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Research Progress on Chitosan Microneedle Arrays in Transdermal Drug Delivery

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Abstract: As a type of transdermal drug delivery system (TDDS), Microneedles (MNs) have garnered significant attention from researchers due to their ability to penetrate the stratum corneum (SC) of the skin, enhance drug permeability and bioavailability, avoid first-pass metabolism, and cause minimal damage to the skin. This makes them particularly suitable for localized transdermal drug delivery. Dissolvable microneedles (DMNs) can encapsulate sensitive particles, provide high drug-loading capacity, and possess biodegradability and biocompatibility, attracting extensive research interest. Chitosan (CS) has been selected as the matrix for manufacturing DMNs due to its excellent properties, including not eliciting an immune response in vivo and having active functional groups such as hydroxyl and amino groups that allow for modifications to impart appropriate mechanical strength and functionality to DMNs for specific applications. This paper provides a comprehensive review of the research status of various chitosan-based microneedles (CSMNs), explores the mechanisms of their dissolution in vivo, and discusses their applications in promoting wound healing, delivering macromolecular drugs, vaccine delivery, and anti-tumor therapies.

Keywords: transdermal drug delivery, microneedles, dissolvable microneedles, chitosan, chitosan-based microneedles

Introduction

Compared to traditional drug delivery methods, the transdermal drug delivery system (TDDS) offers advantages such as avoiding first-pass metabolism and providing prolonged, stable control of drug input rates.[1] TDDS can control drug delivery through the skin at a determined rate to achieve systemic circulation, maintaining the actual clinical concentration over a prolonged period.[2] TDDS includes various methods such as patches,[3] creams,[4] and subcutaneous injections.[5] However, subcutaneous injections can cause pain and discomfort, leading to low patient compliance. The skin serves as a barrier against external environmental stimuli. It comprises the stratum corneum (SC), epidermis, and dermis.[6] The unique structure of the SC limits the penetration of most drugs, posing significant challenges in designing topical formulation.[7,8] The presence of the SC adversely affects the drug penetration rate and drug utilization rate of patches and creams. Compounds that improve penetration are known as "skin enhancers" or "penetration enhancers", but some may disrupt the skin barrier, leading to cytotoxicity.[9,10] Researchers have already attempted various methods such as liposomes,[11] nanoparticles,[12] vesicles.[13] Iontophoresis[14] and sonophoresis[15] to overcome the permeation barrier of the stratum corneum (SC).[16] However, the poor efficiency of traditional transdermal drug delivery strategies, the high cost of expensive equipment, and the painful and invasive treatment process result in low patient compliance. Therefore, there is an urgent need to develop advanced transdermal drug delivery strategies.

Microneedles (MNs), as a novel drug delivery system composed of an array of microneedles, have garnered significant attention due to their minimally invasive nature, ease of use, localized and controlled drug delivery, and excellent drug loading capabilities.[17] Based on the aforementioned advantages, microneedles (MNs) have gained significant attention in the treatment of various diseases, particularly chronic conditions such as diabetes.[18] MNs can be classified into solid microneedles,[19] coated microneedles,[20] dissolvable microneedles,[21] and hollow microneedles.[22] The classification is shown in Figure 1. Solid MNs

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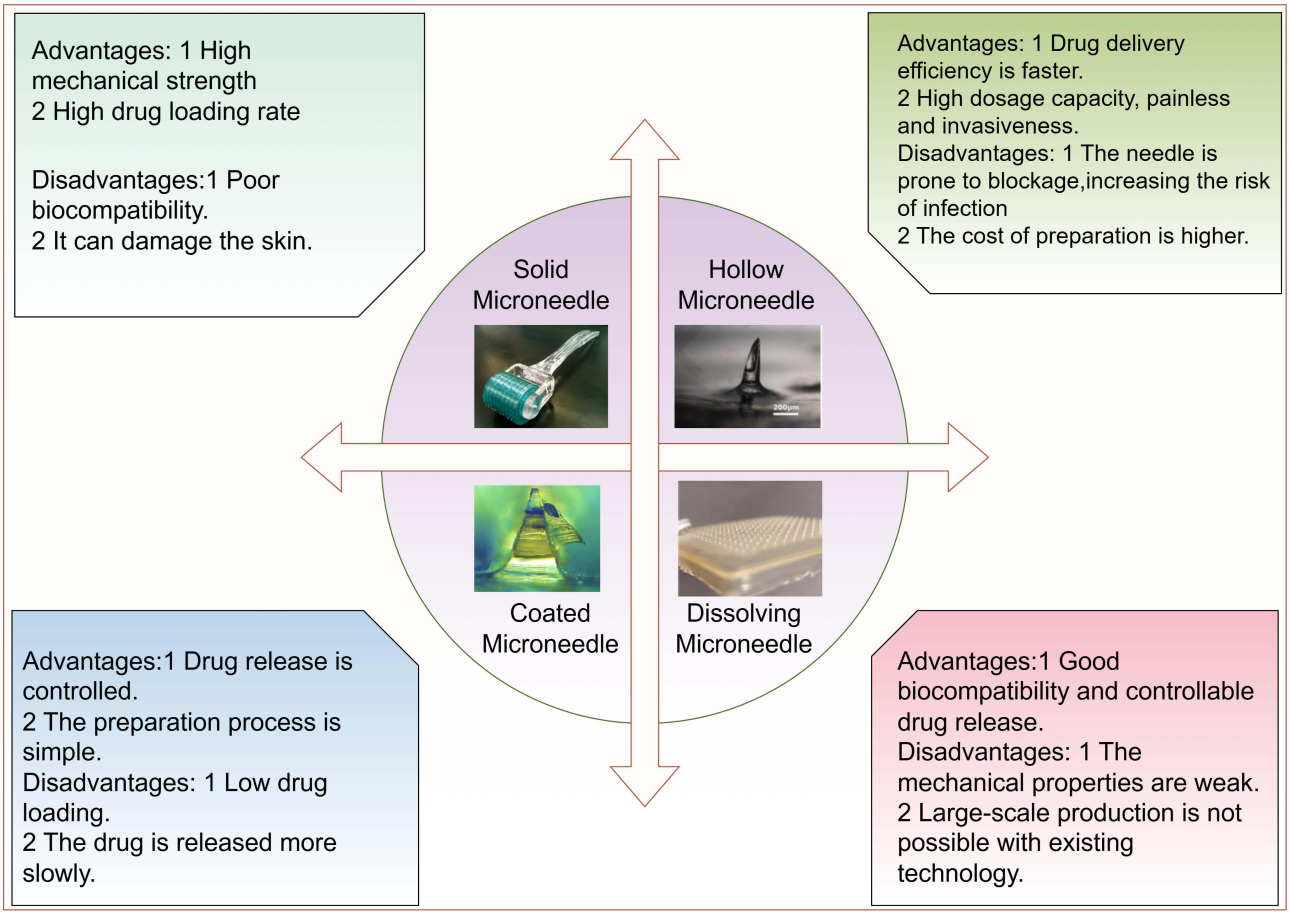

