

Review

Natural Polysaccharide-Based Microneedles for Drug Delivery: Materials, Applications, and Future Perspectives

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Abstract

Transdermal drug delivery is limited by the barrier function of the stratum corneum, which restricts the penetration of many therapeutic agents, whereas hypodermic injection provides efficient drug delivery but is associated with pain and reduced patient acceptability. Microneedle (MN) systems have therefore been investigated as a minimally invasive approach to overcome the stratum corneum and facilitate drug delivery into the skin. Among the materials used for MN fabrication, natural polysaccharides have attracted considerable attention because of their biocompatibility, biodegradability, aqueous processability, and diverse physicochemical properties. In addition, several polysaccharides, including chitosan, hyaluronic acid, and alginate, possess biological properties that may contribute to antimicrobial activity, tissue regeneration, or hemostasis. This review summarizes recent advances in natural polysaccharide-based MN systems, with emphasis on MN types, fabrication methods, material properties, and pharmaceutical applications. Dissolving, hydrogel-forming, and coated MNs are discussed together with fabrication approaches including micromolding, spray coating, and 3D/4D printing. The characteristics and representative applications of hyaluronic acid, chondroitin sulfate, starch, chitosan, cellulose derivatives, alginate, pullulan, dextran, and *Bletilla striata* polysaccharide are reviewed, including their use in insulin delivery, vaccination, cancer therapy, dermatological treatment, and wound healing. Finally, current challenges related to mechanical strength, dissolution behavior, drug loading and uniformity, raw-material variability, moisture sensitivity, manufacturing scalability, and regulatory translation are discussed. Further development of standardized evaluation methods and reproducible manufacturing processes will be important for the pharmaceutical translation of natural polysaccharide-based MN systems.

Keywords: microneedle; natural polysaccharide; transdermal drug delivery; hyaluronic acid; chitosan; dissolving microneedle

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1. Introduction

The skin provides an attractive route for drug administration because it is readily accessible and can permit local or systemic delivery without passage through the gastrointestinal tract [1]. However, transdermal drug delivery is strongly restricted by the stratum corneum, which serves as the principal barrier to the penetration of most therapeutic agents [1]. In particular, hydrophilic compounds and macromolecules generally exhibit

limited passive permeation across intact skin. Conventional topical formulations, such as emulsion gels [2], film-forming gels and hydrogels [3,4], and transdermal patches are therefore suitable only for a relatively limited range of drugs, and various physical and chemical approaches have been investigated to improve skin permeability [1,5].

Microneedles (MNs) have been developed as a minimally invasive approach to overcome the stratum corneum barrier [5]. MN arrays contain micron-scale projections that penetrate the superficial layers of the skin and create pathways for drug delivery while generally causing less pain than conventional hypodermic needles. Depending on their design, MNs can deliver therapeutic agents through transient microchannels, surface coatings, dissolution of the needle matrix, diffusion through swollen hydrogel networks, or direct infusion through hollow structures [5]. These approaches have enabled the delivery of a broad range of compounds, including small-molecule drugs, peptides, proteins, vaccines, and particulate delivery systems. In addition to systemic delivery, MNs have been investigated for localized treatment of dermatological disorders and wounds, where deposition of therapeutic agents directly within or beneath the skin barrier may provide advantages over conventional topical administration [5,6].

A wide variety of materials have been investigated for MN fabrication, including silicon, metals, synthetic polymers, and naturally derived polymers [6]. Material selection is particularly important for dissolving and hydrogel-forming MNs because the physico-chemical properties of the matrix directly affect moldability, mechanical strength, skin insertion, swelling or dissolution, drug release, and storage stability. Natural polysaccharides have received increasing attention in this context owing to their generally favorable biocompatibility, biodegradability, aqueous processability, and chemical functionality. Their abundant hydroxyl, carboxyl, or amino groups also provide opportunities for blending, crosslinking, and chemical modification to adjust mechanical and drug-release properties [6,7].

Several polysaccharides may provide additional biological functions beyond their structural role in the MN matrix. Chitosan (CTS), for example, has been widely investigated because of its antimicrobial, hemostatic, and mucoadhesive properties [8], whereas hyaluronic acid (HA) is a natural component of the extracellular matrix with high water-binding capacity and established roles in tissue hydration and cell–matrix interactions [9]. Alginate is an anionic polysaccharide capable of mild ionic crosslinking with divalent cations, a property that has been exploited to prepare calcium-crosslinked, swellable MN systems [10]. However, these characteristics vary substantially according to the polysaccharide source, molecular weight, degree of substitution or deacetylation, formulation composition, and processing conditions. Therefore, the potential biological activity of a polysaccharide should be distinguished from its primary function as an MN-forming material [7].

A growing number of studies have investigated polysaccharide-based MNs for the delivery of small molecules, proteins, peptides, vaccines, nanoparticles, and other therapeutic agents. Previous reviews have addressed carbohydrate- or polysaccharide-based MNs from different perspectives. Bhadale and Londhe systematically reviewed carbohydrate-based MNs and their materials and applications [7], while Damiri et al. provided an overview of natural polysaccharide-based MNs, including their fabrication, mechanical properties, drug-delivery applications, and translational challenges [11]. More recent reviews have discussed the properties, preparation methods, and therapeutic applications of polysaccharide MNs, including their applications in skin diseases and broader biomedical fields [12,13]. The present review builds on these studies by providing an updated pharmaceutical-development perspective that links polysaccharide-specific material properties and limitations with fabrication strategies, mechanical and moisture-dependent performance, drug loading and biologic stability, manufacturing and quality-control

considerations, and clinical translation. In addition, recent studies published in 2025–2026 and emerging fabrication approaches, including 3D/4D printing, are incorporated to provide an updated assessment of the field.

Accordingly, this review summarizes recent advances in natural polysaccharide-based MNs for drug delivery, with particular emphasis on the relationship between material properties, fabrication strategies, and delivery performance. The principal MN types and fabrication methods relevant to polysaccharide-based systems are first described, followed by the physicochemical and biological characteristics of representative materials, including HA, chondroitin sulfate, starch, chitosan, cellulose derivatives, alginate, pullulan, dextran, and other emerging polysaccharides. Representative applications in peptide and protein delivery, vaccination, dermatological treatment, cancer therapy, and wound healing are subsequently discussed. Finally, current challenges related to mechanical performance, drug loading and uniformity, raw-material variability, moisture sensitivity, manufacturing scale-up, quality control, and regulatory translation are considered [6,7].

Relevant literature was identified through searches of PubMed, Web of Science, and Scopus using combinations of keywords related to microneedles and natural polysaccharides, with studies published through 2026 considered. Original research articles and relevant reviews addressing polysaccharide-based MN materials, fabrication, characterization, drug delivery, and clinical translation were included, whereas studies not directly related to microneedle systems were excluded.

2. Natural Polysaccharide-Based Microneedles

MN systems facilitate transdermal drug delivery by creating transient pathways across the stratum corneum or by directly depositing therapeutic agents within the superficial layers of the skin, depending on the MN design. MN patches generally consist of arrays of microscopic projections that collectively provide a sufficient contact area for drug delivery [5]. The dimensions and geometry of the needles should be carefully controlled to provide adequate mechanical strength and skin penetration while minimizing tissue damage and discomfort. Reported MNs are commonly fabricated with lengths ranging from approximately 150 to 1500 μm and widths of several tens to a few hundred micrometers, although these dimensions vary considerably depending on the MN type and intended application. Needle tips may be designed in conical, pyramidal, cylindrical, triangular, or other geometries. These structural parameters are determined by the fabrication method, delivery mechanism, properties of the matrix material, and characteristics of the incorporated drug [5,6].

Considerable effort has been directed toward improving skin permeability for transdermal drug delivery; however, the stratum corneum remains the principal barrier to the passive transport of many therapeutic agents [14]. MNs provide a minimally invasive approach to overcome this barrier and have been investigated as an alternative to conventional needle-based administration. In particular, their ability to facilitate the delivery of hydrophilic compounds and macromolecules, including peptides, proteins, and vaccines, has contributed to increasing interest in MN-based transdermal delivery systems. The use of natural polysaccharides as MN-forming materials further expands the formulation possibilities because their physicochemical properties can be adjusted to provide suitable mechanical strength, dissolution, swelling, and drug-release characteristics [5,7](Figure 1).

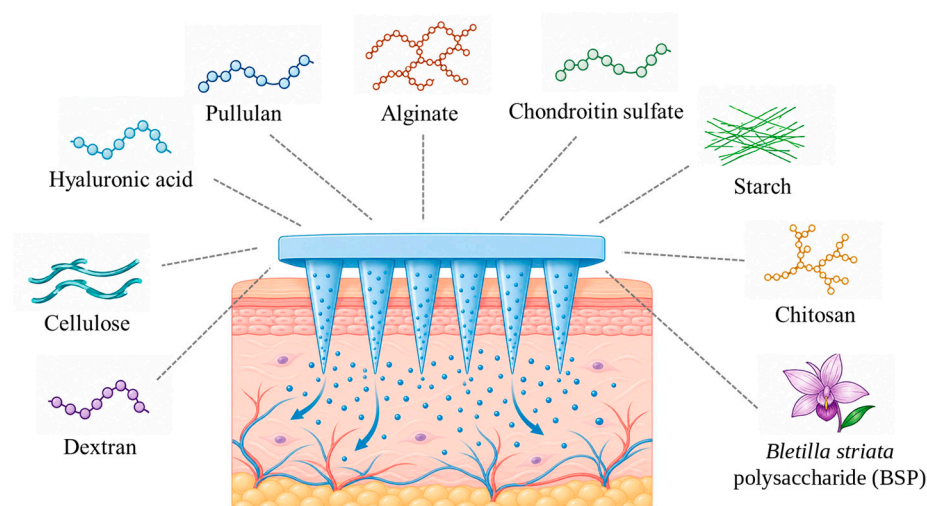


Figure 1. Schematic illustration of transdermal drug delivery using natural polysaccharide-based microneedles. Some graphical elements in this figure were generated with the assistance of ChatGPT (GPT-5, OpenAI), including the skin, microneedles, and selected polymer illustrations. The final figure was assembled and edited by the authors using Microsoft PowerPoint.

2.1. Types of Microneedles

MNs are generally classified into five types according to their structure and drug-delivery mechanism: solid, coated, dissolving, hollow, and hydrogel-forming. Solid MNs are inserted into the skin and subsequently removed, creating transient microchannels through which subsequently applied drugs can permeate. Hollow MNs contain an internal lumen through which liquid formulations can be delivered into the skin by passive flow or externally applied pressure. Hydrogel-forming MNs absorb interstitial fluid after skin insertion and swell to form hydrated polymeric networks, allowing drug molecules to diffuse from the MN matrix or an attached drug reservoir. Dissolving MNs are composed of water-soluble or biodegradable matrices that dissolve or disintegrate upon contact with interstitial fluid, thereby releasing incorporated drugs. Coated MNs consist of solid needles bearing a drug-containing coating that dissolves or detaches following insertion into the skin. These five categories and their principal delivery mechanisms are widely used to describe MN systems [5,6,15,16].

