Biomaterials Translational

Therapeutic potential of natural polymer-based transdermal drug delivery system for musculoskeletal disorders

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ABSTRACT

The transdermal drug delivery system is a highly safe and well-tolerated therapeutic approach with significant potential for treating musculoskeletal disorders. However, its clinical application is limited by the low skin permeability of many active drugs in its formulations. To overcome this challenge, advancements in skin permeation enhancement techniques are essential. Over the past decade, natural polymers have been increasingly incorporated into various nanocarriers due to their availability, biodegradability, and biocompatibility, offering new options for the effective dispersion of suspended solids. Furthermore, surface functionalisation of the numerous functional groups found in natural polymers allows them to be transformed into targeted and stimulus-responsive materials, enabling precise drug delivery to musculoskeletal tissues. This review examines the mechanisms of action of natural polymer-based transdermal drug delivery system, covering penetration enhancers, nanoparticles, microneedles, hydrogels, and nanofibres derived from chitosan, hyaluronic acid, sodium alginate, cellulose, and proteins, and their applications in treating musculoskeletal disorders. Moreover, it outlines the current challenges and prospects of polymer-based transdermal drug delivery system for localised treatment, offering insights into current therapeutic approaches and proposing new directions for advancements in this field.

Keywords:
Microneedles; Musculoskeletal disorders; Natural polymers; Polysaccharides; Protein-based polymer; Transdermal drug delivery system

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1. Introduction

Musculoskeletal tissue, comprising muscles, bones, cartilage, tendons, and ligaments makes up over 40% of the body's mass, providing it shape and structural support. Approximately one-third of the population suffers from chronic pain due to musculoskeletal diseases such as osteoarthritis (OA), rheumatoid arthritis (RA), osteoporosis, low back pain (LBP), and skeletal muscle damage.[1,2] These conditions can lead to physical dysfunction, depression, and various chronic health issues. They are typically marked by joint pain, stiffness, and restricted mobility. Similarly, most musculoskeletal disorders are progressive and long-lasting, exerting considerable pressure on healthcare systems and financial resources.[3,4] For instance, in 2019, the global cost of musculoskeletal disorders associated with high body mass index alone amounted to $180.7 billion.[5]

Hormone replacement therapy, calcitonin, bisphosphonates (BPs), selective estrogen receptor modulators, non-steroidal anti-inflammatory drugs (NSAIDs), and disease-modifying anti-rheumatic drugs are currently available treatments for skeletal disorders in clinical practice.[6-8] Despite their proven therapeutic benefits, these treatments frequently come with serious side effects. For example, hormone replacement therapy, which includes estrogen or parathyroid hormone replacement, is well-known for its effectiveness in significantly reducing osteoporotic fractures;[9] however, hormone replacement therapy may increase the risk of breast cancer, irregular vaginal bleeding, and endometrial hyperplasia.[10] Similarly, BPs like zoledronate, denosumab, risedronate, and alendronate are recognised for their ability to prevent fractures in older adults.[11] Unfortunately,

BP treatments are linked to both short-term and long-term toxicities. Likewise, extended use of NSAIDs and disease-modifying anti-rheumatic drugs is not recommended due to their serious side effects.[12] Thus, despite the range of available treatments for skeletal disorders, there is a pressing need for advanced technologies to minimise their associated side effects.

Transdermal drug delivery system (TDDS) is an attractive route for dermatological disease therapy because it can directly target the lesion site on the skin, reduce adverse reactions associated with systemic administration, and improve patient compliance.[13] TDDS are increasingly being employed to address the significant challenges associated with musculoskeletal diseases.[14] TDDS has made a significant impact on the administration of various therapeutic agents, particularly in pain management, hormonal therapy, and the treatment of cardiovascular and central nervous system conditions.[15,16] It has emerged as a key component of advanced drug delivery systems, offering prolonged bioactivity that reduces dosing frequency and helps to minimise potential side effects. In 2019, the market for transdermal patches was valued between approximately $1.5 billion and $4.5 billion in the US and globally, respectively. Projections indicate that the global market could reach around $31 billion by 2030, with a compound annual growth rate of 10.46%.[17] Advances in TDDS methodologies and the development of innovative delivery systems have broadened its application to include lipophilic, hydrophilic, and amphiphilic drugs.[18] This expansion is often supported by the use of delivery and permeation enhancers and advanced physical delivery techniques designed to minimise damage to the skin's soft tissues.

Natural polymers, sourced from biological materials, are instrumental in fabricating TDDS due to their outstanding biocompatibility, biodegradability, and widespread availability.[19] It broadens the range of natural polymer-based TDDS by integrating natural polymers into diverse formulations. Natural polymers are capable of displaying thermal and pH-response properties, as well as simple chemical modifications and composite formation with other polymers to increase and improve their biomedical applications, especially for TDDS. The synthesised thermos-responsive polymers are widely recognised for their ability to gel in situ. Their simple chemical modifications and composite structures are applied to polymers of other natural or synthetic origin to increase their biocompatibility and reduce toxicity.[20] Specifically, the development of polymer-based TDDS that respond to the microenvironment of musculoskeletal tissues improves therapeutic efficacy while reducing adverse effects on healthy tissues.[21,22] Given the essential role of polymer-based TDDS in the localised treatment of musculoskeletal disorders, extensive research has been conducted. However, a comprehensive synthesis is still lacking.

This review focuses on polymer-based TDDS, including penetration enhancers, hydrogels, nanofibres, microneedles (MNs), and nanoparticles made from hyaluronic acid (HA), chitosan, sodium alginate, cellulose, and proteins. It explores their mechanisms of action and applications in treating musculoskeletal disorders through various therapies, including chemotherapy, phototherapy, gene therapy, immunotherapy, and combination therapy over the last decade. Several natural polymers, that comprise the building blocks of TDDS have been discussed. The review also highlights research challenges and opportunities, providing insights for developing innovative drug delivery methods for musculoskeletal conditions (**Figure 1**). Most of the articles cited in this review were searched in the PubMed database using the following key words: transdermal drug delivery, or natural polymers, or protein-based polymer, or polysaccharides, and MNs. We screened these articles by browsing the title and abstract. In addition, we also searched the articles about the musculoskeletal disorders.

