditions are controlled to ensure the droplets can coalesce into porous structures. Following MN formation, various bonding techniques may be applied to strengthen the MNs, and consequently, pores are formed. These can include thermal bonding or using adhesives to improve the structural integrity and increase the mechanical strength of the MNs. This method is advantageous for its ability to create MNs with tailored properties, such as size, shape, and drug delivery capabilities, while enabling scalability for production.[26]

VII-Chemical blowing. The formation of the internal gaseous phase in polymeric foam material or microstructure is commonly achieved using physical or chemical blowing agents (CBAs) during the manufacturing process. These agents undergo chemical reactions or thermal decomposition, releasing gases that generate the porous structure.[51,52] It is worth noting that CBAs are easily introduced into polymers.

In general, there are two types of CBAs: endothermic CBAs absorb heat continuously during decomposition, whereas exothermic CBAs release heat during decomposition.[52] Gaseous products include nitrogen (N_2), carbon dioxide (CO_2), carbon monoxide, ammonia, and other by-products, with most CBAs releasing N_2 or CO_2 during decomposition. Azodicarbonamide

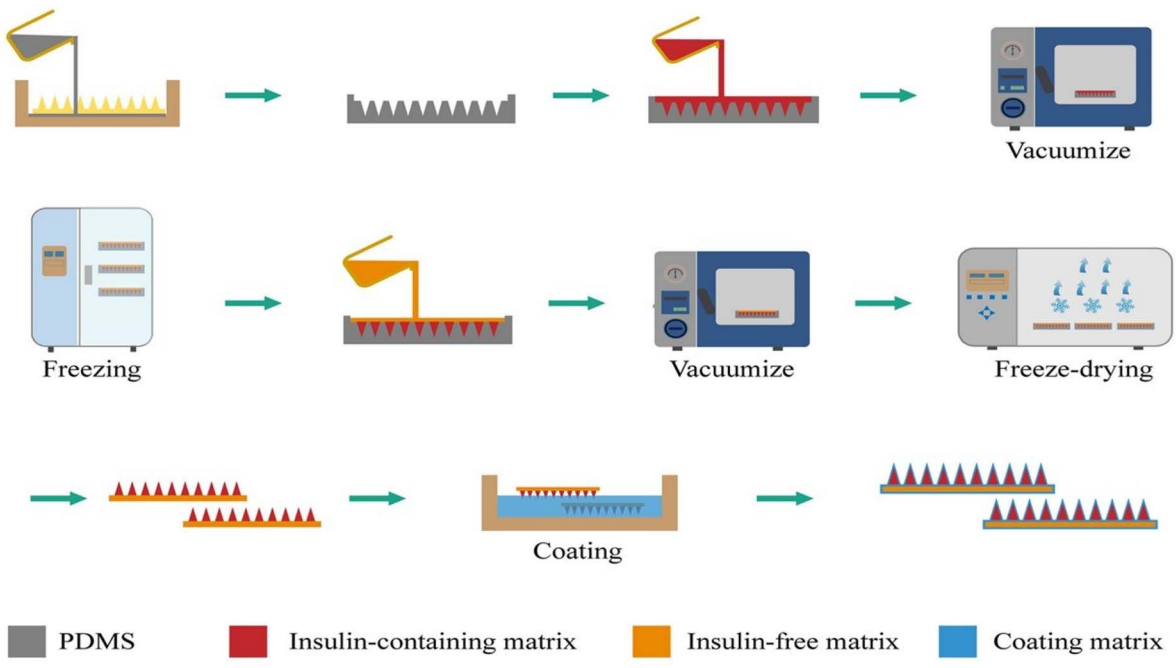

Fig. 7 Schematic illustration of freeze-drying method for fabrication of microneedle loaded with insulin. Reproduced with permission from[49] [Copyright ©2024, Springer Nature].