Figure 1 The specific classification of microneedles and the advantages and disadvantages of each type of microneedling.

are the earliest type of microneedles and are classified into silicon and metal microneedles based on the materials used. Solid microneedles are primarily utilized to create microchannels in the skin, through which therapeutic solutions can be applied. However, they tend to cause significant skin damage, and the wounds created can easily become infected during the healing process.[23] Hollow MNs are designed with a hollow structure within the microneedle, serving as a conduit for drug delivery. When these MNs penetrate the stratum corneum, drugs can be released and delivered into the body through these channels. They function similarly to micrometer-sized injection needles. Hollow MNs offer advantages such as high dosage capacity, painlessness, minimal invasiveness, and high efficiency. Nonetheless, they are prone to clogging during skin penetration, which not only impedes subsequent drug delivery but also increases the risk of infection.[24] Coated MNs were developed based on solid MNs. Drugs are coated on the surface of the needles. Upon penetration into the skin, the coated drugs dissolve into the interstitial fluid, achieving the desired therapeutic effect. However, the low drug loading capacity of coated MNs limits their application.[25] Dissolvable microneedles (DMNs) are composed of biodegradable polymers. Once inserted, the microneedles rapidly dissolve in the skin, releasing the encapsulated drugs. They cause minimal harm to patients and generate less medical waste.[26] Among these, DMNs are particularly notable for their ability to encapsulate sensitive particles, provide high drug loading capacity, and biodegrade without leaving harmful residues, thus causing minimal damage to the skin compared to other types of microneedles.[27] DMNs are primarily fabricated from natural polymers that possess characteristics such as solubility, biocompatibility, biodegradability, and processability. Among them, synthetic polymers such as polylactic acid (PLA), polyvinylpyrrolidone (PVP), and polyvinyl alcohol (PVA) are widely used as matrices for dissolvable microneedles (DMNs).[28] Although PLA possesses excellent biocompatibility and biodegradability, it also has certain drawbacks, including bio-inertness, hydrophobicity, and low degradation and cell adhesion rates due to the acidic byproducts of its degradation.[29–31] PVP is a commonly used material for the fabrication of dissolvable microneedles (DMNs) due to its excellent biocompatibility

and high mechanical strength. However, its high molecular weight can hinder renal clearance, leading to accumulation within the body, which may negatively impact health.[32] PVA is also a commonly used material for the fabrication of dissolvable microneedles (DMNs) due to its strong water retention capacity and thermal stability. However, PVA has limited mechanical strength, making it insufficient for penetrating the stratum corneum to achieve transdermal drug delivery. Additionally, its poor water solubility slows the drug release rate.[33] Therefore, the selection of DMN matrices is gradually shifting towards natural polymers.

About CS

Among natural polymers, polysaccharides are frequently used as the base for microneedles for drug delivery, including chitosan (CS), hyaluronic acid, Starch and dextran. Polysaccharides are non-toxic, readily available, and possess various pharmacological properties, such as prolonged drug efficacy and enhanced drug absorption, making them widely used in the preparation of DMNs.[34,35] Among these, Starch is a naturally occurring, non-cytotoxic, and biodegradable polysaccharide. Due to its non-polluting, renewable, and low-cost properties, it is frequently used as a drug carrier. However, its inherent hardness, brittleness, and poor film-forming ability limit its application in DMNs.[36] In addition to its excellent biocompatibility and biodegradability, dextran exhibits good water solubility and low immunogenicity. However, its high water solubility causes it to dissolve rapidly in aqueous environments, and its hydrophilicity limits its drug loading capacity.[37] Hyaluronic acid is one of the most widely used materials for the preparation of DMN matrices. It has excellent biocompatibility, is non-toxic, and possesses strong moisturizing properties, making it popular in cosmetic applications. However, its low mechanical strength and unsuitability for delivering acid-sensitive drugs limit its broader use.[38] CS stands out due to its relatively easy extraction process, mild nature, non-toxicity, biodegradability, antimicrobial and hemostatic properties, good biocompatibility, and wound healing promotion.[39,40] CS is inherently active due to the presence of amino, acetamido, and hydroxyl groups in its molecular structure, allowing it to be easily modified, activated, and conjugated, which provides a wealth of functionalities and modifiability. As the only naturally occurring polycationic polymer, CS can interact with negatively charged cell membranes, facilitating drug transport across cell membranes.[41,42] Based on the property of chitosan (CS) facilitating drug penetration through cell membranes, researchers have developed various drug delivery forms such as CS nanoparticles.[43] For instance, Siavashy et al[44] utilized microfluidic technology to synthesize magnetic core/shell chitosan nanoparticles (NPs) containing cisplatin for cancer treatment. Experimental results demonstrated that cisplatin loaded in NPs remained active, allowing NPs to enter cells and release the drug more effectively. The developed microfluidic platform exhibits valuable characteristics that could potentially translate NPs into clinical applications for drug delivery. Furthermore, CS has been confirmed for its versatility in oral administration, ophthalmic delivery, nasal drug delivery, vaccine delivery, and other applications.[45] CS and its derivatives are widely used in transdermal absorption formulations, and their specific applications are continually being developed.

Application of CS and Its Modified Forms in DMN

The choice of matrix for DMNs involves multiple factors, as the matrix polymer significantly influences the performance of DMNs. The brittleness, solubility, and biocompatibility of the polymers used to manufacture microneedles are crucial to the mechanical properties, drug loading capacity, and solubility of DMNs.[46,47] Therefore, to address issues such as biocompatibility, biodegradability, reusability, and mechanical strength, researchers have increasingly focused on natural polymers.[48] The various advantages of CS are shown in Figure 2. CS, a natural polymer with unique properties and easy availability, has garnered substantial attention for MN manufacturing. Consequently, CS-based MNs have been extensively studied by researchers worldwide. Wei et al[49] prepared hydrogel-based microneedles loaded with Salvia Miltiorrhiza using CS and pullulan (PL) as raw materials. In vitro transdermal and drug release experiments demonstrated that these microneedles achieved effective transdermal drug delivery, enhanced drug permeability, and exhibited excellent biocompatibility, making them a promising transdermal delivery system.