2. Types of natural polymers for transdermal drug delivery system

Polysaccharides, sourced from microorganisms, algae, plants, and animals, are naturally occurring biopolymers consisting of long chains of monomers linked by glycosidic bonds. Their biocompatibility and ease of manufacturing make them valuable in various biological applications, including drug delivery, tissue culture, biosensing, and wound care.[23,24] Since most polysaccharides are water-soluble at room temperature, solvent casting is the preferred method for fabricating these hydrogels. Additives like plasticisers and crosslinkers are incorporated during the synthesis process to enhance their elongation and strength properties.[25] Porosity can be introduced into the hydrogel matrix through lyophilisation, which improves its water absorption capability.[26] An ideal transdermal dressing should have optimal moisture vapor permeability and ensure continuous release of active agents. These agents provide functional biological properties, such as anti-inflammatory, antioxidant, and circulatory effects.[27,28] Natural polymers used in these dressings include polysaccharide-based and protein-based materials. Polysaccharide-based materials are frequently preferred over protein-based materials due to their favourable properties such as biocompatibility and polyfunctionality with low-cost.[29] Compared to protein-based materials, the physicochemical properties of polysaccharide-based materials, such as solubility and emulsification, are usually better preserved during spray drying. This section outlines the primary applications of various polysaccharides as transdermal dressings for musculoskeletal applications, as summarised in **Figure 2**.[30-33]

2.1. Polysaccharide-based polymers

2.1.1. Hyaluronic acid

HA is an anionic, linear polysaccharide made up of repeating units of N-acetyl-D-glucosamine and D-glucuronic acid, connected by β-1,4 and β-1,3 glycosidic bonds. HA and its

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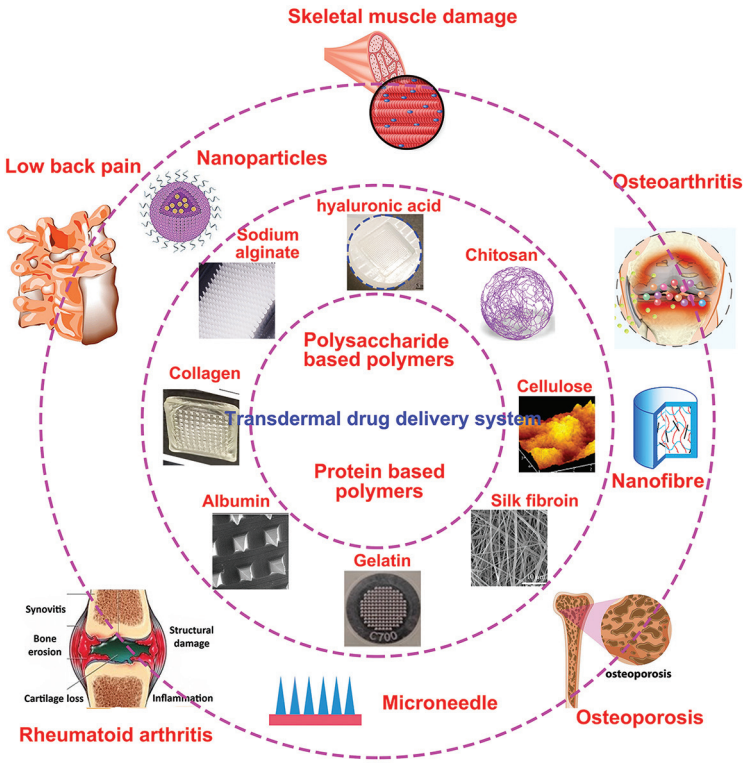

Figure 1. Schematic diagram showing the different types of transdermal drug delivery systems and the application for osteoarthritis, rheumatoid arthritis, osteoporosis, low back pain, and skeletal muscle damage treatment.

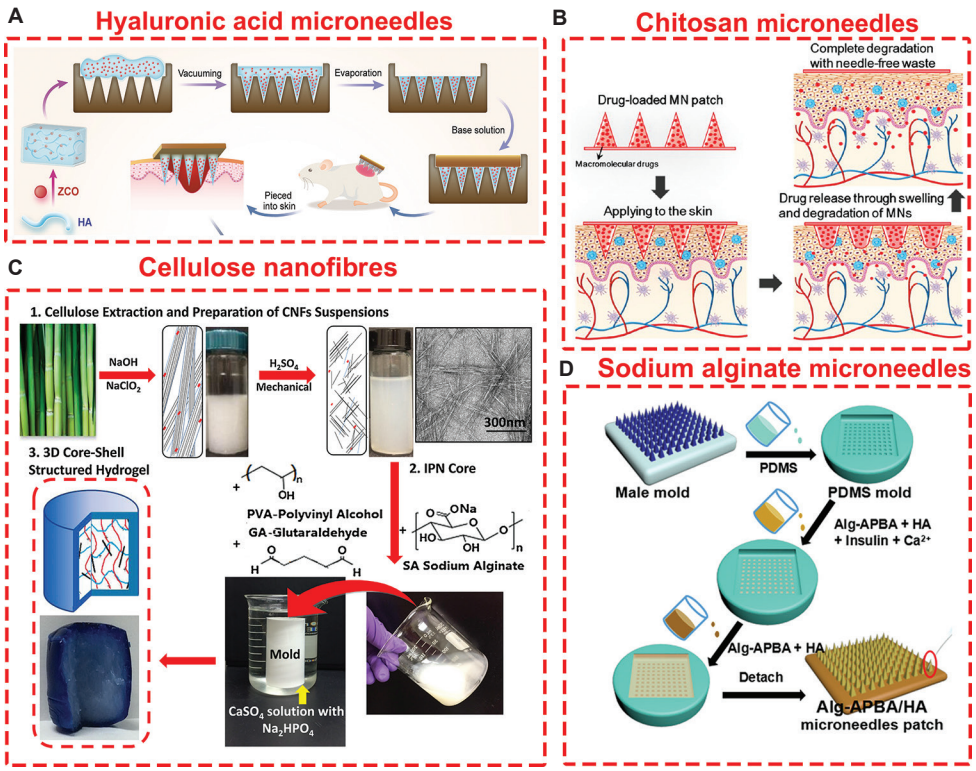

Figure 2. Schematic diagram of the applications of different types of polysaccharide-based polymers as transdermal dressings for the musculoskeletal system. (A) Hyaluronic acid-microneedles. Reprinted from Yang *et al.*[30] Copyright 2023 Wiley-VCH GmbH. (B) Chitosan microneedles. Reprinted from Chen *et al.*[31] Copyright 2012 American Chemical Society. (C) Cellulose nanofibres. Reprinted from Yue *et al.*[32] Copyright 2016 Elsevier Ltd. (D) Sodium alginate microneedles. Reprinted from Yu *et al.*[33] Copyright 2017 Elsevier.
Abbreviations: 3D: Three-dimensional; Alg: Sodium alginate; APBA: 3-aminophenylboronic acid; GA: Glutaraldehyde; HA: Sodium hyaluronate; IPN: Interpenetrating polymer network; MN: Microneedle; PDMS: Polydimethylsiloxane; PVA: Polyvinyl alcohol; ZCO: Zinc-based nanomaterial.