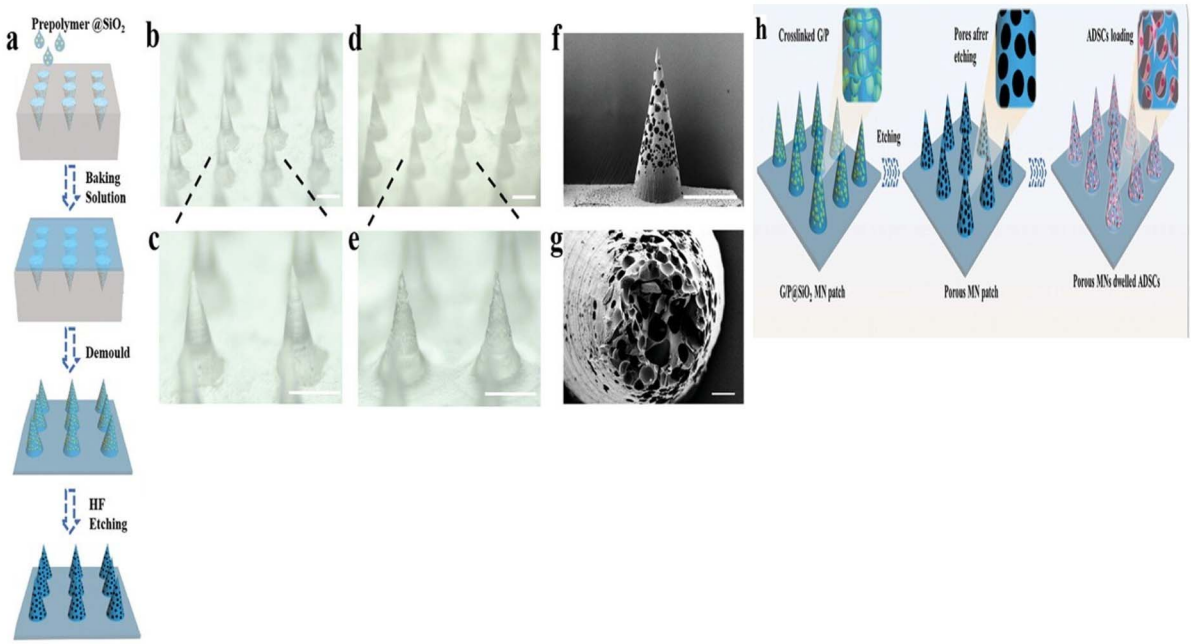

Fig. 8 (a) Scheme of preparation process of porous MN arrays with etching method. (b) Solid MN array without SiO_2 glass spheres etching and (c) local enlarged image; scale bars both are 400 μm. (d) Porous MN array after etching image and (e) local enlarged image; both scale bars are 400 μm. SEM images of (f) side view and (g) cross-sectional view of a needle; scale bar in (f) is 400 μm and in (g) is 50 μm (h) the preparation of porous MNs loaded with ADSCs Reproduced with permission from[77] [Copyright ©2024, John Wiley and Sons].

is the most representative exothermic CBA, often having a high gas yield, whereas sodium bicarbonate and zinc bicarbonate are the most common endothermic CBAs.[53] Other CBAs include isocyanate and water (for polyurethanes, PU), azo-hydrazine and other nitrogen-based materials (used in thermoplastic and elastomeric foams), as well as sodium bicarbonate (for thermoplastic foams). Organic and inorganic CBAs are usually used for the production of closed- and open-cell products, respectively.[54]

VIII-Gas blowing (foaming). The gas blowing process uses a dissolved gas at elevated pressure (physical blowing agent or direct foaming).[55] Saturating the polymer with gas at high pressure and then reducing the pressure rapidly causes the gas to expand, foam, and form a porous core within a compact polymer matrix. However, the mechanical strength may be quite low.[51] Modification in porosity, pore dimensions, and morphology can be achieved by altering processing factors, including the liquid-to-powder ratio, concentration, foaming agent composition, particle sizes of the starting powder, as well as stirring conditions.[51,56]

The gas foaming method typically yields a structure characterized by high porosity and efficiency. The entire process generates minimal pollution, particularly when utilizing an inert gas directly. Tuning viscosity is essential because gas foaming is associated with gelation, which presents challenges for flexible fabrication, particularly in laboratory settings. Low-viscosity blends are detrimental to pore maintenance, whereas a substantial increase in viscosity during gelation inhibits further gel expansion.[57]

IX-Etching. The etching process starts with the fabrication of a template on which the MN patch is designed. This can be executed by several techniques, including photolithography, wax or plastic molding, and laser cutting. Once the template is in place, a chemical etchant, such as hydrofluoric acid or potassium hydroxide, is employed to etch the MNs into the template (Fig. 8 and 9). This process is typically performed using a spray-etching technique, which is a highly precise and controllable method. Etching has two basic types: dry and wet etching. Dry etching uses inert or reactive gases, whereas wet etching uses a chemical etchant for the process. This technique involves using a combination of chemical and mechanical processes to create needles with diameters of <100 μm.[4] Furthermore, high-energy radiation is utilized to break the polymer sample into pieces, producing a trail of broken polymer molecules. Then, an acid or alkaline solution is used to etch the polymer film, which removes the free polymer portions. This method may also be used to get rid of inorganic particles in the polymer composite, which makes the structure more porous. Importantly, the radiation time, inorganic particle size, and etching time all affect the size and form of the pores in the porous structures.[54]

The etching process yields needles of different lengths and shapes depending on the intended purpose. Common forms include hollow or solid cylinders, triangular tips, and conical tips. In addition, the etchant can treat the needle surfaces, resulting in a surface suitable for a variety of applications. The etching method is a cost-effective and efficient way to create MNs.[12]