Among these types, natural polysaccharides have been most extensively investigated as matrix-forming materials for dissolving and hydrogel-forming MNs, while they may also be used as formulation or coating components in coated MN systems. Polysaccharides such as HA, alginate, chondroitin sulfate, and suitably processed chitosan derivatives can be formulated into dissolving MN matrices because of their hydrophilicity, biocompatibility, and ability to form polymeric structures with sufficient mechanical integrity. In hydrogel-forming MNs, polysaccharides may be physically or chemically cross-linked to form networks that swell upon exposure to interstitial fluid, and their swelling and crosslinking characteristics can be adjusted to influence drug diffusion and release. In coated MN formulations, polysaccharides and related carbohydrate excipients may also contribute to coating viscosity, film formation, and stabilization of incorporated therapeutic agents. Accordingly, this review focuses primarily on dissolving, hydrogel-forming, and coated MN systems in which natural polysaccharides serve as structural or functional formulation components [7,15,16](Table 1).

Table 1. Microneedle types, fabrication methods, and applicable natural polysaccharides.

Microneedle Type	Key Material Requirements	Applicable Polysaccharides	Advantages and Limitations
Dissolving MN (DMN)	High aqueous solubility enabling complete self-dissolution; sufficient mechanical strength to penetrate the stratum corneum despite high hygroscopicity; low associated toxicity	HA, trehalose, CTS, CMC, sodium alginate, CS (chondroitin sulfate), starch–gelatin blends	Adv.: No tissue residue; low toxicity; cost-effective; simplified dosing (vaccines, local anesthesia). Lim.: Humidity-sensitive; requires dry, cool storage and stabilizers.
Hydrogel-forming MN (HMN)	Tunable swelling capacity and crosslink density; controlled pore size relative to drug size; moldability; ease of sterilization	Methacrylated HA (MeHA); CTS (physical crosslinking); CTS–gelatin–sodium alginate composites	Adv.: High drug-loading capacity; low infection risk; enables interstitial fluid extraction/diagnostics; tunable release via crosslink density. Lim.: Release often depends on an attached reservoir; behavior affected by multiple interacting variables.
Coated MN (CMN)	Coating uniformity; controlled viscosity; stabilizing/thickening function; compatibility with solid MN substrate	Trehalose, dextran, CTS, sucrose (with PVA, PVP, or PLGA)	Adv.: Preserves drug stability; rapid transient release; suited to DNA/protein/peptide/siRNA/vaccine delivery. Lim.: Limited drug-loading capacity; biocompatibility concerns with metal/silicone substrates.

2.1.1. Dissolving Microneedles (DMNs)

Dissolving microneedles (DMNs) operate on a “poke-and-release” principle and are fabricated from water-soluble or biodegradable polymeric materials that dissolve or disintegrate after insertion into the skin. Commonly used materials include synthetic water-soluble polymers such as polyvinylpyrrolidone (PVP) and polyvinyl alcohol (PVA), as well as natural polysaccharides and their derivatives, including hyaluronic acid (HA), chondroitin sulfate, carboxymethyl cellulose (CMC), dextran, pullulan, and chitosan-based materials. Low-molecular-weight carbohydrates such as trehalose may additionally be incorporated as stabilizing excipients, particularly in formulations containing proteins or vaccines [5,7].

DMNs offer several practical advantages because the needle matrix dissolves following insertion, eliminating the need for removal of intact needles and reducing the generation of sharp waste. Micromolding using aqueous polymer solutions is one of the most widely employed fabrication approaches, often combined with vacuum, centrifugation, or pressure-assisted filling to improve mold filling and drug localization. The composition, molecular weight, concentration, and distribution of the polymer within the MN structure influence mechanical strength, dissolution behavior, and drug-release characteristics [17]. These properties have supported the investigation of DMNs for the delivery of small-molecule drugs, peptides, proteins, and vaccines [4,5,7].

However, the use of water-soluble polymer matrices also presents formulation and storage challenges. Many DMN materials are sensitive to environmental moisture, and moisture uptake may alter needle mechanical strength, dimensional stability, and the stability of incorporated drugs. Appropriate control of residual moisture, packaging, and storage conditions is therefore important, particularly for moisture-sensitive formulations. Stabilizing excipients may also be incorporated when required to maintain the stability of labile therapeutic agents during fabrication and storage [7].

2.1.2. Hydrogel-Forming Microneedles (HMNs)

Hydrogel-forming microneedles (HMNs) are fabricated from crosslinked polymer networks that become hydrated and expand upon exposure to interstitial fluid after skin insertion. Depending on the system design, therapeutic agents can either be incorporated within the MN matrix or supplied from a separate reservoir. Hydration of the inserted MNs creates a swollen network that permits drug diffusion toward the underlying skin. The drug-release behavior of HMNs is influenced by several formulation and structural parameters, including polymer molecular weight, swelling capacity, crosslink density, and the physicochemical properties of the incorporated drug [15]. In particular, modulation of crosslink density can alter hydrogel swelling and molecular diffusion, thereby providing a means of adjusting drug-release behavior [15].

Compared with dissolving MNs, HMNs can offer greater flexibility in drug loading when an external reservoir is used, because the delivered dose is not necessarily limited by the volume of the needle matrix itself. Their ability to absorb interstitial fluid also makes HMNs attractive for minimally invasive diagnostic applications [18]. Swollen HMNs can extract interstitial fluid for subsequent analysis of biomarkers such as glucose, and methacrylated hyaluronic acid (MeHA)-based MN patches have been investigated for glucose monitoring in living mice. In such systems, glucose concentrations measured from extracted interstitial fluid showed trends comparable to those obtained using conventional blood glucose measurements, supporting the potential use of HMNs in minimally invasive sensing [15,19].

From a biomaterials perspective, natural polysaccharides can be converted into hydrogel-forming MN matrices through physical or chemical crosslinking. Depending on their chemical structure and formulation conditions, chitosan and other polysaccharides can form networks through hydrogen bonds, electrostatic interactions, or interactions with multivalent ions. Such crosslinking approaches can be used to modify swelling, mechanical properties, and drug-release behavior. However, the suitability of a particular crosslinking strategy depends on the polysaccharide, degree of modification, crosslinking agent, and intended application [7,20].

2.1.3. Coated Microneedles (CMNs)

Coated microneedles (CMNs) consist of solid MNs whose surfaces are coated with a drug-containing solution or dispersion. Following insertion into the skin, the coating dissolves or detaches from the MN surface, allowing the incorporated drug to be deposited within the tissue [16]. The coating formulation typically contains the active agent together with excipients that control viscosity, surface tension, film formation, and drug stability. Commonly used coating excipients include water-soluble polymers such as polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), and carboxymethyl cellulose (CMC), as well as carbohydrates such as trehalose and sucrose. Hyaluronic acid, alginate, and chitosan derivatives have likewise been evaluated for incorporation into MN coating formulations. These excipients may improve the coating uniformity, adhesion, and stability of sensitive therapeutic agents during preparation and storage. CMNs have been investigated for the delivery of small-molecule drugs, proteins, peptides, nucleic acids, and vaccines [16].

Several techniques have been developed to apply drug formulations onto MN surfaces, including dip coating, immersion coating, spray coating, drop coating, and piezoelectric inkjet printing. Among these, dip coating is widely used because of its simplicity and suitability for selectively coating the needle shafts. Coating performance is strongly influenced by formulation properties such as viscosity and surface tension, as well as by needle geometry and the coating method employed. Layer-by-layer approaches based on electrostatic interactions between oppositely charged materials have also been investigated, particularly for macromolecules such as DNA and proteins [16].

A major limitation of CMNs is their relatively low drug-loading capacity because the amount of drug that can be deposited is restricted by the available needle surface area and coating thickness. In addition, nonuniform coating or deposition of the formulation on the patch base rather than the needle shafts can reduce dose reproducibility and delivery efficiency. Consequently, coating composition and process conditions must be carefully optimized to achieve uniform and reproducible drug loading while maintaining the stability of the incorporated therapeutic agent [16].

2.2. Fabrication Methods

The fabrication method plays an important role in determining the structural and functional properties of polysaccharide-based MNs. An appropriate fabrication process should be selected with consideration of the MN design and matrix characteristics, as well as the drug dose, physicochemical properties, intended release pattern, and site of administration. In particular, fabrication conditions can influence needle morphology, mechanical strength, drug distribution, loading capacity, and stability. This section reviews the principal fabrication approaches used for polysaccharide-based MNs, including micromolding and solution casting, coating-based techniques, other physical and chemical processing methods, and emerging 3D and 4D printing technologies, with emphasis on their advantages and limitations in terms of fabrication reproducibility, mechanical performance, drug loading, and scalability [6,7].

2.2.1. Micromolding and Solution Casting

Micromolding is one of the most widely used approaches for fabricating polysaccharide-based MNs and generally involves MN design, preparation of a master structure and negative mold, filling of the mold with a polymer solution, drying or crosslinking, and demolding. A master structure with the desired MN geometry is first fabricated from materials such as silicon or metal using techniques including photolithography, etching, or micromachining. The master structure is then commonly replicated using an elastomeric material, particularly polydimethylsiloxane (PDMS), to produce a negative mold containing the MN cavities. A polysaccharide solution is subsequently introduced into the mold, and vacuum or centrifugation may be applied to facilitate filling of the needle cavities and reduce entrapped air. The filled mold is then dried or crosslinked, depending on the formulation, to form the MN array, which is subsequently removed from the mold [6,7].

PDMS is widely used as a mold material because of its flexibility, low surface energy, and ability to reproduce microscale structures, which facilitate removal of the fabricated MN arrays. Micromolding and solution casting are relatively simple and versatile and are particularly suitable for aqueous polysaccharide formulations. However, incomplete mold filling, air entrapment, and nonuniform distribution of the drug or polymer may occur, particularly with highly viscous formulations. Vacuum- or centrifugation-assisted filling can reduce these problems, although the additional processing steps may increase fabrication time and complicate scale-up. The solidification method is selected according to the properties of the polymer matrix and MN type; dissolving MNs are commonly formed by solvent evaporation or drying, whereas hydrogel-forming systems may require chemical, thermal, or photo-induced crosslinking. These processing conditions can influence MN morphology, residual moisture, drug stability, and mechanical performance [6,7].