derivatives have been extensively studied in tissue engineering due to their interactions with growth factors, receptors, and adhesion proteins. HA, when incorporated into a chitosan-gelatin matrix, enhances the material's bioactivity, resulting in a hydrogel that supports synergistic interactions with other matrix components.[34] In TDDS, HA helps retain drugs within the skin with minimal transcutaneous absorption.[35] This effect is due to HA's high molecular weight, which increases the viscosity of the formulation and reduces drug diffusion through the skin into the bloodstream.[36] Given its exceptional moisturising properties and skin affinity, HA has become a key focus in recent research on polymer-based TDDS. This review explores HA's applications in the fabrication of MNs and its role as a carrier in topical and TDDS. It highlights HA's contributions to enhancing drug permeation, utilising receptor-mediated delivery mechanisms, boosting skin hydration, interacting hydrophobically with the stratum corneum, and displaying bioadhesive and viscoelastic properties.[37,38] The efficacy of HA-swelling MNs in TDDS is highlighted by their enhanced mechanical strength, rapid swelling performance, and sustained maintenance of microchannels in the skin. These characteristics collectively enhance the overall effectiveness of TDDS.[39] Modified cationic liposomes incorporating HA exhibit enhanced potential and promising applications in TDDS and targeted drug delivery compared to conventional cationic liposomes. Low molecular weight HA, with its optimal permeability through the stratum corneum and targeting ability towards CD44 receptors, is considered a valuable enhancer for skin penetration and retention in the development of topical preparations and skin care products.[40] HA-MNs showed anti-arthritic effectiveness on par with subcutaneous etanercept injections. To enhance their use as a transdermal patch for OA treatment, a self-adhesive lubricating copolymer was applied to the MN tips.[41]

Low molecular weight HA is biologically safe and dissolves easily, reducing the risk of adverse skin reactions and making it ideal for TDDS.[42] In contrast, high molecular weight HA increases viscosity in formulations, enhancing the localisation and sustained release of drugs and nutraceuticals, which is advantageous for TDDS.[43] The physicochemical properties of HA-MNs can be altered through physical interactions, and these formulations may include bioactive substances either chemically conjugated with HA or encapsulated using methods such as hydrogel, nanoemulsion, microemulsion, MNs, liposomes, or hydrosomes.[44,45] Further research is needed to explore the chemical interactions of HA-MNs, and streamlining the manufacturing process is essential for scaling up from laboratory to industrial production.

2.1.2. Chitosan

N-deacetylation of chitin yields chitosan, a linear cationic polymer comprising 2-amino-2-deoxy-β-D-glucan linked together by glycosidic linkages.[46] Chitosan, with its amino, acetamido, and hydroxyl groups, demonstrates exceptional reactivity and versatility. These properties allow for extensive modification, activation, and coupling, highlighting its broad functionality and adaptability in diverse biological applications.[47] The polycationic nature of chitosan and its derivatives facilitates easy interaction with the negatively charged sites on proteins, enhancing the encapsulation of protein drugs.[48] As the sole naturally occurring polycationic polymer, chitosan effectively interacts with negatively charged cell membranes, aiding in the delivery of medications across these membranes.[49] Further, chitosan and its derivatives can chelate heavy metal ions, making them effective agents for trapping these ions. This property positions chitosan as a promising candidate for a range of pharmaceutical applications, including TDDS.

Chitosan and its derivatives are widely used as excipients in TDDS due to their excellent biocompatibility, biodegradability, low toxicity, and inherent antibacterial and anti-inflammatory properties.[50] They enhance permeability in transdermal agents by potentially altering the protein structure of the stratum corneum, affecting tight junctions within the granular layer, modifying intercellular lipids, and increasing the hydration of the stratum corneum.[51] Various techniques have been employed to incorporate chitosan into TDDS, including hydrogels, liposomes, MNs, patches, membranes, nanoparticles, emulsions, and nano-scaffolds, improving drug administration through the skin. A biocompatible fluorocarbon-modified chitosan has been developed to enable effective, non-invasive delivery of biomacromolecules such as antibodies and antigens.[52] Liposomes were developed for prolonged transdermal delivery using a carboxymethyl-modified chitosan/HA thermosensitive hydrogel, which offers a flexible approach for sustained applications.[21] Novel transdermal systems for colchicine have been fabricated by reacting carboxyethyl chitosan with oxidised pullulan. The resulting colchicine-loaded mesoporous silica nanoparticles incorporated into hydrogel patches show significant promise as safe, effective, and patient-friendly solutions for OA management.[53] Future research should focus on rigorous *in vivo* studies and establish strong correlations between in vitro and *in vivo* results to support the findings related to chitosan and its derivatives in TDDS.

2.1.3. Sodium alginate

Sodium alginate is a naturally occurring polymer that is largely generated from brown algae and certain microorganisms. It is made up of β-D-mannuronic acid (M block) and α-L-guluronic acid (G block) units that are either heterogeneously organised or in sequences of 1,4-linked-D-mannuronic acid and 1,4-linked-L-guluronic acid. The physicochemical properties of sodium alginate are significantly influenced by the M/G unit ratio.[54] Alginate can exhibit antibacterial, antifungal, and antiviral properties through specific chemical modifications.[55,56] Its exceptional biocompatibility, favourable rheological characteristics, biodegradability, and ability to form stable gels under mild conditions with metal cations like Ca^{2+} make it an attractive candidate for TDDS.[57] The abundance of hydroxyl and carboxyl groups on alginate's surface facilitates tissue adhesion and supports functionalisation and modification.[58] Since its introduction, sodium alginate has become a standard material for fabricating hydrogels, films, and patches, both standalone and composite, for cutaneous and subcutaneous wound healing applications.[59]

Alginates, either independently or in conjunction with various polymers, are extensively utilised in the development of TDDS incorporating therapeutic agents. They have been employed across various TDD techniques, including MNs, transdermal films, and gel formulations. Khan *et al.* developed MN array patches that utilise sodium alginate/poly(N-vinylcaprolactam)-based in situ forming hydrogels within skin micropores, capitalising on their sol-gel transition properties for sustained transdermal delivery.[57] Given the advantageous physicochemical attributes of alginates and growing patient receptivity towards TDDS, the utilisation of alginates in the development of such systems is anticipated to expand in the coming years. However, their application in MNs has been limited due to insufficient mechanical strength. The "poke-and-release" method employed with alginate MNs is particularly effective, as it prevents reuse of the MNs, reduces biohazard risks, and minimises potential cross-contamination.