X-TPP. TPP is a rapid prototyping technique for MN fabrication that has emerged in recent years. It is a powerful method used to produce small features without compromising the resolution. When optimized, it can print structures with a resolution of <100 nm. TPP can be utilized to create MNs with intricate microfluidic channels and micron-scale structures on their sides. The smallest dimension is 1 μm, promoting capillary action on the MN.[20,58] In TPP, rapid prototyping refers to additive manufacturing (AM), which is the layer-by-layer fabrication of three-dimensional (3D) structures using solid, liquid, or powder materials as precursors. AM can be conducted in standard facilities.[59]

TPP initiates resin polymerization *via* multiphoton absorption, facilitated by the excitation of the photoinitiator. A near infrared (NIR) wavelength laser, such as a titanium–sapphire laser, is used in place of UV light. The TPP method facilitates the curing reaction exclusively at the focal point, rather than along the entire illumination path of the laser beam. Thus, the manufacturing of intricate and complex 3D structures is feasible.[7] The unpolymerized material is then removed using a suitable solvent or solution. One advantage of the TPP process is that it enables 3D processing of photosensitive resins, which are transparent to NIR light.[59] However, TPP is limited by its slow printing speed, often necessitating extended periods to produce an MN array.[58,59] Despite this limitation, TPP offers significant advantages, including the ability to be implemented in a conventional clinical setting, such as an outpatient medical office, to create patient-specific medication delivery systems that are tailored to individual anatomical and medical needs. In contrast, many standard MN production procedures demand cleanroom settings and exhibit high energy consumption, reaching up to 10 200 kW m^{-2}. Notably, the processing capabilities of TPP are compatible with scaling for high-throughput commercial production.[59]

XI-Ice templating (freeze-casting). Ice templating, also known as freeze-casting, has been widely applied to fabricate diverse porous materials. As the ice forms and subsequently sublimates, it leaves behind a well-defined porous network. This technique offers highly tunable morphology and has attracted growing interest in various fields, including medicine, food science, and biomedical engineering. Notably, ice-templating methods that rely solely on water are considered safer and more environmentally friendly compared to those involving organic solvents.[51]

Fundamentally, ice crystallization squeezes out other components upon cooling. Following cryogelation and melting of the ice crystals, the sites occupied by ice become pores, thus acquiring a porous structure. Unlike conventional templating, ice templating does not require organic solvents for washing, presenting a green procedure. Because the water is constantly distributed, the formed ice crystals create interconnected porous structures with high porosities for cryogels. The crosslinked polymer possesses good mechanical properties, and the modulus and mechanical strength tend to improve with repeated freeze–thaw cycles. Intriguingly, the polymer crystals can be melted upon heating; thus, the physically crosslinked polymer can thermo-reversibly convert into a polymer solution, showing a repeatable gelation characteristic.[57] The PPMN patch thickness is controlled by molding the solution.[60] This technique is recommended for drug loading in insoluble, soluble,