Modified forms of CS are also applied in drug delivery.[50] Since CS is insoluble in media with pH < 5.6, trimethylation of CS has been conducted to enhance its solubility under neutral and acidic conditions. The resulting trimethyl chitosan (TMC) is positively charged and soluble over a wide pH range.[51,52] Schipper et al[53] developed a pH-sensitive MN array coated with alternating layers of TMC and diphtheria toxoid for skin vaccination. TMC served as a cationic

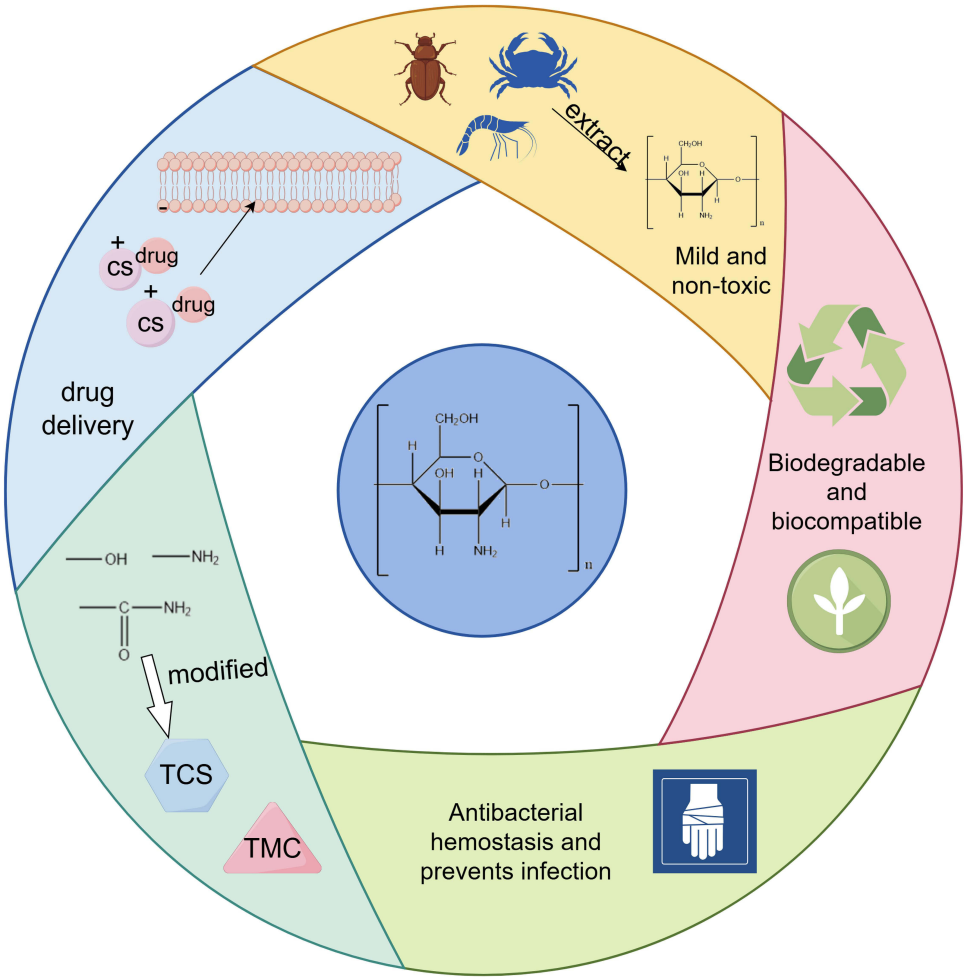

Figure 2 Summarizes the advantages of CS.

adjuvant. Observations showed that the MN array, coated with ten layers of TMC and diphtheria toxoid (equivalent to intradermal administration of ±0.6 μg diphtheria toxoid), elicited an immune response comparable to subcutaneous administration of 5 μg aluminum phosphate adjuvanted diphtheria toxoid, achieving the same vaccination effect with an eight-fold reduction in dosage compared to traditional methods.

Another modified form of CS is thiolated chitosan (TCS).[54] TCS enhances adhesion, permeability, cellular uptake, cross-linking, swelling behavior control, and controlled release.[55] TCS has been widely used in drug delivery systems, including nanoparticles, liposomes, and hydrogel et al[11,56,57] Recently, TCS has also been utilized in MN manufacturing. Ahmad et al[58] developed TCS microneedles (TCS MNs) for transdermal delivery of tacrolimus. TCS was synthesized by reacting CS with thioglycolic acid. The resulting MN patches achieved a skin permeation rate of 84% without causing any surface damage. Histological examination of mouse skin after MN insertion revealed that the MNs penetrated the dermis layer. In vitro release studies showed a release rate of tacrolimus up to 82.5% without burst release, and in vivo biocompatibility studies in rats confirmed the safety of the material and the MN patches. Thus, TCS has potential as a material for MN fabrication.

In addition to modified CS being used for MN fabrication, composite CS has also been utilized in the preparation of MNs. Yi et al[59] investigated the method of removing bacterial biofilms using composite microneedles of chitosan and zinc nitrate (CS-Zn[II]MNs). The CS-Zn(II)MNs combine the structural characteristics of MNs with the antibacterial properties of CS and Zn^{2+}.[60] Due to the needle-like structure of MNs, they can penetrate the extracellular polymeric substances (EPS)[61] and directly deliver CS and Zn^{2+} into the bacterial biofilm, providing a large specific surface area

that promotes the diffusion of antibacterial agents within the biofilm. Both CS and Zn^{2+} exhibit antibacterial properties, and their synergistic effect endows MNs with sufficient antibacterial efficacy to eradicate bacteria within the biofilm. The antibacterial rate (AR) of CS-Zn(II)MNs can reach up to 100%, significantly higher than that of CSMNs. Experimental results demonstrated a sharp reduction in the number of bacteria within the biofilm following treatment with CS-Zn(II)MNs, proving the effectiveness of the MN strategy in transporting CS and Zn^{2+} into the bacterial biofilm. Additionally, CS-Zn(II)MNs exhibited good cytocompatibility, which is crucial for minimizing side effects during drug delivery.

CS imparts biodegradability and biocompatibility to MNs, making it a preferred material for their fabrication. CSMNs have been utilized for the transdermal delivery of various bioactive agents. Currently, their applications have expanded to multiple fields, including vaccination, disease diagnosis and treatment, and drug delivery. The following sections will discuss the mechanisms of action and their applications in these various domains.

Preparation Methods of CSMN

The preparation of CSMN is primarily achieved through techniques such as mold casting, layer-by-layer assembly, and micro-molding. During the process, various crosslinking agents or other materials may be incorporated to enhance mechanical performance or control degradation rates.

Mold Casting Method

The mold casting method is the most widely used technique for CSMN fabrication. This method involves pre-fabricating microneedle molds, filling them with chitosan solution, and then molding through processes such as drying and crosslinking.[62] For example, Badhe et al[63] developed a PLA-coated CSMN array using beeswax as the mold. First, microneedle molds were made using beeswax, then a chitosan solution was evenly applied to the wax mold. After removing air bubbles, the mold was placed in a vacuum drying oven for drying. Once dried, the formed microneedle patch was extracted from the mold, and the MN surface was repeatedly coated with PLA, followed by further drying. The PLA-coated chitosan microneedle patches were then immersed 20 times in a 10 mg/mL BSA solution for an additional coating. Characterization of these patches showed that the polymeric microneedle array was successfully developed using beeswax molds and coated with PLA for effective BSA delivery through the skin's epidermal layer.

Similarly, Ryall et al[64] used PDMS molds to prepare CSMNs for the delivery of asiatic acid (AA). A chitosan-polymer mixture was added to the PDMS molds, and air bubbles were removed by either centrifugation or repeated freeze-drying. The molds were then dried at room temperature, and the CSMNs were demolded. Characterization of the microneedles demonstrated that the array had good mechanical strength and sustained release capabilities, allowing effective dermal delivery of AA.