2.2.2. Spray Drying and Spray Coating

Atomized spraying involves converting a liquid polysaccharide solution into fine droplets using an atomizing spray and depositing these droplets into an MN mold, followed by drying to solidify the MN array. The principal advantage of this method is that

it can reduce the need for centrifugation or vacuum steps commonly used in conventional micromolding, thereby minimizing processing difficulties associated with solution viscosity and surface tension and providing potential for scale-up. This method has been applied to a range of water-soluble materials, including sugars such as trehalose, fructose, and raffinose and polymers such as PVA, PVP, CMC, hydroxypropyl methylcellulose (HPMC), and sodium alginate [21].

McGrath et al. successfully fabricated dissolving MNs using an atomized spray process and demonstrated that the method could produce both horizontally layered and laminate-layered MN arrays. The resulting MNs exhibited sharp tips and good structural fidelity to the master template, while the composition of the sprayed formulation influenced skin penetration. However, careful control of formulation properties, including viscosity and surface tension, as well as spray conditions, is required to obtain consistent MN structures and reproducible performance [21].

2.2.3. Other Physical and Chemical Processing Methods

Laser cutting is commonly used for the fabrication of metallic MNs, particularly stainless-steel MNs. A two-dimensional MN pattern designed using computer-aided design (CAD) software is cut from a metal sheet using a laser, and the needles can subsequently be bent out of the plane, typically at approximately 90°, to form a three-dimensional MN array. Electropolishing may then be performed to remove surface debris and sharpen the needle tips [6].

In contrast to laser cutting, laser ablation removes material locally from a substrate using focused laser energy and can be used to directly fabricate MN structures or master molds. For example, CO₂ laser ablation has been used to generate MN-shaped cavities in polymer substrates such as poly(methyl methacrylate) (PMMA). The dimensions and surface characteristics of the resulting structures depend on processing parameters such as laser power, scanning speed, and focal conditions [6].

Photolithography and etching are widely used for the fabrication of silicon-based solid and hollow MNs and for the preparation of master structures used in subsequent molding processes. In a typical process, a photoresist is coated onto a substrate, patterned by light exposure through a mask, and developed to define the regions to be etched. The underlying substrate is then selectively removed by wet or dry etching. Wet etching employs liquid chemical etchants and may proceed isotropically or anisotropically depending on the substrate and etchant. For example, potassium hydroxide (KOH) is commonly used for anisotropic etching of crystalline silicon. Dry etching techniques, including reactive ion etching (RIE) and deep reactive ion etching (DRIE), use plasma-based processes and provide greater control over high-aspect-ratio structures. The choice between wet and dry etching depends on the required MN geometry, resolution, substrate material, processing time, and cost [6].

2.2.4. 3D/4D Printing

3D printing constructs three-dimensional objects from computer-aided design (CAD) models through the sequential deposition or solidification of materials, enabling the fabrication of MNs with complex and customizable geometries. Various additive manufacturing techniques have been investigated for MN fabrication, including extrusion-based printing, inkjet printing, stereolithography (SLA), digital light processing (DLP), continuous liquid interface production (CLIP), and two-photon polymerization (TPP) [22].

In extrusion-based 3D printing, a material is deposited through a nozzle to form a structure layer by layer. Fused deposition modeling (FDM), one of the most widely used extrusion-based techniques, involves heating and extruding thermoplastic polymers such as poly(lactic acid) (PLA) and thermoplastic polyurethane. Other extrusion-based

approaches can process hydrogel or polymer formulations without requiring thermo-plastic filaments. For example, cactus-inspired MN scaffolds containing MXene, spidroin, polyurethane, and aloe vera gel have been fabricated using extrusion 3D printing for wound treatment, controlled drug release, and wound-motion monitoring. However, the resolution of extrusion-based printing is generally lower than that of photopolymerization-based techniques, and optimization of nozzle diameter and printing conditions is required to obtain sufficiently sharp MN structures [22,23].

Inkjet (IJ) printing uses controlled droplet deposition, commonly generated using piezoelectric actuation, and can be employed to deposit drug formulations onto preformed MN surfaces. Insulin-loaded coated MNs have been prepared by combining SLA-fabricated MN arrays with inkjet printing, using mannitol, trehalose, or xylitol as carriers to maintain insulin stability and facilitate rapid release [24]. Aerosol jet printing (AJP), which differs from conventional inkjet printing, has also been used for direct fabrication of dissolving MNs. PVP-, trehalose-, and glycerol-containing formulations were aerosolized and deposited to form MN arrays, and process variables including flow rate, temperature, printing speed, and focusing ratio were shown to influence MN quality [25].

There are also several photopolymerization-based techniques (SLA, DLP, CLIP, and TPP). These techniques selectively polymerize photosensitive resins using light to fabricate MNs or master structures with relatively high spatial resolution. SLA generally uses a focused light source to cure a liquid photopolymer according to a CAD design and has been employed to fabricate MN arrays and master molds with various needle heights, shapes, aspect ratios, and spacings. DLP projects patterned light onto an entire layer of photosensitive resin, enabling faster layer formation than point-by-point photopolymerization. The performance of SLA- and DLP-fabricated MNs depends strongly on resin composition, printing resolution, and post-curing conditions, while the biocompatibility of photopolymerizable materials remains an important consideration [22].

Continuous liquid interface production (CLIP) is derived from vat photopolymerization but uses an oxygen-permeable window to maintain an uncured “dead zone” between the window and the growing structure. This enables continuous rather than conventional layer-by-layer fabrication and has been used to produce MN arrays with tunable geometries within several minutes. CLIP can also reduce layer-related surface artifacts, although equipment availability and the range of suitable photopolymerizable materials remain limitations [26].

Two-photon polymerization (TPP) uses a tightly focused femtosecond laser to induce localized polymerization through nonlinear two-photon absorption and is particularly suitable for fabricating highly complex microstructures, including hollow MNs. Under optimized conditions, TPP can achieve feature sizes approaching or below 100 nm, although the practical resolution used for MN fabrication is generally determined by the required structure size and printing time. Its broader application is limited by relatively slow throughput, high equipment cost, and the need to ensure the biocompatibility of photoresins and photoinitiators [22]. For natural polysaccharide-based MNs, additive manufacturing can be performed either by direct printing of polysaccharide-containing formulations or by indirect fabrication using 3D-printed master structures followed by conventional casting. Direct printing requires careful control of formulation viscosity, flow behavior, and shape retention, whereas indirect approaches allow high-resolution master structures to be combined with aqueous polysaccharide formulations. Hybrid strategies combining 3D printing and casting have also recently been investigated for chitosan-based core-shell MNs, enabling spatial separation of drug-loaded compartments and sequential release behavior [27].

Four-dimensional printing extends 3D printing by incorporating stimuli-responsive materials whose shape or functional properties change over time in response to

environmental stimuli. Reported stimuli include temperature, pH, light, humidity, magnetic fields, and electrical signals. In MN systems, this concept has been investigated for stimuli-responsive drug delivery and adaptive structures. In particular, chitosan has been explored as a stimuli-responsive polysaccharide for 4D-printed MN fabrication. Dual-sensitive chitosan-based MNs fabricated by DLP printing exhibited temperature-responsive dimensional changes, improved needle sharpness and mechanical strength, and sustained drug-release behavior [28]. However, 4D-printed MN technology remains at an early stage of development, and further studies are required to improve material design, structural reproducibility, and control of stimulus-responsive drug release [28].

While 3D printing provides considerable design flexibility and opportunities for integrating drug delivery with sensing or other functions, several technical and material limitations remain. High-resolution printing systems can be expensive and time-consuming, and many photopolymerization-based processes rely on a relatively limited range of photosensitive materials. This is particularly relevant to natural polysaccharides, which often require chemical modification, blending, or indirect fabrication through 3D-printed master molds. In extrusion- and jet-based processes, formulation viscosity and nozzle dimensions must also be carefully controlled to prevent clogging and maintain printing accuracy, while processing conditions should be selected to minimize the degradation of incorporated therapeutic agents. Hybrid strategies combining high-resolution 3D printing with conventional micromolding therefore represent a practical approach for expanding the use of polysaccharides in MN fabrication. Stereolithography-based printing with improved resolution has already been applied to the preparation of high-resolution MN master molds, demonstrating the potential of high-resolution additive manufacturing for advanced MN design [22,29].

2.2.5. Crosslinking Strategies for Polysaccharide Hydrogels

The successful fabrication and performance of polysaccharide-based hydrogel MNs are strongly influenced by the crosslinking characteristics of the polymer matrix. Crosslinking affects not only mechanical strength and swelling behavior but also mesh size, drug diffusion, structural stability, and moldability. Polysaccharide hydrogels are generally formed through two major strategies: chemical crosslinking and physical crosslinking [20].

Chemical crosslinking forms covalent bonds between polysaccharide chains through the use of crosslinking agents or chemical reactions, thereby generating a stable three-dimensional hydrogel network. Common approaches include the use of aldehydes, epoxide-based crosslinkers, multifunctional carboxylic acids, and photo-induced crosslinking of chemically modified polysaccharides. For example, glutaraldehyde has been used to crosslink chitosan and other polysaccharides, while methacrylated polysaccharides such as methacrylated hyaluronic acid can be covalently crosslinked by photopolymerization. The mechanical properties, swelling behavior, and degradation characteristics of chemically crosslinked hydrogels can be tuned by adjusting the crosslinking density and reaction conditions. The selection of crosslinking chemistry and reaction conditions should therefore also take into account the intended biomedical application and the associated safety requirements [20].

Physical crosslinking forms hydrogel networks through non-covalent interactions such as hydrogen bonding, ionic or electrostatic interactions, hydrophobic interactions, and metal-ion coordination. A representative example is alginate, which forms ionically crosslinked networks with divalent cations such as Ca^{2+} . Chitosan can also undergo ionic gelation with multivalent anions such as tripolyphosphate. Physical crosslinking generally proceeds under relatively mild conditions and can avoid the use of covalent crosslinking reagents. However, the resulting networks are often more reversible and may

exhibit lower mechanical stability than covalently crosslinked systems, depending on the polymer and crosslinking mechanism [20].

2.3. Key Properties Affecting the Performance of Polysaccharide MNs

The core principle underlying MN technology is that the fine needle structures can penetrate the stratum corneum, the primary barrier of the skin, while generally minimizing the stimulation of deeper nociceptive nerve endings. This property enables minimally painful drug delivery and makes MNs an attractive alternative to conventional transdermal and needle-based delivery systems. The performance of polysaccharide MNs is governed by several design variables, including needle size and shape, array density and arrangement, mechanical strength, and storage stability. These factors influence skin penetration, drug-loading and delivery characteristics, structural integrity, and patient comfort [5,6] (Figure 2).