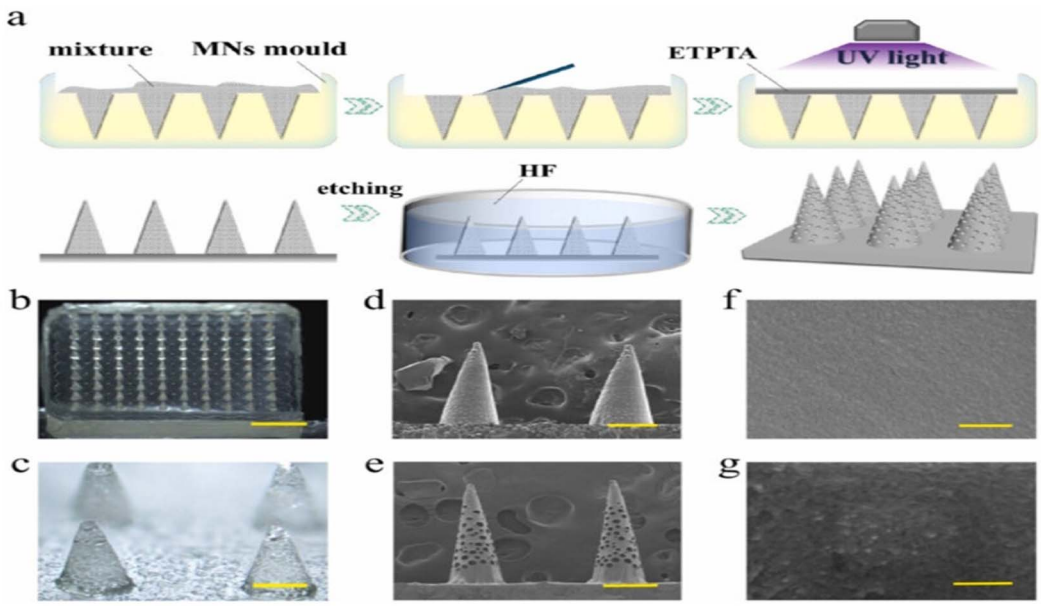

Fig. 9 Fabrication and characterization of the porous MNs. (a) Schematic of the manufacture of the porous MNs array, by replicating glass microspheres filled negative molds with ETPTA. The optical image of (b) the porous MNs array and (c) the magnified MN tips; (d) SEM photo of MNs embedded with glass microspheres; (e) SEM image of the porous MNs after etching by hydrofluoric acid; (f) the pore wall of the porous MNs before PDA coating; (g) surface of the MNs coated with PDA. The scale bars are 2 mm in (b), 350 μm in (c), 300 μm in (d) and (e), 300 nm in (f) and (g). Reproduced with permission from[75] [Copyright ©2021, Elsevier].

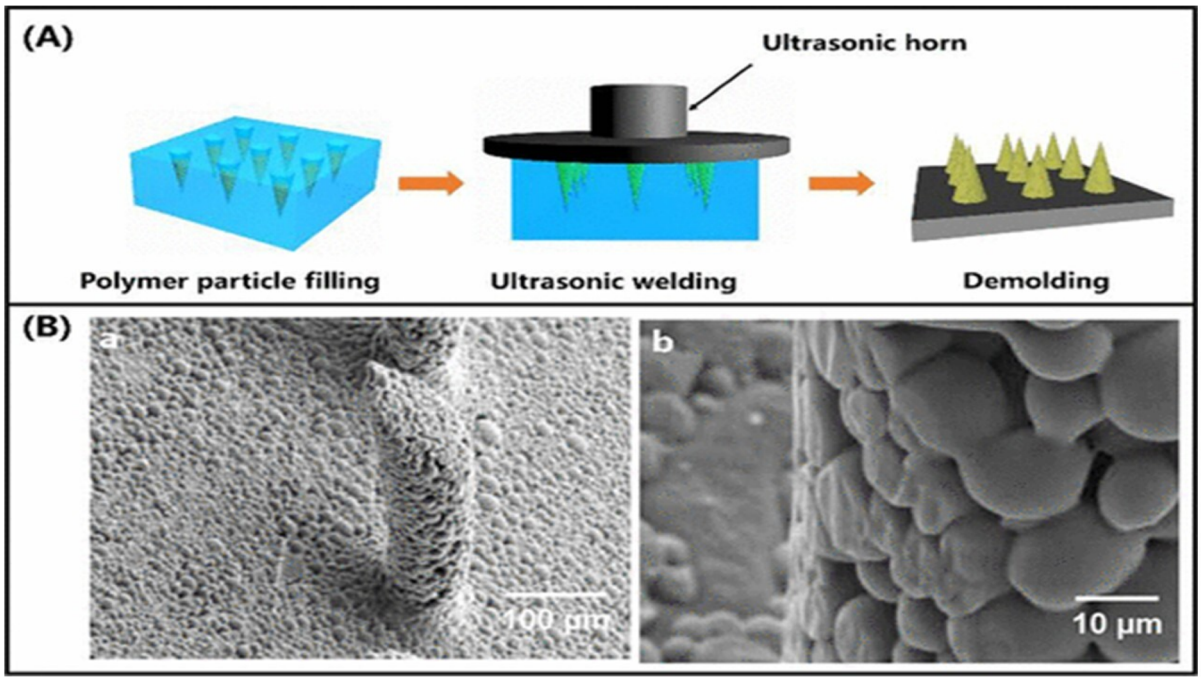

Fig. 10 Process and PPMNs images for the preparation of PPMNs by ultrasonic welding. (A): Ultrasonic welding process for preparing of PPMNs. (B): Porous microstructure fabricated by ultrasonic welding imaged by scanning electron microscopy. (a) A portion of an array of porous, beveled MNs measuring 600 μm in height and 100 μm in base diameter. (b) A magnified view showing the individual PLA microparticles welded together to form the microstructure. Reproduced with permission from[11] [Copyright© 2023, ACS].

and nano systems. This MN preparation procedure requires less time and is therefore simpler than other methods.[18]

XII-Ultrasonic welding. Ultrasonic welding is the fastest available welding technique, with weld times of less than a few seconds. This process involves mechanically vibrating the polymer molecules at high frequencies to form bonds at the microparticle interfaces. Interfacial bonding is primarily achieved by the transfer of energy produced by the vibrating molecules in the polymer, enabling the fabrication of polymeric microstructures with less damage to the encapsulated material (*e.g.*, biological compounds) than would result from high-temperature processes.[61] Fig. 10 depicts the basic principle of the ultrasonic welding method. Mechanical vibration at ultrasonic frequency generates shear force, allowing two surfaces to generate heat *via* friction. The two objects are welded together *via* static pressure, resulting in a porous structure.[11] Microparticles and nanoparticles with fluid-like flow properties can be put into molds and then ultrasonically welded to create polymeric medical devices.[61] This method yields PPMNs with a good needle type and porous structure while eliminating the high-temperature preparation environment. However, although the heating is limited to the particle surface, it may negatively affect the mechanical strength (Table 1).[11]