Layer-by-Layer Assembly Method

The layer-by-layer assembly method builds microneedle structures by sequentially depositing different materials onto a substrate.[65] For instance, Huang et al[66] developed a novel multi-island double-layer microneedle (MDMN) loaded with keratinocytes (KCs) and dermal fibroblasts (FBs) using gelatin-methacryloyl chitosan (GelMA-CS). First, GelMA solution was divided into three portions, and FBs, KCs, and CS were added to prepare FB-GelMA, KC-GelMA, and CS-GelMA solutions. A PDMS mold was filled with 300 μL of FB-GelMA and placed under vacuum at 37°C for 5 minutes to remove surface bubbles. A small amount of FB-GelMA was removed from the tip, and 100 μL of KC-GelMA was added, followed by 2 minutes of vacuum to fill the tip. Finally, CS-GelMA was added to fill the base groove as a backing layer. The mold was then crosslinked under UV light (10 mW/cm², 365 nm) for 3 minutes. Once crosslinked, the MDMNs were carefully peeled off from the PDMS mold. Experimental results indicated that the MDMNs improved wound closure, re-epithelialization, and collagen alignment, while promoting cell proliferation, angiogenesis, and functional skin formation.

Micro-Molding Techniques

Micro-molding techniques utilize precise micro-machining equipment to carve or etch microneedle shapes into the chitosan matrix.[67] This approach enables the creation of more complex and intricate microneedle structures, employing

technologies like photolithography and laser engraving. For example, Moreira et al[68] employed micro-molding and electrospray techniques to produce PVP microneedles coated with CS and PVA for the delivery of doxorubicin and AuMSS nanorods (Dox@MicroN) to cancer cells. PVP solution was first poured into PDMS molds and allowed to settle into the needle cavities under vacuum for 2 hours. After air-drying, the microneedles were gently peeled from the mold. Subsequently, CS (loaded with DOX) and PVA (containing AuMSS nanorods) solutions were electrosprayed onto the PVP microneedle surface using conventional electrospinning equipment, forming the Dox@MicroN system. Results indicated that the microneedles could penetrate agarose gel mimicking tumors and facilitated layer-dependent drug release. The Dox@MicroN patches also demonstrated excellent cytotoxicity against cervical cancer cells by mediating both chemotherapy and photothermal therapy. Overall, the Dox@MicroN patches were shown to be simple macroscopic delivery devices capable of mediating localized drug-photothermal combination therapy, avoiding the systemic complications typically associated with anticancer agents.

Other Preparation Techniques

4D printing is an advanced version of 3D printing, utilizing smart materials and programmable designs to achieve dynamic transformations over time. Unlike traditional 3D printing,[69] the "fourth dimension" in 4D printing is time, where the printed object can adapt to external environmental conditions (such as temperature, humidity, light, pH, etc.) and undergo functional changes.[70] Che et al[71] employed digital light processing (DLP) 3D printing and smart chitosan biomaterials to fabricate microneedles with innovative properties. They used methyl methacrylate hydroxybutyrate chitosan (HBCMA), which has dual temperature and light-sensitive properties, to manufacture microneedles. The DLP technique enabled the rapid production of high-resolution HBCMA-based microneedles. These microneedles exhibited 4D properties, with needle size changing upon exposure to temperature, enhancing resolution, needle sharpness, and mechanical strength. The microneedles demonstrated their ability to load, deliver, and sustain the release of small-molecule drugs, while penetrating soft tissues. Overall, the HBCMA-based microneedles showed promising potential for non-skin drug delivery applications.

In conclusion, the methods for CSMN preparation are diverse, with common approaches including mold casting, micro-molding, and layer-by-layer assembly. Through innovative approaches such as crosslinking, composite materials, multilayer coatings, nanocarrier systems, and 4D printing technology, the application potential of chitosan microneedles in drug delivery, wound healing, and disease treatment has been significantly enhanced. In the future, with the continuous development of new materials and technologies, the performance of CSMN is expected to be further optimized, meeting a broader range of clinical needs.

Mechanisms of CSMN Action

Drug Release Mechanism of Polymer MNs

Compared to metal and other MNs, polymer MNs offer advantages in biodegradability, biocompatibility, cost-effectiveness, and a range of physicochemical and mechanical rigidities, while reducing the risk of material retention within the skin layers.[72,73] DMNs can be further classified into dissolvable MNs and swellable MNs. Dissolvable MNs encapsulate the drug at the needle tip, absorbing skin moisture to fully penetrate the skin and release the drug to the deepest layers, the microneedle body then dissolves within the skin. Swellable MNs, on the other hand, contain a reservoir at the base that includes a lyophilized form of the drug.[74] Upon swelling, these MNs absorb skin moisture, opening the polymer lattice-based matrix and then diffusing the drug through the reservoir to achieve drug delivery into the skin. In both cases, there is no risk of puncture injury or contamination when the microneedle arrays melt or soften, making the disposal of medical waste safer. Because polymers exhibit various forms of swelling or dissolution and responsiveness to physical and biological stimuli, derived polymer MNs can control the physicochemical and pharmacokinetic properties of drug-related molecules and modulate skin performance across a range of biomedical applications.[27]

Degradation Process of CS in the Body

As a natural polymer material, CS possesses a variety of important properties. In addition to its known characteristics such as anti-tumor, antimicrobial, antioxidant, hemostatic, and cholesterol lowering effects, CS also has unique polycationic properties. These properties enable it to interact with the anionic parts of cell membranes. This interaction helps to open the tight

junctions present on cell membranes, thereby enhancing drug permeability and making it applicable in drug delivery.[75,76] CS contains an amino group at the C-2 position and hydroxyl groups at the C-3 and C-6 positions, allowing for various reactions involving these active groups.[77] Researchers have synthesized a range of CS derivatives through these reactions, enhancing molecular properties without altering the fundamental structure and biochemical characteristics of the native molecule.[78] CS and its derivatives can be degraded via physical, chemical, and enzymatic methods.[79–81] Among these, enzymatic degradation is the most ideal as it does not produce toxic by-products. In transdermal drug delivery, CS is degraded in the body by lysozyme, eliminating the need for additional reagents. Lysozyme degrades CS by cleaving the glycosidic bonds between polymer polysaccharide units, resulting in sugars and glucosamine as by-products.[82] The enzymatic degradation of CS is related to its degree of deacetylation; excessive deacetylation makes CS resistant to lysozyme hydrolysis.[83] Therefore, it is crucial to avoid over deacetylation during the modification of CS.