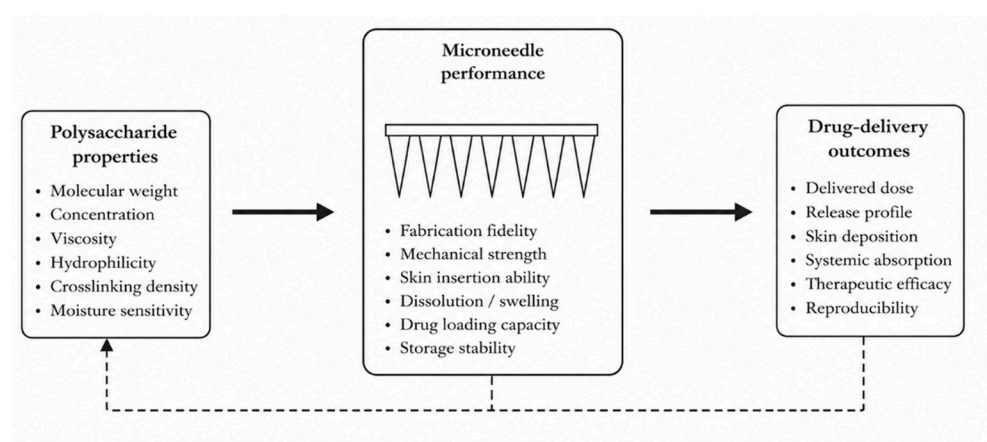


Figure 2. Relationships among polysaccharide properties, microneedle performance, and drug-delivery outcomes. Solid arrows indicate the influence of polysaccharide properties on microneedle performance and subsequent drug-delivery outcomes, while dashed lines represent feedback relationships that guide formulation optimization.

2.3.1. Size and Shape

MN length typically ranges from approximately 150 to 1500 μm , although broader dimensional ranges have been reported depending on the intended application. The needle length should be sufficient to penetrate the stratum corneum and reach the desired skin depth while minimizing the stimulation of deeper nociceptive structures. Needle width or base diameter is also an important determinant of mechanical strength and skin penetration. Smaller dimensions can reduce the force required for skin insertion but may decrease structural strength and increase the risk of bending or fracture. Conversely, increasing the base diameter generally improves mechanical stability but may increase the resistance encountered during insertion. Therefore, MN dimensions should be optimized to balance penetration efficiency, mechanical integrity, and drug-delivery performance [5,6].

Needle geometry also substantially affects mechanical and penetration characteristics [30]. Tapered designs with sharp tips generally reduce the force required to pierce the skin, whereas geometries with larger needle volumes or surface areas may provide greater capacity for drug incorporation or surface coating, depending on the MN type. Hook- or barb-shaped MNs have been developed to improve anchoring and retention within the skin, which may be advantageous when prolonged contact is required. However, the relationship between geometry and performance is complex and cannot be determined solely by the number of edges or vertices. Loizidou et al., using finite element analysis and

computed tomography (CT), reported a linear relationship between the number of vertices of polygonal MN bases and simulated mechanical strength; however, triangular- and square-based MNs showed greater penetration depths than hexagonal MNs in ex vivo porcine skin. Thus, increased geometric complexity does not necessarily result in improved skin penetration [31].

MNs may also be classified as in-plane or out-of-plane according to the orientation of the needle relative to the substrate. In-plane MNs have their longitudinal axis parallel to the substrate surface and can provide considerable flexibility in needle length and integration with microfluidic or sensing components, although the fabrication of high-density two-dimensional arrays can be challenging. Out-of-plane MNs extend perpendicular to the substrate and are more readily fabricated as high-density arrays. With conventional microfabrication techniques, out-of-plane MNs have often been associated with shorter heights and lower aspect ratios than in-plane structures, although these limitations are becoming less restrictive with newer fabrication technologies [6].

Tip geometry is another important determinant of MN insertion and mechanical behavior. Pyramidal and conical MNs are among the most commonly investigated designs; however, their relative mechanical strength and penetration performance depend on base dimensions, the aspect ratio, material properties, and testing conditions, and neither geometry can be considered universally superior. In general, a sharper tip with a smaller tip radius or diameter requires less force to pierce the skin. Studies using single MNs have shown that increasing tip diameter increases the required insertion force and can reduce penetration depth, particularly at low application forces. Consequently, tip sharpness should be optimized together with the overall needle geometry and material strength to achieve reliable skin insertion without fracture [5,6,31].

2.3.2. Mechanical Strength and Skin Insertion Performance

The mechanical strength of MN patches is commonly evaluated by applying an axial compressive force to the entire MN array against a rigid surface and recording the corresponding force-displacement profile. The failure force of the array may be normalized by the number of needles to estimate the average force per needle; however, this approach does not account for variations in mechanical properties among individual needles within the same patch. In addition to compression testing, skin insertion performance is commonly assessed by applying MNs to excised or model skin and subsequently visualizing the resulting micropores using dyes such as methylene blue or trypan blue. Histological or microscopic imaging can also be used to determine penetration depth and structural changes following insertion. AFM has been employed to characterize local mechanical properties of MN materials, although its limited force range makes it less suitable for determining the overall failure strength of conventional MN arrays [6]. Direct comparison of mechanical-strength values reported across different studies should be made with caution because the measured force is strongly influenced by experimental and structural factors. These include needle geometry and tip dimensions, array density, number of needles tested, loading direction and compression speed, failure criterion, and sample-conditioning conditions such as residual moisture and relative humidity. Therefore, mechanical-strength values should be interpreted as study-specific unless these testing conditions are sufficiently comparable [32,33].

A representative study illustrating the influence of polymer molecular weight on MN mechanical properties and drug-delivery performance was reported by Chi et al. HA-MNs prepared using HA with molecular weights of 10, 74, and 290 kDa were loaded with rhodamine B as a model drug. All three formulations exhibited sufficient mechanical strength for skin insertion under the experimental conditions, with the 10 kDa HA-MNs showing the highest compressive strength. Interestingly, the 74 kDa HA-MNs, which

exhibited intermediate mechanical strength, showed the highest transdermal delivery efficiency of rhodamine B in porcine skin and Franz diffusion cell experiments. In vivo fluorescence imaging in mice also demonstrated the highest initial delivery and longest retention of rhodamine B with the 74 kDa HA-MNs. These findings indicate that greater mechanical strength does not necessarily result in greater drug-delivery efficiency and that polymer molecular weight should be optimized by considering both mechanical and delivery characteristics [34].

2.3.3. Moisture Sensitivity and Storage Stability

As noted in Section 2.1.1, many polysaccharide-based MNs, particularly dissolving MNs, are sensitive to environmental moisture because of the hydrophilic nature of their polymer matrices. Moisture uptake can alter the mechanical strength, dimensional stability, and dissolution behavior of the MNs and may also affect the stability of incorporated therapeutic agents. The extent of these effects depends on the type and composition of the polymer matrix as well as the temperature and relative humidity during storage. Appropriate control of moisture and temperature, together with moisture-barrier packaging or desiccants when necessary, is therefore important for maintaining MN performance during storage. Stabilizing excipients may also be incorporated to protect moisture- or temperature-sensitive therapeutic agents. These considerations are particularly important when establishing storage, packaging, transportation, and shelf-life requirements for the clinical and commercial development of polysaccharide-based MN products [7].

2.3.4. Geometric Design Considerations, Summarized

In summary, the design of polysaccharide MNs requires integrated consideration of needle length and width, array density and arrangement, tip geometry, material properties, and the fabrication process, as these factors collectively determine MN performance. MNs must possess sufficient mechanical strength to penetrate the skin and deliver drugs or biomolecules to the intended depth while minimizing tissue damage and discomfort. The mechanical properties and elasticity of the skin should also be considered, as skin deformation during application can reduce the effective penetration depth, particularly for short or blunt needles. At the same time, insufficient mechanical strength may result in needle bending or fracture during insertion. Ultimately, the size, geometry, mechanical strength, and storage stability of polysaccharide MNs should be optimized together to achieve reliable skin penetration, appropriate drug-release behavior, and acceptable patient comfort [5,6].

3. Natural Polysaccharides for Microneedle-Based Drug Delivery

Polysaccharides have been extensively investigated as materials for drug-delivery systems because of their generally favorable biocompatibility, biodegradability, aqueous processability, and diverse physicochemical properties. These characteristics have also led to their widespread use in MN fabrication. Compared with many synthetic polymers, naturally derived polysaccharides offer a broad range of chemical functionalities and can be obtained from plant, animal, algal, and microbial sources. Representative examples include alginate from brown algae; starch, cellulose, and pectin from plants; chitosan derived primarily from chitin in crustacean shells or fungal sources; chondroitin sulfate from animal tissues; and dextran, xanthan gum, and pullulan from microbial fermentation. HA was historically obtained from animal tissues but is now commonly produced by microbial fermentation [9].

These polysaccharides can be used alone or in blends and composite systems, and their molecular weight, functional groups, solubility, viscosity, swelling behavior, and ability to undergo chemical or physical crosslinking can substantially influence MN

fabrication and drug-release characteristics. Polysaccharides also perform diverse biological functions, including structural support, hydration, lubrication, energy storage, and regulation of cellular interactions. In addition, chemical modification provides a means of adjusting their mechanical, swelling, degradation, and biological properties for specific MN applications. The following sections describe the structural characteristics and representative applications of the major polysaccharides investigated for MN-based drug delivery [7,20].

3.1. Hyaluronic Acid (HA)

HA (hyaluronan) is a linear, water-soluble, nonsulfated glycosaminoglycan (GAG) composed of repeating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine linked alternately by β -(1 $\rightarrow$ 3) and β -(1 $\rightarrow$ 4) glycosidic bonds. Its molecular weight varies widely depending on its biological or manufacturing source and may range from approximately 10 to 10,000 kDa. HA is widely distributed in extracellular matrices and biological fluids, with particularly high abundance in the skin, synovial fluid, and vitreous humor. Historically, HA was isolated from animal tissues such as rooster combs, whereas commercial production is now largely based on microbial fermentation. HA is also used in various clinically approved medical products, including dermal fillers and intra-articular preparations [9].

There are physicochemical properties, advantages, and limitations to address with HA as an MN material. HA exhibits favorable biocompatibility and biodegradability together with high water solubility and film-forming ability, making it particularly suitable for dissolving MN fabrication. Its molecular weight and concentration strongly influence solution viscosity, mechanical properties, dissolution behavior, and drug-delivery performance. HA-MNs can dissolve rapidly after insertion into the skin, although the dissolution time depends on the formulation and MN geometry. For example, insulin-loaded HA-MNs reported by Liu et al. dissolved completely within 1 h after application to rat skin, and more than 90% of the incorporated insulin remained after one month of storage at -40 , 4 , 20 , and 40 °C. These results, however, represent formulation-specific findings rather than general properties of all HA-MNs [9,35].

Regarding insulin delivery, insulin-loaded HA-MNs have been investigated as an alternative approach for transdermal insulin administration. In rats, the MNs dissolved completely within 1 h and produced a dose-dependent hypoglycemic effect. Compared with subcutaneous administration of the same insulin dose, MN administration resulted in a lower peak plasma insulin concentration but maintained higher plasma insulin concentrations at later time points, while the overall hypoglycemic effect was comparable to that of subcutaneous injection [35].