3-Intended applications

A plethora of research in recent decades has provided substantial evidence for the versatile potential of the MN system, noted for its key attributes in various biomedical applications, such as immunobiological administration, disease diagnosis, cosmetics, and primarily, drug delivery through the skin.[1] Furthermore, PPMNs have been widely used in DD and medical diagnosis owing to their abundant interconnected pores.[18]

I-Drug delivery. The interworking cavity network in PPMNs allows liquid drugs to be loaded *via* impregnation and tissue fluid to be absorbed after penetrating the skin to elute stored dry drugs[33] for easy delivery.[32] Drug transport from PPMNs through the skin primarily involves drug dissolution in interstitial fluid (ISF)-filled pores or on the surface, followed by diffusion through fluid-filled channels.[1] Solid drug powder particles can also be directly deposited from the pores or microchannels of PPMNs. Utilizing a solid drug formulation enhances the loading capacity of PPMNs and broadens the drug types suitable for transdermal delivery *via* this platform. Upon insertion into the skin, ISF within the skin tissue penetrates the MN matrix and dissolves the embedded drug powder. Then the dissolved drug diffuses out to the surrounding tissue, leaving behind a porous framework with interconnected channels.[1] To improve drug delivery efficacy and control the release characteristics of the[84] drugs delivered,[84] researchers have integrated PPMNs with external devices, such as electroosmotic flow-based pumping for controlled transdermal delivery of larger molecules and drug-loaded particles[1] and iontophoresis for collaborative drug delivery.[13] The drug dosage can be controlled using continuous delivery and by adjusting the porosity. The MN backplate thickness, PPMN diameter, and drug concentration largely determine the released dose per time.[84]

Table 1 Representative examples of PPMNs with materials, fabrication method and applications

Material	Method of fabrication	Suggested application	Reference
PLA as a polymer and PEG as a surfactant	Emulsion and bonding	This work created a patch sensor (PMNIA) that uses porous microneedles and an immunochromatographic test to quickly detect anti-SARS-CoV-2 IgM/IgG in cutaneous interstitial fluid	62
PGMA (a mixture of glycidyl methacrylate), TRIM, TEGDMA, and PEG in methoxy ethanol was poured in a PDMS mold	Leaching followed by UV light curing	Integrated to electrode for electrochemical glucose sensing	63
Polydimethylsiloxane (PDMS) precursor and curing agent, and $NaHCO_3$	Chemical blowing	Physiological signal monitoring	64
Poly(vinyl alcohol) (PVA) and poly(vinyl pyrrolidone) (PVP)	Freeze drying	For treatment of ocular diseases such as keratitis or glaucoma	65
PGMA (GMA, monomer), and porogen solution of 10 kDa PEG.	Leaching	Dual-mode delivery of molecules. (Methylene blue, rhodamine B, and fluorescein isothiocyanate–dextran)	66
Biocompatible/photo-curable resin and a colloidal mixture of the solid drug powder	Molding and UV light curing	Large area transdermal delivery of solid drug formulations of lidocaine and ibuprofen	67
PLGA and CMC.	Molding and freeze-drying	The electrical monitoring of the skin condition and iontophoresis for drug delivery and medical diagnosis	68
TRIM and TEGDMA were used as a crosslinker for PGMA as a polymer, and PEG solution in 2-methoxyethanol is used as (as porogen)	Photopolymerization followed by leaching	For rapid fluid transport from and into a body through the skin	69
PLGA and NaCL	Salt leaching and molding	The formed MN was integrated to paper-based bio-sensors for the purpose painless, disposal and fast screening and diagnostic testing for patient, as well as those with prediabetes	70
A nanoscribe polymer (IP–S) was used to create the MNs	Two-photon polymerization (2 PP). The MNs were printed using a 2 PP printer (photonic professional GT2) with a 780 nm laser	Drug delivery and biological sampling	20
Polymer solution made of different polymers (PSF, PLA, and PVDF). PDA and PEG for hydrophilic and anti-adhesive coating	Phase inversion method followed by freeze-drying	Which provides a new way to prepare porous MNs suitable for dermal ISF extraction for POCT.	71
CA and DMSO	Casting and phase separation	Noninvasive quantification of topically applied pharmaceutical products	8
PLGA powders	Hot embossing method	Transdermal insulin delivery	16
CSA solution	Ice templating and freeze-drying	Suitable for insoluble, soluble, and nano system drug loading	60
CA and DSMO	Phase separation method followed by a deacetylation process	Rapid fluid transport suitable drug delivery and ISF sampling	32
PGMA and PEG was used as the porogen	Photopolymerization followed by leaching Then the enzymes were introduced into the porous matrix by immersion to improve reaction efficacy	Microneedle-based sensing with minimally invasive sample has significant implications for point-of-care diagnosis and diabetic health management	72
CA polymer solution, and silica nanoparticles	Direct ink drawing technique	Transdermal collection of ISF for transdermal diagnosis and therapy	73
Mixing the monomer solution GMA, TEGDMA, as cross-linker, and TRIM as a co-cross-linker and 10 kDa PEG solution as a pore forming agent	Leaching process	Dual delivery of a variety of molecules (methylene blue, rhodamine B, and fluorescein isothiocyanate–dextran)	74