2.1.4. Cellulose

Cellulose, the most prevalent hydrophilic natural polysaccharide, consists of glucose monomers linked by β-(1,4) glycosidic bonds.[60] It is abundantly found in plant cell walls, as well as in cotton, bacteria, and algae. Cellulose's wide availability, outstanding biocompatibility, degradability, and high hydrophilicity make it highly suitable for drug delivery applications, especially in TDDS using cellulose-based gels. Moreover, carboxymethyl cellulose, a derivative designed to enhance moisture retention, viscosity, and stability, is among the most widely used cellulose derivatives today.[61] Certain cellulose esters, such as nitrocellulose, cellulose phthalate acetate, and cellulose acetate, are primarily utilised in polymer membranes.

Cellulose esters and derivatives are integral components of cellulose-based polymers, which are extensively utilised in the production of films and fibres. Cellulose is particularly suited for wound dressing applications due to its excellent gas permeability, high water-retention capacity, and mechanical durability.[62] Although much focus has been on its antimicrobial properties and wound dressing applications, cellulose also shows promise in areas such as cartilage and meniscus implants, bone tissue engineering, and neural tissue engineering. However, further research is needed to fully explore cellulose's potential in TDDS. Weyell *et al.*[63] investigated the dual functionality of cellulose in wound dressing and drug delivery, assessing its use in dental extractions and mucosal transplantation. The study highlighted the enhanced degradation of cellulose through periodate oxidation, which disrupts the fibre network and improves its efficacy in dental applications. Similarly, Madaghiele *et al.*[64] developed cellulose-based superabsorbent hydrogels to address obesity. This biomimetic approach proved effective and safe for weight management, with the hydrogels' impact on gut tissue assessed through an ex vivo organ culture model. The study emphasised that the mechanical properties of these hydrogels are crucial for maintaining gut tissue health and managing obesity. In orthopedic medicine, researchers have explored creating multi-layered coatings for AISI 316LVM stainless steel by combining the NSAID diclofenac with carboxymethyl cellulose. This biocompatible polysaccharide is essential for ensuring corrosion resistance and controlled drug release.[65]

Despite the advantageous properties of cellulose-based TDDS in wound healing and tissue regeneration, a significant drawback is their inherent lack of antimicrobial activity, which restricts their broader biomedical and tissue engineering applications. Recent efforts aim to address this limitation by integrating antimicrobial biomaterials into cellulose matrices using various physical and chemical techniques. The highly crystalline nature of cellulose enables it to assume a wide range of forms, from simple films to complex structures. Furthermore, cellulose can be chemically and enzymatically modified to produce active biomedical structures.

2.2. Protein-based polymers

Proteins, as key components of the human body, have achieved significant advancements in drug delivery in recent years. Examples include collagen, gelatin, silk fibroin, and albumin (**Figure 3**).[66-69]

2.2.1. Collagen

Collagen constitutes about 35% of the body's total protein composition and is a key structural protein rich in glycine, proline, and hydroxyproline, primarily found in mammalian connective tissues.[70] Its exceptional mechanical strength, biocompatibility, and non-immunogenic properties render it rather essential for tissue engineering applications, particularly in musculoskeletal systems and wound healing.[71,72] Collagen can be utilised in several forms, including porous sheets and sponges, and can be chemically modified to enhance its properties or regulate its degradation rate.

In the realm of drug delivery, collagen primarily takes the form of protein cages and gels designed to release internal medications through gel swelling or enzymatic hydrolysis *in vivo*, which facilitates outstanding slow-release effects. Collagen's application extends beyond bioprosthetic implants and tissue engineering to numerous biomedical procedures, surgeries, cosmetic formulations, and drug delivery. Lv *et al.*[66] utilised hydrolysed collagen derived from skin cells as a primary material and employed a two-step casting method to develop a rapidly dissolving MN patch for simple and minimally invasive collagen delivery. By integrating hydrolysed collagen with various biocompatible materials, the inherent mechanical limitations of hydrolysed collagen were addressed, producing a flexible MN patch that conforms to the skin for effective collagen delivery and enhancement of skin quality. Their findings suggest that these collagen-based dissolving MN patches hold significant promise in medical cosmetology and could become a popular method for delivering collagen and improving skin conditions in the future. Shi *et al.*[73] developed a series of transdermal nano collagens and optimised a highly biocompatible and bioactive formulation, marking the first successful enhancement in the efficacy of transdermal nano collagen. This formulation demonstrated a robust potential in effectively treating ultraviolet-damaged skin, with a stable triple-helical collagen structure, excellent biocompatibility, and significant bioactivity. It enhanced fibroblast proliferation