In psoriasis treatment, HA-based dissolving MNs have been investigated for intraleisional delivery through the thickened epidermis associated with psoriasis. MTX-loaded HA-MNs successfully penetrated imiquimod-induced psoriatic skin in mice and produced greater therapeutic efficacy than the same dose administered orally [36]. HA-modified MTX-loaded liposomes have also been incorporated into dissolving MNs, where HA-CD44 interactions enhanced cellular association and contributed to reduced erythema, scaling, epidermal thickening, and inflammatory cytokine expression in a psoriasis model [37]. A representative example is the β -elemene-loaded dissolving HA microneedle developed by Wang et al. The MNs successfully penetrated IMQ-induced psoriatic skin and dissolved almost completely within 10 min after insertion. In vivo, HA-ELE-MNs significantly alleviated psoriasis-like symptoms by suppressing keratinocyte proliferation and inflammation and reducing M1 macrophage infiltration [38] (Figure 3A).

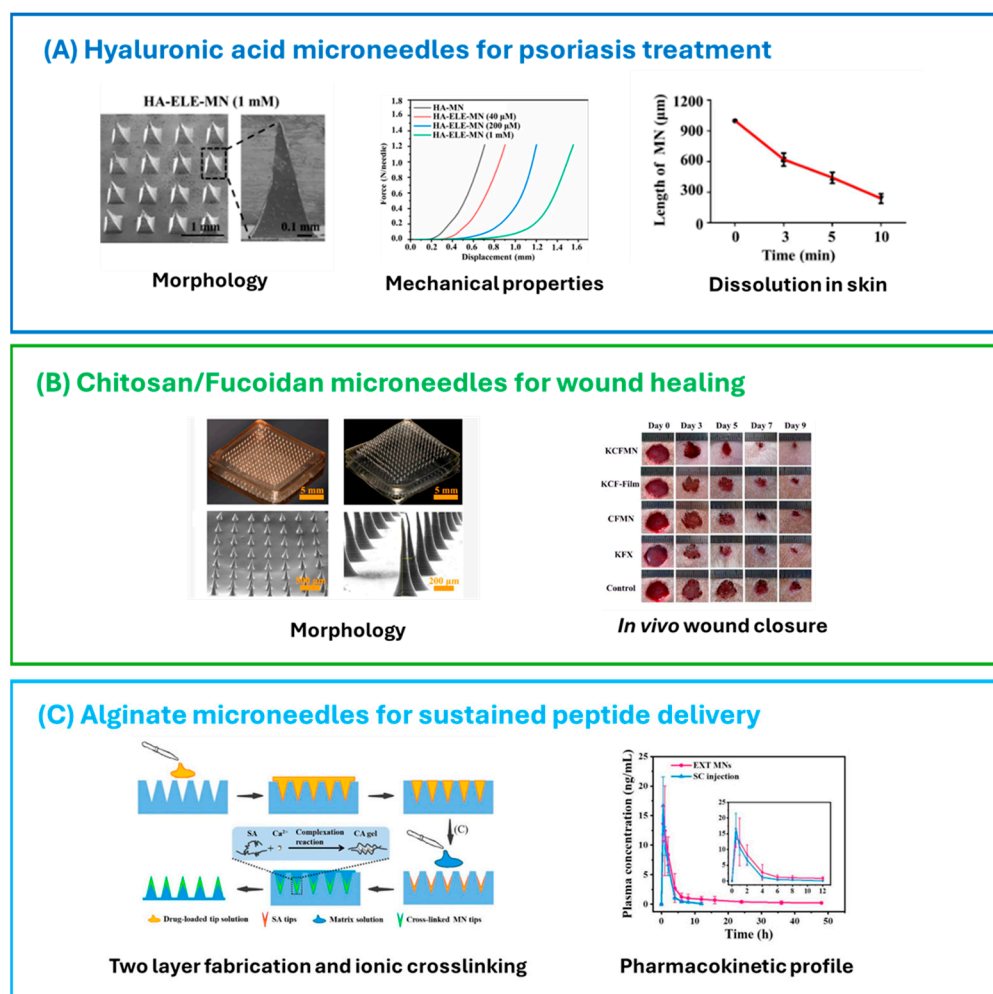


Figure 3. (A) β -Elemene-loaded hyaluronic acid dissolving microneedles for psoriasis treatment. (B) Kangfuxin/chitosan/fucoidan microneedles for wound healing. (C) Two-layer calcium-crosslinked alginate microneedles for sustained exenatide delivery. Panels were reproduced and rearranged from Wang et al. [38], Yu et al. [39], and Liu et al. [40], respectively, under the Creative Commons Attribution 4.0 (CC BY 4.0) license.

More recently, HA-based dissolving MNs have progressed to clinical evaluation. In a randomized controlled study involving 22 patients with 132 paired psoriatic lesions, adjunctive application of HA-based dissolving MN patches enhanced topical drug delivery and resulted in greater improvement in psoriasis severity than topical treatment alone or treatment combined with a no-needle patch. No infection or exacerbation of psoriasis was observed during the study [41].

HA-MNs have also been investigated for localized cancer therapy. Zhu et al. developed 5-aminolevulinic acid (5-ALA)-loaded HA dissolving MNs for photodynamic therapy of superficial tumors. In addition to improving transdermal delivery of 5-ALA, the HA-MN matrix provided an acidic and oxygen-restricted environment that reduced 5-ALA dimerization and the formation of inactive pyrazine derivatives, thereby improving its chemical stability [42]. Other combination approaches include rapidly dissolving HA-MNs co-loaded with p53 DNA and IR820 for combined gene and photothermal therapy [43], as well as HA-MNs incorporating 5-fluorouracil- and indocyanine green-loaded nanoparticles for combined chemotherapy and photothermal therapy of skin tumors [44].

There are also important immunomodulatory effects of HA. The biological effects of HA depend strongly on molecular weight and chemical modification. Low-molecular-weight HA fragments can promote pro-inflammatory signaling and activate macrophages

and dendritic cells through pathways involving Toll-like receptors, whereas high-molecular-weight HA is generally associated with anti-inflammatory or pro-resolving responses. Chemical modification can further alter these responses. For example, reacylated low-molecular-weight HA has been reported to stimulate pro-inflammatory cytokine production, whereas partial N-butyrylation reduced this response. Sulfated HA has also shown anti-inflammatory and immunomodulatory activity. These findings indicate that the immunological effects of HA cannot be generalized solely from its presence in the MN matrix but depend on molecular size, chemical structure, and biological context [45,46].

HA-based dissolving MNs have also been investigated for recombinant adenovirus vaccine delivery. The HA matrix enabled solid-state vaccine incorporation, while the route of administration influenced the resulting immune responses. Sublingual administration produced stronger mucosal and systemic immune responses than transdermal administration, and the solid-state HA formulation showed improved stability under elevated-temperature and freeze–thaw conditions [47].

In ophthalmic applications, HA is attractive for ocular drug delivery because of its biocompatibility, hydration and viscoelastic properties, and natural occurrence in ocular tissues. A dissolving HA-based hybrid MN patch containing curcumin-loaded polymeric micelles reversibly penetrated the corneal epithelium and provided prolonged pre-corneal residence. In a rabbit model of endotoxin-induced uveitis, the MN patch produced greater anti-inflammatory effects than curcumin eye drops [48]. More recently, MnOx-decorated graphdiyne nanozymes were incorporated into HA/PMMA-based ocular MNs for infectious keratitis. The system exhibited antimicrobial and anti-inflammatory effects and showed greater therapeutic efficacy than commercial voriconazole in experimental bacterial and fungal keratitis models [49].

Despite these advantages, the performance of HA-based MNs is strongly dependent on polymer molecular weight, concentration, and chemical modification. These variables can substantially affect solution viscosity, mechanical properties, dissolution behavior, and drug-delivery performance, and the biological effects of HA may also vary according to molecular size and chemical structure. Therefore, formulation-specific optimization is required, and the performance observed for one HA-based MN system should not be generalized to other HA formulations [9,45,46].

Collectively, HA is a versatile material for MN fabrication because of its water solubility, biocompatibility, biodegradability, and readily modifiable physicochemical properties. These characteristics have supported its use in a wide range of experimental MN systems for dermatological [36–38,41], metabolic [35], oncologic [42–44], and ophthalmic [48,49] applications.

3.2. Chondroitin Sulfate (CS)

Chondroitin sulfate (CS) is a sulfated glycosaminoglycan (GAG) composed of repeating disaccharide units of D-glucuronic acid and N-acetyl-D-galactosamine linked alternately by β -(1 $\rightarrow$ 3) and β -(1 $\rightarrow$ 4) glycosidic bonds. CS is a major component of proteoglycans in connective tissues and the extracellular matrix and has traditionally been obtained from animal tissues, including cartilage, porcine skin, bovine trachea, and marine sources. Its structural and physicochemical properties vary depending on the degree and position of sulfation, which are influenced by the biological source. The sulfate and carboxyl groups of CS confer a high degree of hydrophilicity and negative charge, supporting its use as a water-soluble matrix material for dissolving MNs [50].

CS has been used in many drug and vaccine delivery applications: Liu et al. developed rSEB-loaded dissolving MNs composed of 2% chondroitin sulfate and 0.8% trehalose. The MNs penetrated mouse skin to a depth of approximately 260 μ m, dissolved

within several minutes, and significantly prolonged antigen retention in vivo. Full-dose MN immunization provided 100% protection against a lethal SEB toxin challenge in mice [51]. In another study, Fukushima et al. developed two-layered dissolving MNs using chondroitin sulfate or dextran as matrix materials for the delivery of recombinant human growth hormone (rhGH) and desmopressin (DDAVP). For rhGH, the chondroitin sulfate-based MNs achieved a bioavailability of $89.9 \pm 10.0\%$, compared with $72.8 \pm 4.2\%$ for dextran-based MNs, while high drug bioavailability was also observed for DDAVP [52]. Sinomenine hydrochloride-loaded dissolving MNs prepared from PVP and chondroitin sulfate also showed adequate mechanical properties and enhanced transdermal delivery. The needle tips were almost completely dissolved within 4 h after skin insertion, and the drug penetrated to approximately 200 μm beneath the skin surface [53]. More recently, Lin et al. developed flexible tip-concentrated dissolving MNs using chondroitin sulfate and carboxymethyl chitosan as the matrix. A layered design localized the drug predominantly within the needle tips, while photothermal nanoparticles incorporated into the shaft and backing layer enabled light-responsive enhancement of drug release and transdermal delivery. The flexible patch also showed adaptability to curved skin surfaces [54].