Table 1 (*Contd.*)

Material	Method of fabrication	Suggested application	Reference
1% HMPP (v/v) was dissolved in ETPTA (monomer) to achieve a uniform solution, serving as a photo initiator. Glass microspheres were incorporated into the solution with complete mixing to achieve suspension solution	Molding, UV curing, and then chemical etching	Extraction and detection of skin interstitial fluid biomarkers	75
MNA is a mixed product of polydimethylsiloxane and $NaHCO_3$	Chemical blowing	Integrated to electrodes. Porous MNA-based pressure sensor flexible pressure sensors have many potential applications in the monitoring of physiological signals	76
PLGA powders	Hot embossing	Transdermal delivery of rhodamine B (*in vitro*) in the rabbit skin dermis. The GPMA can efficiently administer an insulin solution (*in vivo*) in diabetic rats	16
Salt-mixed liquid PDMS	Salt leaching	ISF is extracted both *in vitro* and *in vivo* by repetitive compressions rather than capillary action. Flexible MNs are effective for continuous blood glucose monitoring, according to the study's findings	21
Polymer microparticles of 1 to 30 μm in size were made from PLA, PGA and PLGA.	Ultrasonically welding	To assess possible applications, microstructures were designed as microneedles for minimally invasive drug delivery	38
The porous MN arrays were fabricated by simply using UV-curable GelMA and PEGDA hybrid mixed with glass microspheres	Template filling, and particle etching method	Porous MNs can act as excellent stem cell scaffolds and will find many practical values in clinic wound healing	77
5% (w/v) solution of either traditional GelMA or porous GelMA at 37°	Molding and blue light curing (405 nm, 30 mW/cm2) for 30 s	PPMN patch with sustained delivery of extracellular vesicles for treatment of severe spinal cord injury	78
A monomer stock solution of (GMA), crosslinker (TRIM), and crosslinker (TEGDMA) A porogen stock (PEG, 10 kDa) A photoinitiator irgacure 184 was added	Molding process and porogen method	For local monitoring of intercellular swelling, edema	79
PGMA and negatively charged hydrogel	Molding process and the porogen method	To induce the EOF for efficient TDD and extraction of ISF	80
PDMS and silica nanoparticle	Casting and etching method	Potential as platforms for biomedical applications such as drug delivery	17
Starch, PVA solution, sulfuric acid, formaldehyde solution (37 wt%), and pentane	Micro-molding and gas blowing (foaming)	Promising application prospects in antibacterial MNs-based sampling and medical devices for biomarker monitoring	81
PGMA	Molding and leaching methods	A wearable patch device for minimally invasive monitoring of *trans*-epidermal potential	82
PGA	Nonsolvent-induced phase separation (NIPS) method	Great potential as a diagnostic device for interstitial fluid (ISF) sampling and diagnosis	83
PP and CBA.	3D PPP technology based on chemical blowing process	Application to various fields	52

II-Biosampling. PPMNs, which have randomly distributed but interconnected pores, extract ISF from the epidermis and dermis *via* capillary action.[69] Their pore structure provides a built-in interface with sensors, allowing them to be directly integrated into an analysis system.[70] This enables the direct transport of absorbed ISF to the sensor for analysis, eliminating the need for an additional extraction step from the MN. Previous research on PPMNs has mainly focused on sample extraction rather than diagnostic applications due to the low liquid volume absorbed.[1,70] Moreover, PPMNs can be used as biosensing devices by connecting them to a lab-on-a-chip for direct analysis of the extracted ISF.[32]

Challenges and limitations

Porous MNs are viewed as a more agile alternative to hollow MNs because they are produced from a porous material that seamlessly integrates MNs with a reservoir function.[1] However, numerous factors, such as the drug binding affinity, geometric design, and surface characteristics of the porous medium, considerably influence the drug adsorption and release processes.[1]