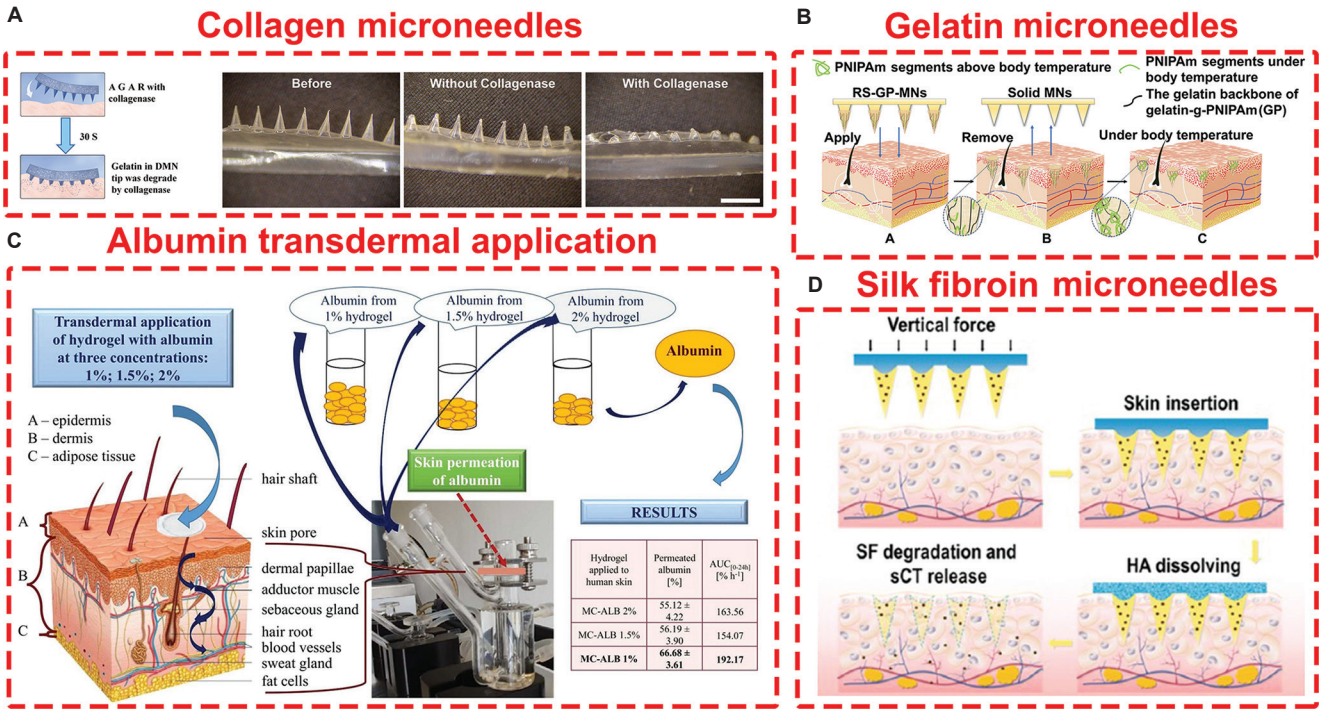

Figure 3. Schematic diagram showing the different types of protein-based polymers as transdermal dressings for the musculoskeletal system. (A) Collagan microneedles. Reprinted from Lv *et al.*[66] Copyright 2023 Wiley-VCH GmbH. (B) Gelatin microneedles. Reprinted from Li *et al.*[67] Copyright 2022 Acta Materialia Inc. (C) Albumin transdermal application. Reprinted from Siemiradzka *et al.*[68] (D) Silk fibroin microneedles. Reprinted from Li *et al.*[69] Copyright 2022 American Chemical Society.

Abbreviations: AGAR: Agar; ALB: Albumin; DMN: Double-layer drugloaded microneedles; GP: gelatin-g-poly(N-isopropylacrylamide); HA: Haluronic acid; MC: Methylcellulose; MN: Microneedle; PNIPAm: Poly(N-isopropylacrylamide); RS: Rapidly separating; sCT: Salmon calcitonin; SF: Silk fibroin.

and adhesion, highlighting its potential in cosmetics and dermatology for promoting skin repair and regeneration.

Nevertheless, using collagen as a cellular substrate comes with certain challenges. Depending on the processing method, collagen can alter cell behaviour, have inadequate mechanical properties, or cause contraction. Rapid interaction between cells and collagen fibres can lead to fibre pulling and reorganisation, potentially deforming the scaffold. This problem can be addressed by stabilising the scaffold through appropriate cross-linking or blending with less reactive materials.

2.2.2. Gelatin

Gelatin is a protein blend derived from the partial hydrolysis of collagen and is classified into alkali gelatin, acid gelatin, and enzymatic gelatin based on the hydrolysis method.[74] Gelatin solutions form three-dimensional network structures below 25°C and revert to a soluble state above 30°C, making them ideal for designing thermoresponsive drug release systems.[75] Furthermore, hydrogels doped with polymers such as chitosan and gelatin show enhanced drug delivery potential due to their sol-to-gel transition capabilities near body temperature.[76]

Gelatin has recently attracted attention in bio-industrial applications such as tissue engineering (especially in cell-interactive coatings), TDD, biological adhesives, and tissue scaffolds. Gelatin is easily fabricated into various forms and is readily available. Demir *et al.*[77] fabricated MNs fabricated from molybdenum sulfide nanosheets placed onto gelatin methacrylate crosslinked using polyethylene glycol diacrylate to deliver insulin on demand. The cargo was released from the MNs via photothermal activation rather than MN breakdown. This offered a promising platform for the release of insulin under regulated conditions when exposed to near-infrared light. This on-demand delivery method was believed to have the potential to transform current insulin treatments and could be adapted for the delivery of other proteins as well. Li *et al.*[67] successfully grafted poly (N-isopropylacrylamide) onto gelatin to create gelatin-g-poly (N-isopropylacrylamide) (GP), which inherits the temperature-induced reverse sol-gel transition property. For regulated drug delivery, GP was processed into a rapidly separating MN system. This system includes GP-MNs mounted onto solid polylactic acid MNs covered in polyvinyl alcohol. The proposed rapidly separating GP-MNs system offers a painless, noninvasive, and efficient mode of administration with minimal safety risks, making it potentially applicable for various hydrophilic small molecule and peptide medications requiring frequent dosing. However, due to its strong hydrogen bonding and its solidification at low temperatures, gelatin cannot be employed in the manufacture of fibres.

2.2.3. Silk fibroin

Silk fibroin, an ancient natural protein derived from the silk secreted by Bombyx mori, is well known for its fibrous structure and composition. It contains 18 amino acids,

with glycine, alanine, and serine making up over 80% of its composition.[78] Silk fibroin's strong affinity for skin, biocompatibility, degradability, and moisturising properties make it highly valuable for natural polymer-based TDDS.[79] Compared to other polymers, such as collagen and polylactic acid, silk fibroin offers superior biocompatibility due to its β-sheet structure.[80] Silk fibroin-derived carriers, which can be processed under various conditions, facilitate controlled drug release by modulating degradation rates based on polymerisation degree.[81] Silk fibroin has diverse applications in films, hydrogels, nanoparticles, and MNs, impacting fields like medical cosmetology, tissue engineering, and drug delivery. Sakunpongpitiporn *et al.* developed silk fibroin hydrogels using solution casting as the insulin matrix and studied their release and permeation behaviours. They varied silk fibroin concentrations and applied electric fields to observe changes in diffusion coefficients. Lower concentrations of silk fibroin resulted in higher diffusion coefficients due to reduced chain entanglement and larger mesh sizes. These results demonstrate the potential of adjusting silk fibroin concentration and electric fields either separately or together to control the rate, quantity, and duration of insulin delivery through transdermal iontophoresis.[82] Li *et al.*[69] fabricated a composite separable MNs system with a HA base and silk fibroin needle tips for transdermal salmon calcitonin (sCT), distribution intended for the treatment of osteoporosis. Silk fibroin conformational structure is modulated by poly (ethylene glycol) to allow for the controlled and sustained release of sCT. Soluble HA rapidly dissolves in tissue fluid once the MNs are inserted into the skin, allowing it to detach from the silk fibroin tips. These tips then embed subcutaneously, serving as reservoirs for the drug. The silk fibroin matrix swells and gradually breaks down, facilitating a steady and controlled release of the loaded sCT (synthetic calcitonin). Consequently, this composite MN system shows significant potential as a reliable and effective alternative to traditional subcutaneous injections for transdermal delivery of sCT.