Regarding immunomodulatory effects, CS has been reported to modulate inflammatory responses, although its effects depend on the sulfation pattern, molecular structure, and biological context. In macrophages, certain forms of CS suppress NF- κB signaling and reduce the production of pro-inflammatory mediators such as TNF- α , IL-1 β , and IL-6. CS has also been reported to interfere with LPS binding to CD44, thereby attenuating LPS/CD44/NF- κB signaling. However, different CS structures and chemically modified derivatives may exert distinct or even opposing immunological effects. These properties, together with its hydrophilicity and suitability for dissolving MN fabrication, support continued investigation of CS as a matrix material for transdermal drug and vaccine delivery [55].

However, the use of CS as an MN-forming material also presents several limitations. Its molecular structure and sulfation pattern vary according to the biological source, which may influence physicochemical properties and biological activity. In addition, compared with more extensively investigated materials such as HA, the number of studies evaluating CS-based MN systems remains relatively limited, and further studies are required to establish reproducible formulation and manufacturing conditions.

3.3. Starch

Starch is a naturally abundant and biodegradable polysaccharide that has been widely investigated in pharmaceutical and biomedical applications owing to its favorable processability, film-forming ability, and compatibility with other polymeric materials. In MN formulations, starch is often combined with other polymers to improve structural integrity and facilitate dissolution after skin insertion [7].

Zhang et al. developed dissolving microneedles composed of gelatin and starch, incorporating glucose-responsive insulin-releasing gold nanocluster (AuNC) nanocarriers. The incorporated AuNC nanocarriers increased the mechanical strength of the MNs and enabled glucose-responsive insulin release. A single application of the MN patch to diabetic mice maintained blood glucose levels within the normoglycemic range for approximately 1–2 days [56].

Starch–gelatin blends have also been used for the intradermal delivery of losartan. In this system, dissolving gelatin–starch MNs exhibited sufficient mechanical strength to penetrate hypertrophic scar tissue and enhanced local losartan delivery following dissolution of the needle matrix. In a rabbit ear model, losartan-loaded MNs reduced scar elevation, fibrosis, and collagen deposition, demonstrating the potential of starch-containing MNs for localized treatment of hypertrophic scars [57].

More recently, Zhang et al. investigated whole-grain seed-derived starch materials as matrices for dissolving MN fabrication. The resulting MNs showed favorable cytocompatibility and were able to penetrate mouse skin and dissolve rapidly after insertion, with complete dissolution reported within approximately 30 s for selected formulations [58]. This study further demonstrates the feasibility of minimally processed starch-rich natural materials for rapidly dissolving MN systems.

Despite its favorable biodegradability and processability, starch has been less frequently used as a standalone MN-forming material, and reported formulations often combine starch with gelatin or other polymers to obtain adequate structural integrity. Consequently, the mechanical and dissolution properties of starch-containing MNs may reflect the characteristics of the composite formulation rather than starch alone, and further systematic evaluation of starch-specific formulation parameters is required.

3.4. Chitin and Chitosan (CTS)

Chitosan (CTS) is a natural polysaccharide obtained by partial deacetylation of chitin, one of the most abundant natural polysaccharides and a major structural component of crustacean exoskeletons, insect cuticles, and fungal cell walls. During deacetylation, a portion of the N-acetyl-D-glucosamine residues of chitin is converted to D-glucosamine, resulting in a linear copolymer composed of D-glucosamine and N-acetyl-D-glucosamine units linked by β -(1 $\rightarrow$ 4) glycosidic bonds. Commercial CTS is commonly produced by alkaline deacetylation of crustacean-derived chitin, although fungal and other sources are also available. CTS exhibits limited solubility at neutral and basic pH but becomes soluble under acidic conditions as its primary amino groups are protonated. It is biodegradable and can be enzymatically degraded by chitosanase, although the rate of enzymatic degradation depends on its molecular weight, degree of deacetylation, and acetylation pattern [8].

CTS has been widely investigated for biomedical applications because of its biocompatibility, biodegradability, cationic character, film-forming ability, and reported antimicrobial, hemostatic, and wound-healing properties. Under mildly acidic conditions, protonation of the amino groups imparts a positive charge to CTS, enabling electrostatic interactions with negatively charged biological surfaces. This cationic character contributes to its mucoadhesive properties and has also been associated with enhanced epithelial permeability in mucosal drug-delivery systems. However, these biological and formulation properties depend strongly on molecular weight, the degree of deacetylation, concentration, and chemical modification [8].

The mechanical performance of CTS-based MNs is similarly dependent on polymer concentration, molecular weight, the degree of modification, and formulation composition. Blending or coating CTS with other polymers has therefore been investigated to improve mechanical or hydration properties. For example, PLA coating has been used to reinforce CTS MNs with insufficient mechanical strength [59], while CMC–CTS composite MNs showed reduced moisture uptake compared with unmodified CMC MNs [60].

Regarding drug-delivery applications, PVP MNs coated with CTS and PVA have been developed for combined chemo-photothermal delivery of doxorubicin and gold–silica (AuMSS) nanorods. The MNs were fabricated by combining micromolding with electrospraying to form layer-by-layer coatings of doxorubicin-loaded CTS and AuMSS-containing PVA. Under near-infrared irradiation, the system produced a temperature increase of approximately 12 °C and showed controlled drug release associated with the photothermal effect and the pH-responsive behavior of CTS. The MNs were also able to penetrate a tumor-mimicking agarose gel [61]. In another study, CTS MNs containing bovine serum albumin (BSA) as a model hydrophilic macromolecule provided sustained release for at least 8 days, with approximately 95% cumulative release over this period. The

MNs penetrated approximately 250 μm into porcine skin *in vitro* and 200 μm into rat skin *in vivo*, demonstrating the potential of CTS matrices for sustained transdermal delivery of macromolecules [62].

More recently, Babapour et al. developed a dual-release core-shell MN system by combining 3D printing and casting, using a chitosan core surrounded by a PVA/PVP shell. The shell provided relatively rapid release of a hydrophilic model compound, whereas the chitosan core enabled slower release of a hydrophobic model compound over 24 h. This study illustrates the potential of chitosan in compartmentalized MN designs for sequential drug release [27].

There have been many vaccine and immunological applications of CTS. Chen et al. developed implantable CTS MNs containing influenza vaccine. The patch consisted of vaccine-loaded CTS MNs and a dissolvable supporting array that facilitated implantation of the CTS needles into the dermis. After insertion, the supporting array dissolved while the CTS MNs remained within the skin, functioning as an antigen depot and providing immune-enhancing activity. The enhanced immune response became evident approximately 4 weeks after vaccination and persisted for at least 16 weeks. Mice immunized using the CTS MNs were completely protected against subsequent H1N1 viral challenge [63].

CTS has also been incorporated into composite MN systems for wound repair. An MN array patch prepared from a blend of Kangfuxin, CTS, and fucoidan exhibited antibacterial activity and cytocompatibility and accelerated full-thickness wound healing in rats with increased epithelial thickness and collagen deposition [39] (Figure 3B).

In ophthalmic applications, CTS has also attracted interest as a material for ocular drug delivery because of its biocompatibility, biodegradability, mucoadhesive properties, and capacity for chemical modification. Its molecular weight, degree of deacetylation, and chemical substitution can be adjusted to modify solubility, drug interaction, and release characteristics. These properties may be advantageous for MN-based ocular delivery; however, the number of studies specifically evaluating CTS-based ocular MNs remains relatively limited compared with those involving HA-based systems. Therefore, further investigation is required to establish the performance and safety of CTS-based MNs for ocular administration [64].

Important formulation limitations of CTS include its limited solubility at neutral and basic pH and the strong dependence of its properties on molecular weight, the degree of deacetylation, concentration, and chemical modification. In addition, some CTS-based MN formulations may require blending, coating, or other reinforcement strategies to obtain adequate mechanical performance. These characteristics can increase formulation complexity and should be considered when selecting CTS for a specific MN application [8,59,60].

3.5. Cellulose and Its Derivatives

Cellulose is a linear homopolysaccharide composed of β -(1 $\rightarrow$ 4)-linked D-glucose units and is one of the most abundant natural polymers [65]. Extensive intra- and inter-molecular hydrogen bonding contributes to its high crystallinity, chemical stability, and limited solubility in water and most common solvents [65]. Consequently, water-soluble cellulose derivatives, particularly carboxymethyl cellulose (CMC)[66,67] and hydroxypropyl methylcellulose (HPMC)[68,69], have been more extensively investigated for MN fabrication.

There are physicochemical properties, advantages, and limitations of cellulose as an MN material. Chemical substitution of cellulose alters its aqueous solubility, viscosity, film-forming ability, and interactions with incorporated therapeutic agents [65]. These properties influence mold filling, MN morphology, mechanical strength, skin insertion,

dissolution, and drug release [69,70]. Among cellulose derivatives, sodium CMC has been widely used as a matrix material for dissolving MNs because of its aqueous processability and film-forming ability [66,67]. CMC may be used alone, blended with other polymers, incorporated into nanocomposite systems, or used as a supporting layer in multilayer MNs.

In drug-delivery applications, CMC-based MNs have been investigated for the delivery of small molecules, proteins, and other therapeutic agents. Early CMC-based dissolving MNs successfully penetrated skin and preserved approximately 96% of lysozyme activity after two months of storage at room temperature [66]. The mechanical and delivery properties of CMC MNs have been further modified by incorporating sugars [71], layered double hydroxide nanoparticles [72], or PVP [70,73]. Sodium CMC MNs containing diclofenac sodium penetrated ex vivo human skin, dissolved within 10 min in a skin-simulant system, and released approximately 98% of the drug within 40 min [67]. Multilayer designs have also been reported, including donepezil MNs in which HPMC formed the drug-containing tips and CMC served as the supporting base [74].

In biomacromolecule and vaccine delivery applications, gelatin/CMC MNs have been used for insulin delivery and produced hypoglycemic responses in diabetic mice [75,76]. CMC- and hyaluronan-based MNs have also been evaluated for transcutaneous vaccination, with slower dissolution observed in human skin than in rat skin [77]. In addition, CMC MNs containing formalin-inactivated *Aeromonas hydrophila* induced immune responses and protection against bacterial challenge in fish [78].

There are also HPMC and composite MN systems. HPMC is commonly combined with other water-soluble polymers to adjust MN morphology, mechanical strength, dissolution, and drug release [68,69]. HPMC-containing MNs have been investigated for lidocaine hydrochloride [79] and α -arbutin [68] delivery, while formulation variables such as HPMC grade and the HPMC-to-PVP ratio were shown to influence mechanical and dissolution properties [68,69,80]. CMC has also been combined with fucoidan to produce multifunctional MNs, which showed mechanical strength sufficient for insertion and reduced A375 melanoma cell viability in two- and three-dimensional in vitro models [81].