Drug Release Mechanism of CSMNs

The swelling process of CSMNs can be illustrated through several examples. For instance, Ajeesh et al[84] prepared water-soluble CS by acid hydrolysis with trifluoroacetic acid, followed by dialysis in 0.1 M NaCl solution and successfully fabricated bullet-shaped MN arrays through a single molding process. In this system, drug release in the initial phase (24 hours) is primarily governed by a swelling-controlled release mechanism, followed by diffusion and erosion-controlled release mechanisms. Drugs can be loaded into the hydrogel-forming MN patches, including both the MN tips and the backing layer, with the backing layer serving as a reservoir for continuous drug delivery. Transdermal experiments showed that upon insertion into pigskin, the hydration of the CSMNs matrix led to swelling, and subsequently, the release rate increased as the drug-loaded on or near the surface was released. After reaching swelling equilibrium, the loaded drug was gradually released through diffusion across the swollen matrix. This swellable CSMN system is beneficial for prolonged transdermal drug delivery. Rukhshanda et al[85] prepared TCS by thiolation modification of CS. Due to TCS's excellent mechanical strength and high water absorption, the group used TCS as the MN fabrication material and developed a thiolated chitosan microneedle patch loaded with levosulpiride (LS-TC-MNP). Experimental results indicated that LS-TC-MNP increased drug permeability. In in vitro release experiments, the release time extended beyond 48 hours, with a maximum release of 60%. The presence of thiol groups significantly controlled the water absorption of LS-TC-MNP, providing moderate swelling and higher viscosity, thus achieving sustained release over a longer period. Upon insertion of LS-TC-MNP into the skin, the polymer absorbs interstitial fluid from the skin. Following this absorption, the polymer partially swells, and the drug slowly diffuses into the bloodstream. Post-administration, the skin showed no significant damage or inflammatory response, indicating high safety. The specific mechanism of action can be shown in Figure 3.

Upon insertion of the chitosan-based microneedle array into the skin, the needle tips penetrate the SC and reach the dermal layer. The matrix then swells, releasing the drug, which is subsequently degraded by lysozyme within the body into non-toxic by-products, posing no harm to the skin. Additionally, CS promotes wound healing and exhibits anti-inflammatory properties, enhancing the safety of CSMNs. However, the degradation mechanism of CSMNs is not yet well understood, necessitating further indepth research.

Applications of CSMNs in Disease Treatment

Due to the excellent performance of CSMNs, they have been extensively studied in various areas such as wound healing, drug delivery, anti-tumor treatments, and the treatment of skin diseases. The Table 1 below summarizes the applications of different types of CSMNs in these fields. Figure 4 summarizes the application of CSMN in the treatment of diseases.

Promoting Wound Healing

Skin injuries can easily lead to bacterial infections, which in turn can result in chronic wounds characterized by bacterial biofilms several to hundreds of micrometers thick. These biofilms form barriers that hinder timely drug penetration, leading to prolonged wound healing and, in severe cases, can cause death, posing a significant threat to human health.[97,98] Yang et al[86] prepared CS/Bletilla striata polysaccharide (BSP) composite microneedles through a stepwise centrifugation process. The positively charged CS provides antibacterial activity, while BSP is known for its hemostatic,

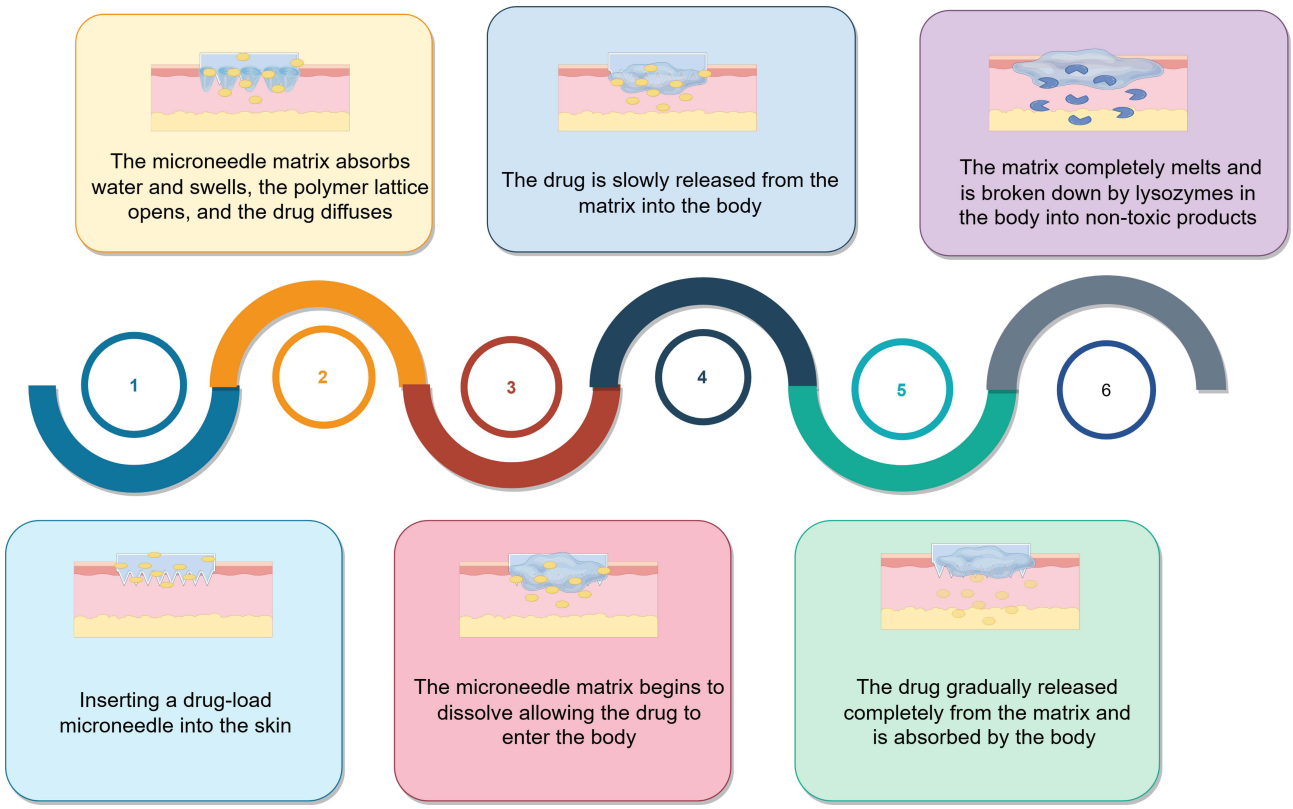

Figure 3 The simple drug release process of CSMNs in the body and the matrix swelling mechanism.

antioxidant, immunomodulatory, and tissue regeneration properties.[99] This composite microneedle system is used to deliver the phenolic hydroxyl-rich natural product tannic acid (TA) and in situ silver nanoparticles (CT/AgB-MNs), demonstrating notable antioxidant and anti-inflammatory properties by reducing inflammatory cytokines and reactive oxygen species (ROS). Due to the bioactive functions of BSP, the expression of EGF and VEGF is upregulated, promoting epithelialization and angiogenesis. Consequently, treatment with CT/AgB-MNs significantly accelerates wound healing. Therefore, this composite microneedle system shows great potential in clinical applications for treating infected and vulnerable wounds.

Any damage to the skin can provide an entry point for pathogens into the body. To prevent further infection, the wound-healing process is essential.[100] Yu et al[87] developed a microneedle array patch using a mixture of Kangfuxin Liquid (KFX),[101] CS, and fucoidan (FD), named KCFMN, to accelerate full-thickness wound healing. Experimental results showed that the KCFMN patch exhibited significant antibacterial properties and good cell compatibility. Specifically, the KCFMN patch significantly accelerated the healing process of full-thickness wounds in rats by improving epithelial thickness and collagen deposition. Therefore, this multifunctional KCFMN patch holds great promise as a dressing for full-thickness wound healing.