Traditional production methods often result in particles with inconsistent sizes due to erratic forces, which can jeopardise the bioactivity of encapsulated cells, growth factors, and enzymes. Further, the degumming process, used to purify silk fibroin, affects the size, shape, surface potential, and drug release effectiveness of microspheres, with variations in molecular weight playing a role. Untreated silk fibroin MNs are also prone to breaking during insertion, and their rapid disintegration can lead to sudden drug release and potential side effects such as hypoglycemia.

2.2.4. Albumin

Albumin, the predominant globular protein in plasma, has garnered significant interest in drug delivery owing to its excellent biocompatibility, non-toxicity, stability, and high capacity for drug loading.[83] With a free sulfhydryl group and eight disulfide linkages, albumin is highly soluble in water and salt solutions with pH values between 4.0 and 8.5, capable of dissolving up to 40% w/v in water at pH 7.4. This solubility enables albumin to form soluble complexes with a variety of insoluble organic compounds and inorganic ions *in vivo*.[84] As a versatile transport protein, albumin leverages its natural biomaterial attributes such as biocompatibility, non-immunogenicity, and biodegradability. Albumin-based nanoparticles are particularly known for their large specific surface area, high affinity for skin tissues, numerous surface-active sites conducive to functional modifications, and potential to significantly enhance drug circulation *in vivo*. Siemiradzka *et al.*[68] illustrated albumin's permeation following topical application for potential therapeutic carrier roles. Among various polymers tested, methylcellulose emerged as the optimal choice for albumin release, while hypromellose proved less favourable. The concentration of albumin influenced both the quantity and rate of protein permeation. Methylcellulose-based hydrogels showed the highest permeation, followed by combinations of methylcellulose with chitosan, alginate, and hypromellose. Xia *et al.*[85] developed a minimally invasive programmable MN platform by incorporating HA with bovine serum albumin nanoparticles loaded with methotrexate. Their study confirmed that bovine serum albumin nanoparticles loaded with methotrexate MNs effectively reduced reactive oxygen species (ROS), increased oxygen levels, decreased inflammatory M1 macrophages, and enhanced beneficial M2 macrophages. This innovative approach combines anti-inflammatory therapy with TDD, suggesting a promising new method for managing and treating RA in the future.

3. Application of natural polymer transdermal drug delivery system in the musculoskeletal system

The following section presents a review of pathological features of various musculoskeletal disorders (**Figure 4**)[86-90] and current treatments for prevalent musculoskeletal disorders that employ TDDS based on natural polymers. Furthermore, a framework for future treatments that integrates advanced therapeutic approaches with natural polymer-based TDDS for managing musculoskeletal disorders has also been proposed (**Figure 5**).[41,69,91-93]

3.1. Osteoarthritis

OA is a chronic inflammatory condition characterised by pain, stiffness, loss of function, and swelling in various joints. The etiology of OA is multifactorial and not fully understood, involving both inflammatory and metabolic factors. Consequently, clinical treatment focuses on symptomatic relief, aiming to reduce pain, control inflammation, and improve quality of life. Celecoxib, a selective cyclooxygenase-2 inhibitor, stands out among NSAIDs for its superior anti-inflammatory and analgesic effects, as well as its reduced risk of side effects, making it particularly effective for OA management.[94] However, the therapeutic effectiveness of oral administration is limited by low bioavailability and poor water solubility. Intra-articular injections of certain nutritional supplements are employed to prevent cartilage destruction, and disease-modifying OA medications are used to manage the progression of the disease.[95] However, these conventional methods share similar adverse effects as discussed previously. Therefore, natural polymer-based TDDS present an ideal solution.