Overall, cellulose derivatives provide considerable flexibility in MN formulation. CMC can function as a sole matrix [66,67], composite component [70,72,73], or supporting layer [74], whereas HPMC is commonly combined with other polymers to modify structural and drug-delivery properties [68,69]. However, native cellulose has limited aqueous solubility, and the performance of cellulose derivatives depends strongly on polymer grade, the degree of substitution, composition, moisture content, and fabrication conditions. High-viscosity formulations may also complicate mold filling and formation of reproducible needle structures. Therefore, individual cellulose derivatives should not be considered interchangeable MN-forming materials.

3.6. Alginate

Alginate is a naturally occurring anionic polysaccharide obtained primarily from brown algae and consists of β -D-mannuronic acid and α -L-guluronic acid residues linked through (1 $\rightarrow$ 4) glycosidic bonds [82]. The relative distribution of mannuronic- and guluronic-acid-rich blocks influences its viscosity, gelation, swelling, and mechanical properties. Alginate is attractive for MN fabrication because of its aqueous processability, biocompatibility, and ability to undergo ionic crosslinking with divalent cations such as Ca^{2+} under mild conditions [82]. These properties have enabled its use in dissolving [83,84], swellable [10], sustained-release [40], and stimulus-responsive [85] MN systems.

There are physicochemical properties, advantages, and limitations of alginate as an MN material. The performance of alginate MNs depends on polymer concentration, molecular characteristics, formulation composition, crosslinking conditions, and drying

processes [10,83,84,86]. Increasing alginate concentration may improve the mechanical strength of dried MNs, whereas excessive viscosity can hinder mold filling and the formation of sharp needle tips [84,86]. Alginate is therefore frequently blended with other polymers [87,88] or sugars [89,90] or subjected to ionic crosslinking [10,40] to improve moldability, mechanical strength, and drug-release behavior.

There are many drug and vaccine delivery applications of alginate. Sodium alginate has been used as a dissolving MN matrix for proteins and small-molecule drugs. Alginate MNs enhanced the transdermal delivery of bovine serum albumin compared with needle-free patches, although their mechanical strength was lower than that of PLGA MNs evaluated under similar conditions [83,84]. Alginate/hyaluronate and calcium-crosslinked alginate/maltose MNs have also been investigated for insulin delivery and produced hypoglycemic effects in diabetic animals [87,89]. Other applications include cetirizine hydrochloride delivery [91] and BCG vaccination using alginate/trehalose MNs, which induced cellular and humoral immune responses comparable with conventional intradermal administration under the tested conditions [90].

Regarding sustained and controlled drug delivery, ionic crosslinking provides an important means of controlling drug release from alginate-based MN systems. Alginate gel layers have been used to reduce drug loss from coated MNs and prolong the release of proteins such as bovine serum albumin and recombinant interferon α -1b [92]. Calcium-crosslinked alginate MNs can swell after skin insertion while maintaining structural integrity, with swelling and drug permeation affected by alginate concentration and crosslinking conditions [10]. A two-layer calcium alginate MN developed for exenatide delivery retained crosslinked drug-loaded tips within the skin after dissolution of the backing layer, providing sustained exenatide release for approximately 48 h and a prolonged hypoglycemic effect [40] (Figure 3C).

Alginate has also been applied in many composite and multifunctional applications. Alginate has been combined with gelatin, synthetic polymers, and nanoparticle systems to improve mechanical properties or provide additional release functions. Alginate–gelatin MNs containing clindamycin inhibited *Cutibacterium acnes* growth without detectable toxicity toward normal human dermal fibroblasts under the tested conditions [88]. Dexamethasone-loaded PLGA nanoparticles incorporated into dissolving alginate MNs enabled rapid nanoparticle deposition followed by sustained drug release for up to approximately 120 h [93]. Fe³⁺-crosslinked alginate MNs have also been developed for light-responsive release of ammonium lactate [85]. More recent applications include blending MNs for vitamin B12 delivery [94], sodium alginate MNs for localized vancomycin delivery [95], and flexible alginate/PVP MN patches designed for delivery to curved anatomical surfaces such as the scalp [96].

More recently, alginate-based hydrogel-forming MNs have been investigated for localized dermal delivery of resveratrol. Mujica et al. prepared 400 μ m MN arrays from alginate alone or in combination with κ -carrageenan and demonstrated effective skin insertion with preferential retention of the delivered compounds within the skin rather than extensive transdermal permeation. These findings highlight the potential of alginate hydrogel-forming MNs for localized dermatological delivery [97].

Overall, alginate is a versatile material for MN fabrication because its dissolution, swelling, mechanical properties, and drug-release behavior can be modified through polymer blending [87,88,94] and ionic crosslinking [10,40,85]. However, its performance depends strongly on polymer concentration, mannuronic-to-guluronic acid composition, molecular weight, crosslinking conditions, moisture content, and accompanying excipients [10,82,84,86]. In particular, the need to balance solution viscosity, moldability, mechanical strength, and crosslinking-dependent swelling or release behavior can

complicate formulation optimization. Thus, the versatility of alginate is accompanied by substantial formulation sensitivity, particularly in crosslinked and sustained-release MN systems.

3.7. Pullulan

Pullulan is a water-soluble microbial polysaccharide produced mainly by *Aureobasidium pullulans* and consists of maltotriose units connected through α -(1 $\rightarrow$ 6) glycosidic linkages [98]. Its high aqueous solubility, film-forming ability, and compatibility with pharmaceutical compounds make it suitable for dissolving MN fabrication under mild aqueous processing conditions [98–100]. However, its hydrophilic nature can also make dried pullulan MNs sensitive to environmental moisture, which may affect mechanical strength and dimensional stability [98–100].

There are physicochemical properties, advantages, and limitations of pullulan as an MN material. The performance of pullulan MNs depends on polymer concentration, molecular weight, drug loading, and drying conditions [98,100,101]. Increasing polymer concentration can improve the formation of complete needle structures and mechanical resistance, whereas excessive viscosity may hinder mold filling and bubble removal [99,100]. Drug incorporation can also influence polymer-chain organization, mechanical strength, and dissolution behavior [100–102]. These formulation variables should therefore be optimized according to the intended therapeutic application.

Regarding drug and peptide delivery applications, pullulan has been used as a dissolving MN matrix for both small molecules and biomacromolecules. Pullulan MNs successfully incorporated fluorescein sodium, fluorescein-labeled bovine serum albumin, and insulin, penetrated *ex vivo* porcine skin, and enhanced transdermal delivery compared with corresponding needle-free formulations [99]. Insulin-loaded pullulan MNs also showed sufficient mechanical strength for skin penetration and maintained insulin stability during aqueous fabrication [100]. More recently, lidocaine-loaded pullulan MNs penetrated excised human skin, dissolved rapidly after insertion, and released pharmacologically active lidocaine [101].

In vaccine delivery applications, pullulan-based dissolving MNs have also been investigated for influenza vaccination [103,104]. Trehalose/pullulan MNs penetrated *ex vivo* human skin and dissolved within approximately 15 min, with trehalose serving primarily as a stabilizing excipient and pullulan as the structural matrix [103]. Further process optimization enabled the preparation of whole-inactivated influenza-vaccine-loaded pullulan MNs using an automated dispensing approach that reduced antigen waste [104]. The vaccine retained hemagglutination activity during four weeks of storage at room temperature and 37 °C under the investigated conditions [104].

In wound-healing and multifunctional applications, pullulan has been used to incorporate multiple therapeutic agents and nanoparticle systems within dissolving MNs [102,105]. A pullulan MN patch containing thrombin, lidocaine, and moxifloxacin-loaded chitosan/fucoidan nanoparticles provided differential drug release and accelerated wound closure in mice [102]. In another system, LL37-loaded zeolitic imidazolate framework-8 nanoparticles and Prussian blue nanozymes were incorporated into pullulan MNs for infected wound treatment, resulting in reduced inflammation and enhanced angiogenesis, collagen deposition, re-epithelialization, and wound closure in rats [105].

Overall, pullulan is a versatile matrix for rapidly dissolving MNs containing small molecules [99,101], peptides, proteins [99,100], vaccines [103,104], and nanoparticle-based therapeutics [102,105]. Its aqueous processability and rapid dissolution are advantageous for drug delivery, whereas polymer concentration, molecular weight, residual moisture, incorporated excipients, and storage conditions should be carefully controlled to maintain reproducible mechanical and dissolution properties [99,100,104]. Accordingly, the high

water solubility that enables rapid dissolution is accompanied by sensitivity to moisture and formulation viscosity, which may limit processing robustness and storage stability unless these variables are carefully controlled.

3.8. Other Emerging Polysaccharides

In addition to the more extensively investigated polysaccharides described above, xanthan gum [106,107], dextran [108–111], gum arabic [112], and *Bletilla striata* polysaccharide (BSP) [113–115] have been explored as MN-forming materials or functional components of MN formulations. However, the extent of their application and supporting evidence varies among these materials. Dextran and BSP have been directly used as structural matrices for MN fabrication, whereas xanthan gum has mainly been investigated as a viscosity-modifying excipient in coated MN formulations. Gum arabic has also been explored in MN systems, although the number of reported applications remains relatively limited. These differences should be considered when comparing the functions and potential applications of emerging natural polysaccharides in MN-based drug delivery.

3.8.1. Xanthan Gum

Xanthan gum is a high-molecular-weight microbial polysaccharide characterized by strong viscosity-enhancing and shear-thinning properties [106,107]. These rheological characteristics are useful in coated MN formulations where appropriate viscosity is required to maintain the coating on the MN surface while allowing uniform application during processing.

In coating and vaccine applications, xanthan gum has been investigated as a viscosity enhancer in coating formulations for influenza vaccines [106,107]. In an influenza virus-like particle vaccine formulation, replacement of CMC with xanthan gum resulted in somewhat greater retention of hemagglutinin activity after drying; however, the coating dose obtained with xanthan gum was substantially lower than that achieved with CMC, and CMC was therefore selected for subsequent formulation development [106]. In another study, xanthan gum at 0.075% *w/v* was combined with trehalose in a whole-inactivated influenza vaccine coating formulation. Under matched-viscosity conditions, the xanthan-gum-containing formulation retained approximately 81% of hemagglutinin activity after drying, compared with approximately 45–56% for trehalose alone [107]. These findings indicate that viscosity modification can contribute to vaccine stability during drying, although coating performance depends on both rheological and formulation properties.

Overall, current evidence supports xanthan gum primarily as a viscosity-modifying excipient for coated MNs rather than as an independently established structural matrix for dissolving MN fabrication [106,107]. Its high viscosity at relatively low concentrations may complicate mold filling and therefore requires careful formulation optimization.

3.8.2. Dextran

Dextran has been investigated in MN systems as a water-soluble dissolving matrix [108], whereas chemically modified derivatives such as dextran methacrylate (DexMA) can form crosslinked hydrogel MNs for sustained or controlled drug delivery [109].