I-PPMN design and insertion ability

The MN structure is another important factor for MN designs because it determines the drug delivery and sampling mechanisms.[15] MN design determines drug release by adjusting several factors, such as the polymeric material composition, fabrication methods, and MN array geometry, including the base diameter, tip radius, height, aspect ratio, inter-needle distance, needle surface density, and base thickness.[85] The PPMN dimensions should be designed according to the biological characteristics of human skin. PPMNs must penetrate the SC to access the epidermis, while avoiding the dermal layer. Therefore, the MN length must exceed the thickness of the SC layer, while remaining less than the combined thickness of the SC and epidermis.[86] In addition, changing the PPMN geometry can alter the mechanical strength and insertion depth, which determines the force required for inserting into the skin.[3] Because of the inherent elasticity of the skin, penetration of PPMNs through the skin is a major challenge influencing the reproducibility of drug release.[85] PPMN skin insertion force is also dictated by the polymer composition and MN geometry, such as the MN wall thickness, wall angle, tip radius, length, and inter-needle space.[85]

II-Porosity and mechanical strength

As a channel-based MN system,[1] pore size and porosity are important parameters of PPMNs that influence the efficacy of drug delivery. The pore size influences the type of drug that can be incorporated because MNs with smaller pore sizes are unsuitable for loading high molecular weight drugs. Consequently, during MN preparation, it is essential to select an appropriate pore size according to specific requirements to ensure that PPMNs possess adequate pore size for drug adsorption. Porosity affects MN loading capacity, with manufacturers favoring larger porosity, particularly for drugs requiring high doses for efficacy. Porosity influences the mechanical strength of PPMNs, with hardness and Young's modulus decreasing as porosity increases. Increased porosity facilitates crack formation, thereby lowering hardness and Young's modulus, which hinders the penetration of PPMNs through the skin.[11]

Because mechanical strength is generally negatively correlated with surface porosity,[18] numerous studies have shown that the mechanical strength of PPMNs can be increased by selecting materials with superior mechanical properties, minimizing overall MN porosity, strategically introducing pores in specific regions of the needle body, or applying coatings to ensure sufficient mechanical strength for effective skin penetration.[11] Another approach to increase the mechanical strength is to fabricate a denser network structure; however, this usually results in a loss of porosity and permeability of the drug load,[11,28] which is not ideal for drugs that require high doses to function.[11] To overcome this issue, hybrid PPMN arrays fabricated using a hard scaffolding material and soft permeable material could provide both greater mechanical stability and efficient drug release abilities.[28] The coating enhances the mechanical strength of MNs while maintaining porosity and functions as a drug carrier to improve the drug loading capacity of MNs. Notably, selecting the appropriate coating formula and coating process is essential to prevent the coating from affecting the sharpness and piercing effect of the MNs.[11] Another suggested approach involves filling the pores of a PPMN array with a hydrogel to facilitate both higher mechanical stability and continuous drug release.[28] The physical properties of PPMNs, such as heat resistance, stiffness, and mechanical strength, are critical for efficient drug delivery.[85] Therefore, improving the mechanical properties of the PPMN material without compromising sample quality or volume is a goal for researchers in this realm.[18,85]

III-Hydrophilicity of the polymeric matrix

A porous polymeric structure is generally composed of a polymer matrix and interconnected pores.[87] PPMNs, characterized by their interlinked architectures, hold significant promise for dermal interstitial fluid (ISF) extraction.[71] Hydrophilicity, defined as the affinity of a material for water molecules, plays a crucial role in this context.[65] Specifically, the hydrophilicity of the PPMN array matrix is vital for effective drug adsorption.[11] Conversely, poor hydrophilicity and inadequate adhesion of polymeric microneedles (PMNs) hinder the extraction rate and recovery of ISF.[71] It is noteworthy that water adsorption in such systems can induce structural alterations, often manifested macroscopically as hygroscopic expansion and a reduction in mechanical stiffness.[88] Importantly, mechanical strength remains a key factor, as it directly impacts product performance, durability, and safety.[87] Furthermore, polymers with hydrophobic surfaces struggle to adsorb drugs and ISF solely through capillary action, thereby limiting their efficiency, particularly with hydrophilic drugs,[19] and greatly restricting their use in microneedles for transdermal delivery and ISF

extraction.[71] Therefore, tailoring the surface functionality of the porous matrix is essential, especially for applications requiring host–guest interactions or stimuli-responsive behavior.[89] To enhance fluid extraction rates and ensure the stability of PPMNs, hydrophilic modification of hydrophobic polymers is a critical and necessary process.[71]

IV-Fabrication technique and industrialization

The main advantage of PPMNs is that their porous structure does not require the micromachining processes used for hollow structures, allowing the use of biodegradable polymers without the risk of broken MNs. However, the formation of the porous structure of PPMN using certain techniques such as phase separation or emulsion methods necessitates strict process conditions, including temperature and time control. Compared to other techniques used to create porous structures, the particle leaching method, which involves blending a matrix material with insoluble particles that are removed after the MNs are formed, has been developed as a simpler method.[90] The variation in pore sizes and porosities of PPMNs can be attained through the use of diverse materials and preparation methods, thereby enhancing the adaptability of PPMNs for various applications.[84]