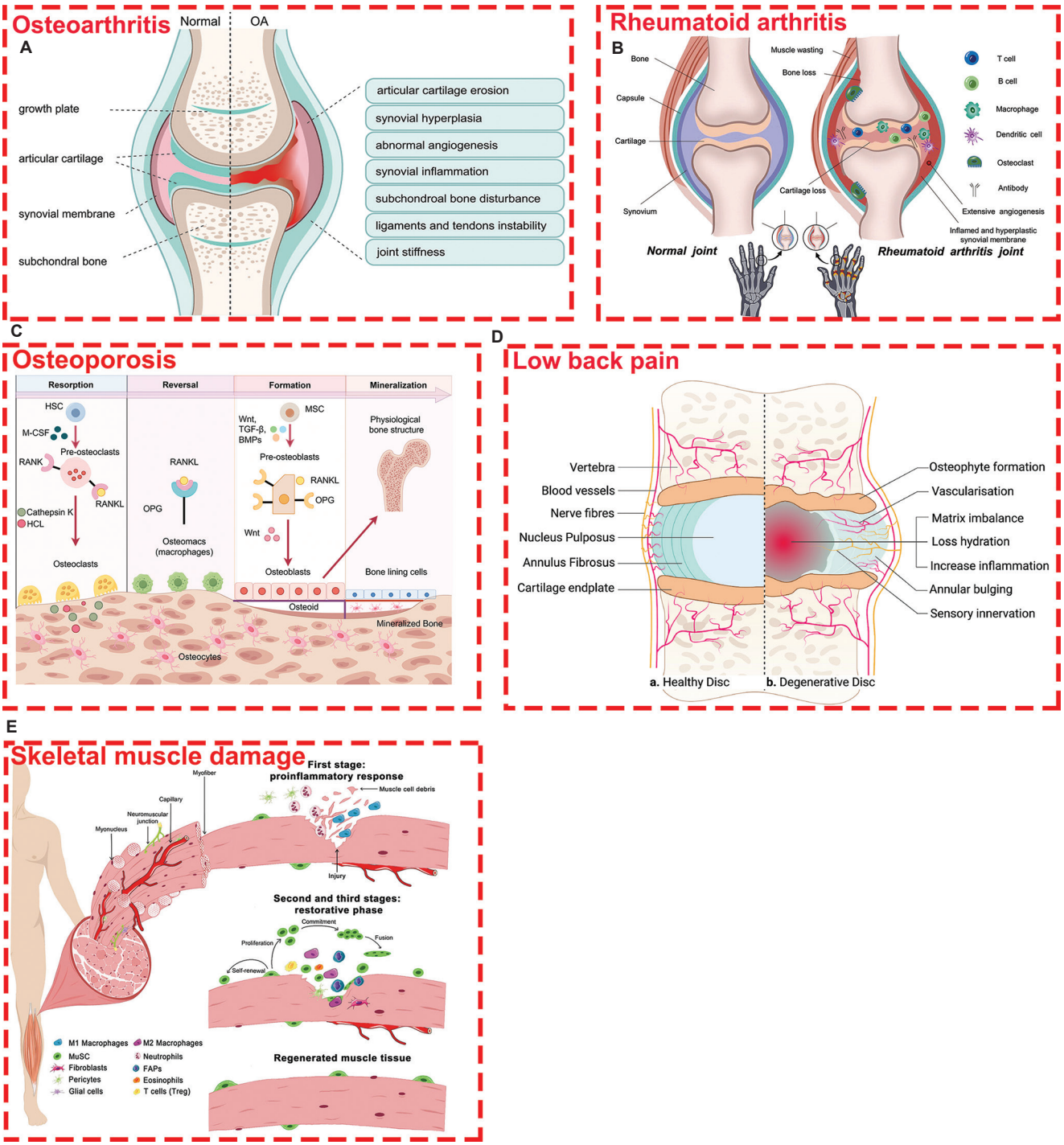

Figure 4. The pathological features of various musculoskeletal disorders. (A) The structure of the normal synovial joint and phenotypes of osteoarthritis. Reprinted from Yao *et al.*[86] (B) Normal joint and pathological changes of rheumatoid arthritis. Reprinted from Ding *et al.*[87] (C) Bone remodeling cycle of osteoporosis under physiological and pathological conditions. Reprinted from Chen *et al.*[88] (D) An illustration of a healthy and degenerative intervertebral disc. Reprinted from Mohd Isa *et al.*[89] (E) A schematic overview of different steps during muscle repair. Reprinted from Loreti *et al.*[90]

Abbreviations: BMP: Bone morphogenetic protein; HCL: Hydrogen chloride; HSC: Haematopoietic stem cell; M-CSF: Macrophage colony-stimulating factor; MSC: Mesenchymal stem cell; OA: Osteoarthritis; OPG: Osteoprotegerin; RANK: Receptor activator of nuclear factor kappa B; RANKL: Receptor activator of nuclear factor kappa-B ligand; TGF-β: Transforming growth factor-β.

Since most NSAIDs are hydrophobic, there is a need for advanced dissolving MNs to enhance their transdermal delivery for OA treatments. MN array-mediated TDD offers reduced pain and improved patient compliance compared to oral intake or intra-articular administration, making it a viable option for delivering anti-OA medications.[41] To enhance therapeutic effects, Zhou *et al.*[96] developed a HA-based liposomal triptolide-loaded MN, which can reduce serum cytokines and decrease knee joint swelling in OA-model rats. Similarly, Li *et al.*[97] created microemulsion-incorporated