In drug-delivery applications with dextran, two-layer dissolving dextran MNs were developed for percutaneous delivery of sumatriptan and successfully delivered the drug following application to rat abdominal skin [108]. The dextran MNs had a mean length of approximately 495 μm and achieved a bioavailability of $93.6 \pm 10.2\%$, while sumatriptan remained stable in the dried MNs for three months under the evaluated storage conditions [108]. Chemical modification has also expanded the application of dextran to hydrogel systems. Photocrosslinkable DexMA MNs containing doxorubicin and trametinib enabled

continuous local drug delivery and showed greater inhibition of melanoma growth with the combined treatment than with the individual drugs [109].

In composite and therapeutic applications, dextran has also been incorporated into multicomponent MN matrices. Dextran-modified PVA/PVP dissolving MNs containing hesperidin showed adequate mechanical strength and enhanced local drug delivery in an imiquimod-induced psoriasis model, resulting in reduced epidermal hyperplasia and inflammatory cell infiltration [110]. Because dextran was combined with PVA and PVP, the performance of this system reflects the properties of the composite matrix rather than dextran alone. More recently, a DexMA-based hydrogel MN patch was developed to co-deliver safflower polysaccharide and ROS-responsive tetramethylpyrazine-loaded micelles for diabetic wound repair [111]. The multifunctional system reduced oxidative stress and inflammation and promoted neurovascular regeneration and wound healing in diabetic rats [111].

Overall, dextran is a versatile MN material that can be used either as a water-soluble matrix for dissolving MNs or, following chemical modification, as a crosslinked hydrogel for sustained and multifunctional drug delivery [108–111]. Its performance can be further adjusted through polymer modification and combination with synthetic polymers, therapeutic polysaccharides, or responsive nanocarriers.

3.8.3. Other Polysaccharides

Gum arabic is a branched plant-derived polysaccharide containing both carbohydrate and protein fractions and exhibits high water solubility and film-forming ability [112]. A double-layer gum arabic MN patch was developed for transdermal delivery of sumatriptan, with the drug preferentially localized in the needle-containing layer to minimize unnecessary drug retention in the supporting layer [112]. The resulting MNs exhibited sufficient mechanical properties for skin insertion and enhanced transdermal drug delivery, supporting the potential of gum arabic as a dissolving MN matrix [112]. However, its application in MN systems remains relatively limited.

Bletilla striata polysaccharide (BSP) is a plant-derived glucomannan obtained from the tubers of *Bletilla striata* and has been investigated as a dissolving MN-forming material [113–115]. BSP alone formed MNs with suitable moldability and mechanical strength for skin penetration and gradually dissolved after insertion, enabling the release of rhodamine B as a model compound [113]. BSP MNs were subsequently investigated for transdermal delivery of a model protein antigen, demonstrating their potential for macromolecule and vaccine delivery [114].

More recently, BSP has been incorporated into multifunctional MN systems for wound repair [115]. A pH-responsive BSP-based MN patch containing astragaloside IV-loaded ZIF-8 nanoparticles provided enhanced drug release under mildly acidic conditions. In full-thickness wound and rabbit-ear scar models, the system accelerated wound healing and reduced hypertrophic scar formation [115]. These findings indicate that BSP can serve both as an MN-forming matrix and as a component of multifunctional wound-healing systems.

Overall, emerging polysaccharides provide additional options for adjusting the rheological, mechanical, dissolution, and drug-release properties of MN formulations. Xanthan gum has mainly been investigated as a viscosity-modifying excipient for coated MNs [106,107], whereas dextran can be used as either a dissolving matrix or a chemically modified hydrogel network [108–111]. Gum arabic and BSP have demonstrated direct MN-forming ability, although their formulation characteristics, long-term stability, and manufacturing reproducibility remain less extensively investigated than those of more established materials such as HA, CMC, and alginate [112–115]. To facilitate a practical comparison among polysaccharide-based MN systems, representative quantitative performance

parameters, including skin penetration, dissolution or release time, bioavailability, and storage stability, are summarized in Table 2.

Table 2. Representative studies of natural polysaccharide-based microneedles.

Polysaccharide	Microneedle Type	Polymer/Formulation	Therapeutic Agent	Application	Representative Quantitative Findings	Ref.
HA	Dissolving MN	Hyaluronic acid	β -Elemene	Psoriasis	Almost complete dissolution within 10 min	[38]
CS	Dissolving MN	CS/trehalose	rSEB	Vaccination	~260 μ m penetration; dissolution within several minutes	[51]
Chitosan	MN	Chitosan	BSA	Macromolecule delivery	~95% release over 8 days; ~200–250 μ m penetration	[62]
CMC	Dissolving MN	CMC	Diclofenac sodium	Anti-inflammatory delivery	Dissolution within ~10 min; ~98% release within 40 min	[67]
Alginate	Crosslinked MN	Calcium-crosslinked alginate	Exenatide	Diabetes	Sustained release for ~48 h	[40]
Pullulan	Dissolving MN	Trehalose/pullulan	Influenza vaccine	Vaccination	Dissolution within ~15 min; activity retained for 4 weeks	[103,104]
Dextran	Two-layer dissolving MN	Dextran	Sumatriptan	Migraine	93.6 $\pm$ 10.2% bioavailability; 3-month stability	[108]

Note: The quantitative values were obtained under different formulation, microneedle geometry, skin model, and experimental conditions and therefore should be interpreted as representative study-specific findings rather than direct head-to-head comparisons among polysaccharides.

4. Conclusions and Future Perspectives

Natural polysaccharides offer several advantages as MN-forming materials, including biocompatibility, aqueous processability, chemical functionality, and suitability for the delivery of small molecules, proteins, peptides, vaccines, and particulate carriers. HA, chondroitin sulfate, starch, chitosan, cellulose derivatives, alginate, pullulan, and other polysaccharides have been investigated in dissolving, hydrogel-forming, implantable, and coated MN systems. Nevertheless, successful pharmaceutical development requires coordinated control of mechanical performance, dissolution or swelling, drug loading, raw-material quality, storage stability, manufacturing reproducibility, and clinical safety.

A major formulation challenge is achieving an appropriate balance between mechanical strength and dissolution or swelling after skin insertion. Increasing polymer concentration, molecular weight, or crosslinking density may improve structural strength but can also increase solution viscosity, can hinder uniform mold filling [10,99,116], and may delay dissolution or drug release [69]. Blending polysaccharides with sugars [71,89,103], proteins [88], synthetic polymers [70,96], or reinforcing nanoparticles [72] has been used to improve this balance. Mechanical strength, however, should not be considered independently of skin insertion because measured performance is influenced by MN geometry and testing conditions [32,33]. Standardized evaluation should therefore combine mechanical testing with insertion depth and efficiency, dissolution or swelling in skin, and actual dose delivery.

Drug-loading capacity and uniformity also remain important limitations, particularly for therapeutics requiring relatively high doses. Excessive drug loading can disrupt the polymer matrix, reduce mechanical strength [74,116], promote crystallization [17], or result in nonuniform distribution between the needle and backing layers [79,101]. Tip loading and multilayer fabrication can reduce drug loss [54,74,112], whereas nanoparticles and other carriers can provide sustained release after rapid deposition from dissolving

MNs [93,102,105]. These approaches, however, increase formulation complexity. A quality-by-design approach may therefore be useful for defining acceptable ranges for polymer composition, drug loading, mechanical strength, insertion, dissolution, and content uniformity [116,117]. Stability of proteins [66], peptides [75,100], and vaccines [103,104] also requires particular attention because drying, residual moisture, interfacial stress, and polymer–drug interactions may affect biological activity even when total drug content is maintained. Accordingly, formulation variables such as pH, polymer concentration, drying temperature and time, and residual moisture should be carefully optimized. Stabilizing excipients, including sugars such as trehalose or sucrose, may be incorporated when appropriate to reduce loss of biological activity during drying and storage. In addition to drug content, stability evaluation should include biological activity or antigenicity and, where relevant, assessment of aggregation or degradation. These parameters should be evaluated together with residual moisture under appropriate long-term and accelerated storage conditions.

The natural origin of polysaccharides introduces additional challenges related to raw-material variability. Molecular weight, branching, degree of substitution or deacetylation, monosaccharide composition, and impurity profiles can vary according to biological source and processing conditions [65,82,98]. Relevant structural and rheological characteristics should therefore be included in raw-material specifications together with appropriate control of bioburden, endotoxin, residual proteins, and other source-related impurities. Moisture is another important variable because water uptake can alter stiffness and dissolution behavior [32,118]. Appropriate residual-moisture specifications, moisture-barrier packaging, and, where necessary, desiccants should therefore be established through long-term and accelerated stability studies.

Translation from laboratory-scale fabrication to reproducible manufacturing remains a major challenge. Manual casting, centrifugation, vacuum filling, and prolonged drying can introduce variability in mold filling, needle geometry, drug distribution, and dose recovery. Scalable molding and pressure-assisted filling processes have demonstrated the potential to increase production throughput [119], while automated dispensing has reduced formulation waste during pullulan-based vaccine MN fabrication [104]. Nevertheless, process standardization, drying, microbial control, in-line quality assessment, and suitable manufacturing infrastructure remain important considerations [120]. Quality-control strategies should include MN dimensions and tip integrity, drug content and uniformity, residual moisture, mechanical strength, skin insertion, dissolution or swelling, microbial quality, and packaging integrity [33,116,117,120].

Clinical studies provide important evidence for the broader feasibility of MN-based drug delivery. A phase 1 trial of a dissolving influenza vaccine MN patch demonstrated acceptable safety and tolerability, immunogenicity comparable with intramuscular vaccination, and feasibility of self-administration [121]. More recently, a phase 1/2 trial conducted in The Gambia demonstrated the safety and immunogenicity of a measles and rubella vaccine MN patch in adults, toddlers, and infants [122]. These studies support the clinical feasibility of microneedle-based vaccination; however, they should be considered platform-level clinical evidence rather than direct validation of the specific natural polysaccharide matrices discussed in this review. Most natural polysaccharide-based MN systems remain at the *in vitro* or preclinical stage. Therefore, polymer-specific clinical evaluation is still required to establish delivered-dose reproducibility, local tolerability, repeated-application safety, biodegradation or residual material, storage stability, and clinical efficacy.

In summary, natural polysaccharides provide a versatile materials platform for MN-based drug delivery, but their advantages must be supported by reproducible pharmaceutical quality. Future development should move beyond proof-of-concept formulation

studies toward standardized raw-material and product specifications and quality-by-design-based control of polymer composition, mechanical performance, skin insertion, dissolution or swelling, and delivered dose. Greater emphasis should also be placed on scalable and automated manufacturing, appropriate in-line quality assessment, and stabilization and packaging strategies for moisture-sensitive formulations and biologics. Finally, successful clinical translation of natural polysaccharide-based microneedles (MNs) requires polymer-specific clinical trials that account for the distinct properties of individual materials, alongside rigorous evaluations of dose reproducibility, repeated-use safety, stability, user compliance, and therapeutic efficacy.

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