Organic reagents are an essential component of the pharmaceutical industry and play an important role in manufacturing. The concentration of organic reagent must be carefully controlled in the final pharmaceutical product, as excessive levels can pose health risks to humans. These reagents are frequently used as solvents or porogen leaching processes for the fabrication of PPMNs; however, these reagents may leave residual traces within the microchannels of the PPMNs, potentially introducing hidden risks in drug delivery applications, particularly when loading proteins or other sensitive bioactive compounds. Currently, organic solvents are avoided primarily by altering the preparation method. For example, polymer particles are welded together *via* ultrasonic welding, resulting in a porous structure that does not require the use of organic solvents. However, this approach only welds the particle surfaces together, resulting in MNs with low mechanical strength. To achieve piercing requirements, additional adjustments of preparation conditions are necessary. Similarly, freeze-drying is another nonorganic solvent-based PPMN preparation method. In addition to modifying the preparation process, developing a test technique for determination of organic reagent residues in PPMNs is crucial for ensuring product safety, stability, and efficacy.[11] Indeed, research on PPMNs is still in its early stages, and their industrial production and practical clinical application still show limitations that hinder their development.[18]

Despite certain technical breakthroughs, the industrialization and commercialization of PPMN devices have been impeded for the following reasons. The current PPMN patches are designed to be small, primarily for utilization in *in vivo* experimental tests. Thus, large MN patches should be considered for practical applications involving humans. Moreover, the PPMN patch substrate should be thin and flexible enough to be adhered to the skin. In addition, certain fabrication methods that are suitable for laboratory-scale production may not be feasible for industrial-scale manufacturing. For instance, the relatively high cost of matrix materials and production processes may present significant challenges to large-scale commercialization. Furthermore, sophisticated and time-consuming manufacturing processes with several phases may raise prices while diminishing production efficiency. When integrated into biosensors for early diagnosis, a low price and appropriate reliability are also important in gaining a competitive edge in the current POC device market. In addition, regulations and rules mandate long-term clinical experiments to assess accuracy and reliability that take several years of design time for MN-based sensing systems before commercialization. Furthermore, sterilization, usage, and disposal should be standardized so that customers or patients can handle medical devices appropriately and safely at home.[26]

Conclusion

PPMN systems represent a promising advancement in the field of TDD and biosampling. Polymeric materials have emerged as a promising alternative to conventional MN fabrication materials due to their biocompatibility, biodegradability, and versatility.[31] Porous MNs have lately been explored due to their distinctive and unique qualities. Porous structures inside MNs with continuous nano- or micro-sized holes can transport medications or biofluids by capillary action.[26] This review focused on the fabrication techniques of PPMNs and the associated challenges. Key methods such as phase separation, hot embossing, leaching, etching, and chemical and gas blowing were discussed and compared based on their underlying mechanisms and structural outcomes. Emphasis was placed on the principles guiding pore-formation, alongside an overview of published studies that highlighted the applications of PPMNs in drug delivery, diagnostic biosampling, and transdermal sensing.

In spite of their promise, the PPMN technology form laboratory to commercial scale production faces many challenges. Chief among these is fabricating and developing PPMN arrays with sufficient mechanical strength to pierce the skin without fracturing, and ensuring structural integrity suitable for their intended clinical applications. Nevertheless, PPMNs offer a minimally invasive, patient-compliant, and highly adaptable versatile platform for administering a wide range of therapeutic agents, positioning them as a transformative tool in the future of transdermal therapies.

Abbreviations

3D:	Three-dimensional
API:	Active pharmaceutical ingredient
CA:	Cellulose acetate
CMC:	Carboxymethylcellulose
CSA:	Chondroitin sulfate A sodium salt
DSMO:	Dimethyl sulfoxide

GelMA:	Gelatin methacryloyl
HA:	Hyaluronic acid
MNs:	Microneedles
PAA:	Polyacrylic acid
PCL:	Polycaprolactone
PDA:	Polydopamine
PDMS:	Polydimethylsiloxane
PEG:	Polyethylene glycol
PES:	Polyethersulfone
PEGDA:	Poly(ethylene glycol)diacrylate
PGA:	Polyglycolic acid
PGMA:	Poly(glycidyl methacrylate)
PLA:	Polylactic acid
PLGA:	Poly(lactic-*co*-glycolic acid)
PP:	Polypropylene
PPMNs:	Polymeric porous microneedles
PMMA:	Poly(methyl methacrylate)
PSF:	Polysulfone
PVA:	Polyvinyl alcohol
PVP:	Polyvinylpyrrolidone
PVDF:	Polyvinylidene fluoride
SC:	Stratum corneum
TDD:	Transdermal drug delivery
TDDS:	Transdermal drug delivery system
TRIM:	Trimethylolpropane trimethacrylate
TEGDMA:	Triethylene glycol dimethacrylate

Data availability

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

Conflicts of interest

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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