Cameron Ryall et al[64] prepared a CS/PVP composite microneedle for delivering the active component of AA. AA is a highly lipophilic molecule and is impermeable through the stratum corneum.[102] Thus, CS/PVP MNs were prepared to increase AA's permeability. Experimental results showed that the MNs had sufficient length and mechanical strength to successfully penetrate the epidermis without breaking. The MNs exhibited good biocompatibility with keratinocytes and fibroblasts (with a survival rate >75% at 100% concentration), a drug release rate of 52.2%, and a release duration of over 48 hours. In animal experiments, Van Gieson staining confirmed complete reepithelialization and closure of the wound surface in tissue sections from the AA-loaded CSMNs treatment group. Tissue remodeling occurred below the epidermal surface of the skin, with mature collagen deposition in the dermis. Ki-67 staining[103] results indicated that AA-loaded MNs promoted keratinocyte proliferation. Moreover, wounds

Table 1 Summary of Applications of Different Types of CSMNs

Type	Function	Effectiveness	References
CS/BSP Composite MNs	Delivery of TA silver nanoparticles	Upregulation of EGF and VEGF expression, promotes epithelialization and angiogenesis, accelerates wound healing	Yang et al[86]
KCFMN	Delivery of KFX	Exhibits significant antibacterial properties and good cell compatibility. Promotes wound healing by improving epithelial thickness and collagen deposition	Yu et al[87]
CS/PVP Composite MNs	Delivery of AA	It has good mechanical strength and biocompatibility, promoting keratinocyte proliferation	Cameron Ryall et al[64]
CSMNs	Delivery of BSA	Drug release rate reaches 95%, with a release duration of up to 8 days. It successfully penetrates the dermal layer, and the device does not alter the secondary structure of BSA	Chen et al[88]
CS for the needle tips, PVP/PVA for the support array |	Delivery of OVA	It releases for up to 28 days and maintains a sustained high level of antibodies. Compared to intramuscular injection, it saves at least 2.5 times the dosage	Chen et al[89]
Polymer MNs composed of PVA, PVP, and CS	Immune-regulating peptide mediating protein-lipid-protein (PLP)139–151	Good mechanical properties, 40% release rate in 4 days, achieves release of PLP therapeutic dose under physiological conditions	Pires et al[90]
Embeddable CSMNs and soluble PVA/PVP support array	Delivery of LHRHa	Serum LH levels increased and then decreased below baseline by day 7. Serum testosterone levels peaked by day 14 and decreased to castration levels by day 21, maintaining this level for 2 weeks.	Chen et al[91]
Composite MNs composed of HA tips and CS matrix	Delivery of antigens	The induced antibody response is much higher and more durable than traditional two-dose or double-dose subcutaneous vaccination. This composite MN exhibits strong adjuvant properties, enhancing the immunogenicity of the antigen.	Chiu et al[92]
CSMNs	Delivery of intradermal (ID) vaccines	CSMNs are not only feasible tools for precise delivery of intradermal (ID) vaccines but also exhibit strong adjuvant properties, enhancing vaccine efficacy and inducing protective immunity against influenza virus infection.	Chen et al[93]
BGC-MNs	Treating psoriasis	BGCMNs cleared cfDNA, reduced levels of inflammatory factors in the dermis, and had a beneficial therapeutic effect on psoriasis mice.	Liu et al[94]
CSMA hMNs	Delivery of MTX	CSMA hMNs patch effectively suppressed skin thickening and splenomegaly in psoriasis mice and exhibited good biocompatibility at adequate therapeutic doses.	Dai et al[95]
CMCH/BSP MNs	Delivery of TA and VRP	It significantly reduces hypertrophic scar (HS) thickness, decreases the expression of hydroxyproline (HYP) and TGF-β1 in HS, improves collagen fiber arrangement, and reduces dermal congestion and hyperplasia.	Zhang et al[96]

Abbreviations: KCFMN, a microneedle array patch using a mixture of KangFuxin Liquid (KFX), chitosan (CS), and fucoidan (FD), named KCFMN; CSMNs, chitosan microneedle (CSMNs) patch; BGC-MNs, biguanide-chitosan microneedles; CSMA hMNs, methacryloyl chitosan hydrogel microneedle; CMCH/BSP MNs, modified carboxymethyl chitosan (CMCH) and Bletilla striata polysaccharide (BSP) to prepare microneedles (MN).

treated with AA-loaded CS/PVP MNs healed smoothly without scarring, suggesting the potential of this microneedle system for anti-scar applications.

Drug Delivery

Hydrophilic macromolecular drugs, such as peptides and proteins, often face limitations in TDDS due to their molecular weight exceeding the permeability limit of the SC.[104] This results in low drug penetration rates, preventing them from achieving effective therapeutic levels. Chen et al[88] developed a CSMN patch for efficient and sustained transdermal delivery of hydrophilic macromolecules. Using bovine serum albumin (BSA) as a model protein, they explored the potential of CSMNs for transdermal protein drug delivery. In vitro, drug release studies showed that CSMNs allowed for

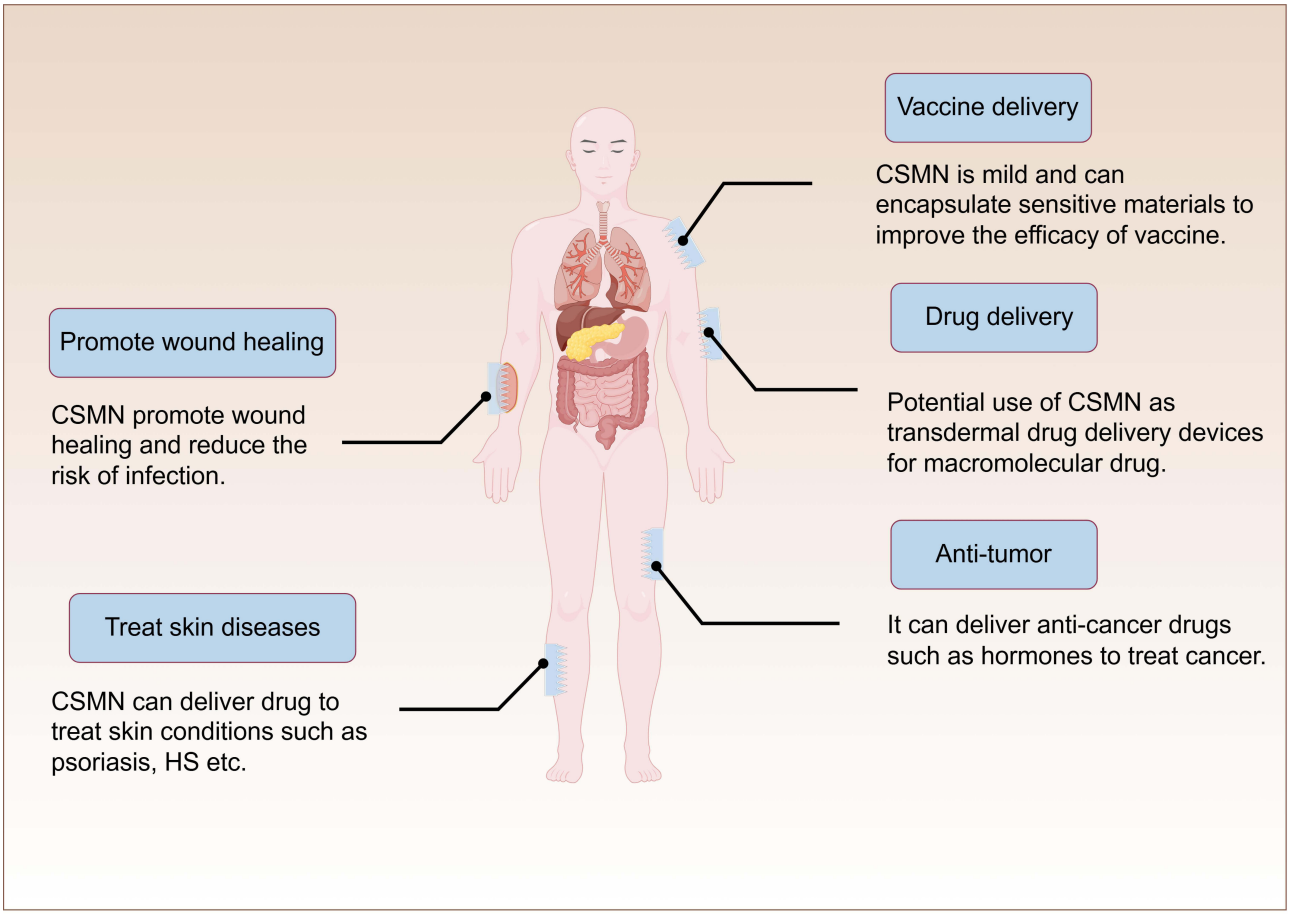

Figure 4 Application of CSMN in the treatment of various diseases.

the sustained release of BSA, with a release duration of up to 8 days and a drug release rate of 95%. When Alexa Fluor 488-labeled BSA (Alexa 488-BSA) MNs were applied in vivo to rats, confocal microscopy images demonstrated that BSA could gradually diffuse from the puncture site into the dermis, with fluorescence observed at a depth of 300 μm. Additionally, the MN matrix did not alter the secondary structure of BSA, indicating that the mild preparation process allowed for the encapsulation of delicate biomolecules. These results suggest that the developed CSMNs could be a promising device for the sustained transdermal delivery of macromolecules. Chen et al[89] also developed microneedle patches with CS as the needle tips and hydrophilic PVA/PVP as the supporting array for delivering ovalbumin (OVA). The study showed that OVA could be released intradermally for up to 28 days, and rats immunized with low dose OVA (approximately 200 μg) via MNs maintained high antibody levels for 18 weeks. This was significantly higher than the levels observed with full-dose intramuscular OVA (approximately 500 μg), saving at least 2.5 times the dosage. Therefore, this dissolvable MN system provides precise and reliable intradermal delivery of antigens, with the potential as a sustained intradermal delivery device. Pires et al[90] fabricated polymer MNs composed of PVA, PVP, and chitosan for mediating the delivery of proteolipid protein PLP139-151-associated immunoregulatory peptides. The study found that incorporating a chitosan scaffold into the MN structure did not significantly affect the mechanical performance of the MN patch. Drug release experiments revealed that the release of PLP peptides reached 40% within 4 days and achieved therapeutic doses of PLP under physiological conditions.

Anti-Tumor Applications

Prostate cancer[105] is the leading cause of cancer-related death among men in Western countries, and long-term administration of luteinizing hormone-releasing hormone analogs (LHRHa) is a primary treatment for androgen

deprivation therapy (ADT) in lethal prostate cancer.[106–108] Chen et al[91] developed a fully encapsulated chitosan microneedle (CSMN) system, composed of implantable CSMNs and a dissolvable PVA/PVP supporting array, for the sustained delivery of LHRHa to the skin. In vitro tests demonstrated that CSMNs could be fully embedded in the skin, and the micropores generated by the MNs healed within 7 days. The LHRHa content per microneedle patch was measured at 73.3±2.8 μg. When the LHRHa-loaded microneedles were applied to mice, serum LH levels initially increased and then dropped below baseline by day 7. In contrast, serum testosterone levels peaked at day 14 before decreasing to castration levels by day 21, maintaining this level for an additional 2 weeks. Thus, encapsulated CSMNs for transdermal delivery of LHRHa show strong potential for the treatment of prostate cancer.

Vaccine Delivery

Vaccines typically consist of inactivated/attenuated pathogens, pathogen subunits, or nucleic acids encoding pathogen antigen proteins, which can trigger an immune response in the body. However, subcutaneous or intramuscular injections often cause pain and fear, leading to poor patient compliance. Additionally, the instability of vaccines and the need for administration by trained medical personnel have prompted researchers to explore alternative transdermal delivery systems.[109,110] Repeated injections increase the cost of immunization and impose stress and inconvenience on vaccine recipients. Recently, the development of controlled-release vaccine delivery systems using biodegradable polymers has emerged as a promising strategy to reduce the need for multiple vaccinations.[111,112] CS can be processed in an aqueous medium without the need for chemical solvents or high temperatures, making it capable of encapsulating sensitive proteins while maintaining their biological activity. Due to its low cost, mild preparation process, and desirable characteristics, CS has been identified as a preferred material for developing controlled-release vaccine delivery systems.[89]

Chiu et al[92] developed a composite MN system composed of sodium hyaluronate (HA) tips and a CS matrix for biphasic antigen release. Upon insertion into the skin, the dissolvable HA tips dissolve to quickly release the encapsulated antigen, initiating the immune response, while the biodegradable CS matrix remains in the dermis to prolong antigen release for up to 4 weeks, thereby enhancing the immune response. Experimental results showed that a single immunization with HA/CS MNs containing ovalbumin (OVA) (100 μg ×1) stimulated both Th1 and Th2 immune responses in rats, with induced antibody responses significantly higher and more sustained than those from traditional two-dose (100 μg OVA ×2) or double-dose (200 μg OVA ×1) subcutaneous injections. Thus, the composite MNs demonstrated a strong adjuvant effect, greatly enhancing the immunogenicity of the antigen.

Chen et al[93] studied an MN patch composed of vaccine-loaded CSMNs and a dissolvable support array. The CSMNs could be rapidly and completely embedded in the dermis, serving as both a reservoir for prolonged vaccine release and an immune system activator. The influenza virus-specific antibody levels induced by CSMNs were significantly higher than those induced by intramuscular (IM) injection of the same vaccine. Four weeks postvaccination, the MN-induced immune enhancement was evident and lasted for at least 16 weeks. Most importantly, mice immunized with CSMNs were fully protected against H1N1 virus infection, with no significant weight loss, whereas 60% of the mice receiving the same dose via IM injection died and exhibited noticeable weight loss post-infection. These results demonstrate that CSMNs are not only a feasible tool for precise intradermal vaccine delivery but also possess strong adjuvant properties, enhancing vaccine efficacy and inducing protective immunity against influenza virus infection.

Treatment of Skin Diseases

Psoriasis is a common chronic inflammatory skin disease characterized primarily by thickening of the epidermis and dermis.[113] Current clinical treatments for psoriasis mainly involve Vitamin D analogs and glucocorticoids, but long-term use of these medications can irritate the skin and weaken the immune system.[114] For severe psoriasis, immunosuppressive therapy, including drugs like cyclosporine and tacrolimus, is the mainstay. However, immunosuppressants can inhibit normal immune responses, reducing the body's ability to combat pathogens.[115]

Abnormally increased levels of cell-free DNA (cfDNA) have been identified as a pathogenic source in several inflammatory diseases. Elevated cfDNA levels can aberrantly activate immune cells, contributing to the progression of psoriasis. Existing treatments for psoriasis face challenges such as poor penetration, suppression of normal immunity, and skin irritation.

To address these issues, Liu et al[94] developed biguanide-chitosan microneedles (BGC-MNs) to remove cfDNA from the dermis through the skin barrier for treating psoriasis. The study compared the effects of different biguanide content in CS on DNA-binding ability, biocompatibility, and inflammation suppression. It was found that CS containing 20% biguanide (BGC2) exhibited the best overall performance. In vitro, BGC2 effectively cleared cfDNA and inhibited the production of inflammatory factors. BGC-MNs made from BGC2 demonstrated good mechanical and dissolution properties. In vivo, BGC-MNs cleared cfDNA, reduced the levels of inflammatory factors in the dermis, and showed therapeutic efficacy in a psoriasis mouse model. These results indicate that BGC-MNs provide a novel approach to psoriasis treatment by removing cfDNA and exerting anti-inflammatory effects.

Additionally, Dai et al[95] developed a safe and effective methacryloyl chitosan hydrogel microneedle (CSMA hMNs) patch for delivering methotrexate[116] (MTX) and nicotinamide[117] (NIC) to treat psoriasis. By systematically optimizing the CSMA formulation, CSMA hMNs with excellent morphological characteristics and strong mechanical properties were prepared at a concentration of only 3% (w/v) CSMA. This patch demonstrated sustained drug release of 80% within 24 hours in vitro. In vivo experiments showed that CSMA hMNs effectively inhibited skin thickening and spleen enlargement in psoriasis mice, with good biosafety at therapeutic doses. This study provides new insights into the use of modified CS or other biocompatible materials for the preparation of hMN systems, offering an effective treatment option for psoriasis.

In addition to treating psoriasis, CSMNs can also be used to treat hypertrophic scars (HS), a common skin condition that is difficult to manage. HS is mainly caused by excessive deposition of collagen by dermal fibroblasts. Current treatments for HS may bring side effects with long-term use, making microneedles a potential effective transdermal drug delivery method for HS treatment.[118–120]

Zhang et al[96] used modified carboxymethyl chitosan (CMCH) and BSP to prepare MN through a micro-molding method. Hydroxypropyl-β-cyclodextrin (HP-β-CD) was used to encapsulate triamcinolone acetonide[121] (TA), and the resulting inclusion complex, along with verapamil[122] (VRP), was loaded into the MN. The MN was then attached to an ethyl cellulose (EC) base layer to obtain a MN patch. The MN patch exhibited uniform needle tips, sufficient mechanical strength, good skin penetration and dissolution, and low cytotoxicity. It significantly reduced HS thickness, decreased hydroxyproline (HYP) and transforming growth factor-β 1 (TGF-β 1) expression in HS, improved collagen fiber arrangement, and reduced dermal congestion and hyperplasia. This type of microneedle shows great potential in the treatment of HS.

Conclusion Remarks and Future Perspective

Traditional transdermal drug delivery methods, such as subcutaneous injections and ointments, have issues like pain, low drug utilization, and limited permeability. Consequently, researchers have turned to MN as a novel transdermal drug delivery system. Synthetic polymer-based DMNs offer certain advantages in terms of mechanical strength and controlled degradation. However, they exhibit limitations in biocompatibility and potential biological toxicity. In contrast, natural polymers such as CS are highly favored due to their excellent biocompatibility and biodegradability. Nevertheless, natural polymer matrices tend to have lower mechanical strength and are challenging to control in terms of solubility. As a result, in some applications, they need to be combined with other materials to enhance their performance. CSMN possess unique biological properties such as biodegradability and biocompatibility, which enhance drug delivery efficiency and transdermal penetration. Compared to other materials, CSMN holds significant potential in drug delivery and controlled release. Moreover, CSMN exhibits immunomodulatory effects, promotes cell proliferation, and facilitates tissue regeneration, making it highly promising for applications in wound healing and skin repair. In addition, CS is abundant and environmentally friendly, offering sustainability advantages over other materials. The use of CS in MN is not limited to drug delivery but also extends to areas such as gene therapy and vaccine delivery. Although the application of CSMN in anti-tumor therapies is still limited, it is expected to see further development as research progresses in this field.

Compared to metal microneedles, which, despite their superior mechanical properties and relatively high drug loading capacity, suffer from poor biocompatibility and potential to cause skin allergies, CSMNs offer better biocompatibility and biodegradability. Hollow microneedles, though faster in drug delivery, are more costly and complex to manufacture. Coated microneedles, while simpler to prepare and capable of controlled drug release, have limited drug loading capacity and slower release rates, potentially failing to meet the requirements for drugs that need rapid release. In addition to its advantages such as excellent biocompatibility, strong biodegradability, high drug release controllability, the ability to carry multiple drugs,

environmental responsiveness, and the capability for intelligent delivery in combination with other materials, CSMN also offer benefits such as reducing the risk of wound infection after administration and exerting antibacterial properties that promote wound healing. Moreover, CSMN's good biocompatibility helps to prevent skin allergies and related issues. However, there are some limitations. For example, the mechanical strength of CSMN is relatively weak, and its strong hygroscopicity may cause deformation during skin insertion. This often necessitates the combination with other materials to improve its performance. Additionally, as the technology is relatively new, further research is required to optimize its properties for drug delivery applications. Key future directions include the development of new crosslinking methods and surface modification techniques to enhance CSMN's stability, drug-loading capacity, and controlled smart release.

As a novel drug delivery technology, CSMNs have broad application prospects. With ongoing research and deeper understanding of microneedle technology, CSMNs are expected to play an increasingly important role in the pharmaceutical field, particularly in local treatments, vaccine delivery, and cosmetic applications. Currently, CSMNs are still at the experimental stage but may face the demand for large-scale production in the future. Therefore, further optimization of CSMN fabrication processes is needed to improve their mechanical properties and drug loading capacity. Additionally, more research is required to enhance their efficacy in drug delivery and vaccine administration, exploring their clinical advantages. In summary, CSMNs hold vast potential and represent a significant research focus in the future of transdermal drug delivery systems.

Data Sharing Statement

No data was used for the research described in the article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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