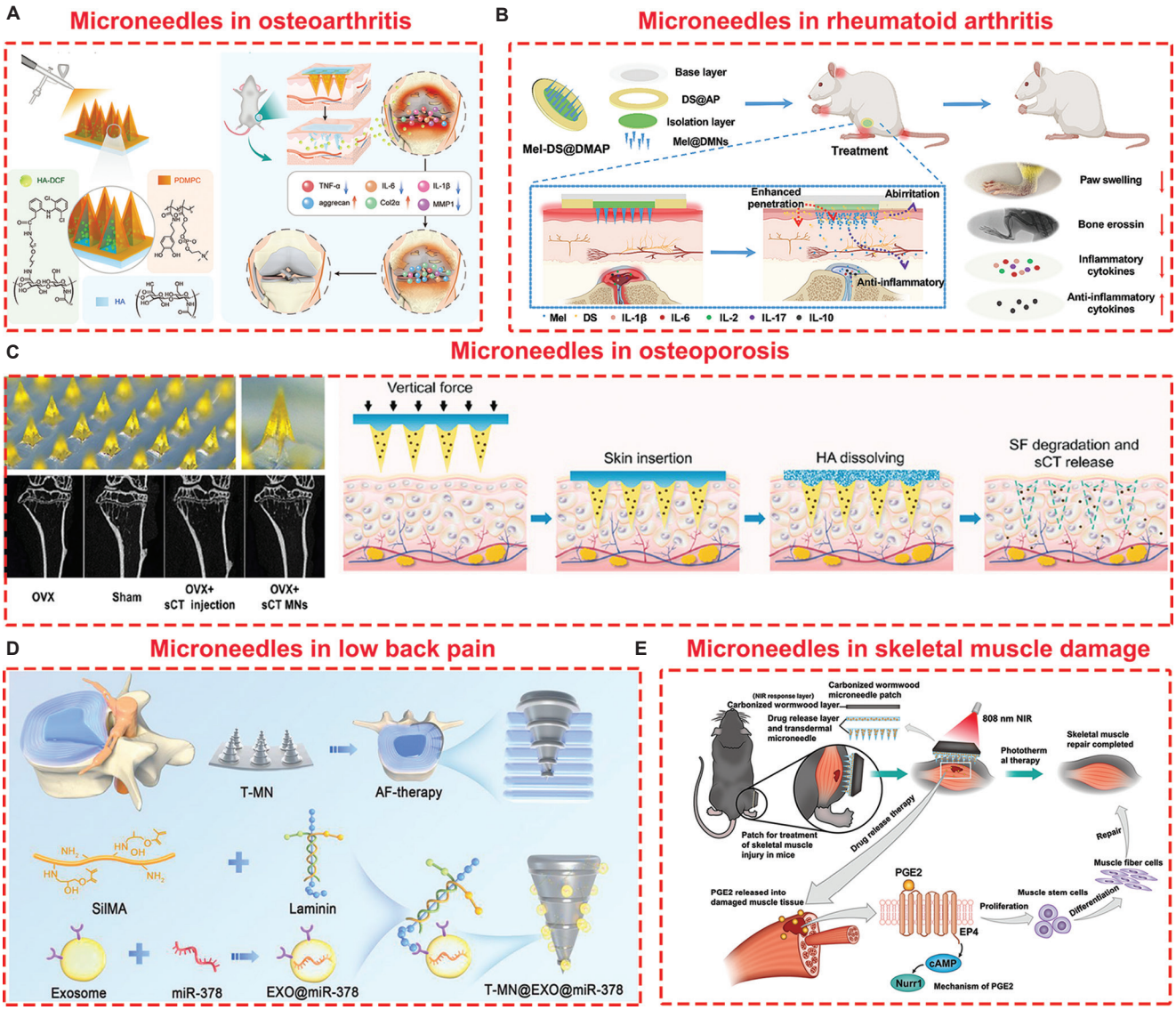

Figure 5. Schematic illustration of the application of natural polymer transdermal drug delivery systems in the musculoskeletal system. (A) Microneedles treatment in osteoarthritis. Reprinted from Li *et al.*[69] Copyright 2022 American Chemical Society. (B) Microneedles treatment in rheumatoid arthritis. Reprinted from Chen *et al.*[41] Copyright 2024 Wiley-VCH GmbH. (C) Microneedles treatment in osteoporosis. Reprinted from Zheng *et al.*[91] Copyright 2023 Elsevier B.V. (D) Microneedles treatment in low back pain. Reprinted from Hu *et al.*[92] (E) Microneedles treatment in skeletal muscle damage. Reprinted from Zhang *et al.*[93] Copyright 2021 Royal Society of Chemistry.
Abbreviations: AF: Annulus fibrosus; AP: Adhesive transdermal patch; cAMP: Cyclic adenosine monophosphate; Col2α: Collagen type II alpha; DCF: Diclofenac; DMN: Double-layer drug-loaded microneedles; DS: Diclofenac sodium; EP4: Prostaglandin E receptor 4; EXO: Exosome; HA: Hyaluronic acid; IL: Interleukin; Mel: Melittin; MMP: Matrix Metalloproteinase; MN: Microneedle; NIR: Near Infrared; Nurr1: Nuclear receptor related protein 1; OVX: Ovariectomy; PDMPC: A self-adhesive lubricating copolymer; PGE2: Prostaglandin E2; sCT: Salmon calcitonin; SF: Silk fibroin; SilMA: Silk fibroin methacryloyl; T-MN: Thread-structural microneedle; TNF-α: Tumour necrosis factor-alpha.

dissolving MNs that co-load celecoxib and α-linolenic acid, providing potent transdermal administration and synergistic anti-inflammatory effects for improved OA treatment. This design not only resolves the issue of MNs dissolution for hydrophobic drug loading but also addresses the problem of microemulsions causing unwanted epidermal retention. Administering the celecoxib and α-linolenic acid-containing microemulsion through array holes to areas rich in dermal vascularisation ensures effective co-delivery to OA lesion sites and provides synergistic anti-inflammatory effects. The physical penetration of the MNs enhances this process. Dissolving MNs opens new possibilities for the transdermal delivery of hydrophobic drugs with the potential to treat OA. Chattopadhyay *et al.*[98] developed a TDDS incorporating a xanthan hydrogel loaded with glucosamine sulfate and diacerein loaded in a nanoemulsion. This system demonstrated the potential to slow the progression of experimental OA *in vivo* investigations. To enhance the transdermal administration of niflumic acid for an improved treatment for OA, Abdelbari *et al.*[99] encapsulated niflumic acid in Brij®-integrated bilosomes. This approach offers a practical and effective method for transdermal niflumic acid delivery. Chen *et al.*[41] developed a bilayer dissolvable MN system designed to provide sustained drug release through a three-step mechanism. This system,

known as HA-diclofenac@ a self-adhesive lubricating copolymer (PDMPC) MNs, operates as follows; diclofenac is covalently bonded with HA, ensuring stable incorporation into the MNs; the MNs facilitate the physical diffusion of the drug through the skin; a lubricant coating on the MNs' surface further slows the drug release, providing extended therapeutic effects. This bilayer dissolvable MN system is anticipated to offer improved therapeutic efficacy compared to traditional HA/diclofenac MNs, potentially reducing skin damage and speeding up recovery, thereby representing a novel, convenient, and effective treatment option for OA, focusing on safety and efficacy. A novel transdermal delivery method for colchicine was evaluated using a combination of confocal laser imaging, ex vivo permeation experiments on isolated rat skin, and *in vivo* assessments of its effectiveness in treating OA in a rat model.[53] Compared to traditional free colchicine, this approach enhances the drug's skin penetration and therapeutic effectiveness. The TDDS for colchicine is safe, patient-friendly, easy to use, and offers prolonged release, making it a promising new option for treating OA.

As OA prevalence increases with age, the need for extended conservative therapy with slow-acting medications becomes more critical. Utilising TDDS based on natural polymers can reduce the adverse effects associated with long-term oral NSAID use. Future research should focus on improving the penetration, robustness, and skin comfort of transdermal systems to advance OA treatment.

3.2. Rheumatoid arthritis

RA is a chronic inflammatory disease characterised by joint degradation, bone erosion, and synovial hyperplasia. This condition often causes severe joint pain, significantly affecting patients' quality of life and leading to varying degrees of disability. The disease disrupts the immune system, as indicated by increased activation and infiltration of neutrophils, macrophages, lymphocytes, and dendritic cells, as well as the proliferation of cells in the synovial membrane.[100] The cells of the adaptive immune system produce autoantibodies as a result of this activation and infiltration process. These antibodies can recognise a broad variety of altered proteins through post-translational modifications.[101] Disease-modifying anti-rheumatic drugs are the primary therapeutics utilised for treating RA and are associated with lower morbidity and mortality rates in patients. Their widespread use has significantly enhanced the long-term prognosis of RA by reducing the incidence of extra-articular symptoms, such as systemic vasculitis.[102]

However, issues such as low bioavailability, rapid metabolism, poor absorption, first-pass effect, and significant side effects limit the effectiveness of these oral and parenteral drugs. TDDS presents a promising alternative by bypassing these challenges. Recent advancements in transdermal technology have enabled the effective management of RA by delivering various therapeutic drugs directly through the skin.[103] A liposomal formulation based on cholesterol and egg lecithin was developed by Chen *et al.*[104] for triptolide transdermal administration. The integration of triptolide-loaded liposomes into a MN array-based hydrogel system significantly enhanced skin absorption and penetration. Pharmacodynamic results demonstrated that in a collagen-induced RA rat model, this treatment significantly reduced joint swelling and decreased levels of fetal liver tyrosine kinase-4, fetal liver kinase-1, and hypoxia-inducible factor 1-α. Zheng *et al.*[91] aimed to improve the adhesive properties of the patch by making it thinner and more flexible, thereby increasing its effectiveness for joint applications, given the proximity of RA treatment sites to joint lesions. A novel composite drug delivery system termed the dissolving MNs and adhesive transdermal patch (DMAP), was developed for simultaneous delivery of multiple drugs to treat RA. Using the anti-inflammatory macromolecular drug melittin as a model, the DMAP-MNs successfully delivered melittin through skin pores created upon application. This novel dosage form, DMAP, shows potential as an effective strategy for RA treatment, paving the way for multi-drug synergistic therapies and offering new perspectives on treating other diseases. The strategy proposes restoring synovial homeostasis and achieving effective RA therapy by simultaneously promoting apoptosis in fibroblast-like synoviocytes (FLS) and inhibiting inflammation through macrophage-mediated mechanisms. To reduce synovial inflammation and prevent bone deterioration, Hua *et al.*[105] developed a HA-based dissolvable MN loaded with dual nanomedicines designed to induce RA FLS apoptosis and modify macrophage activity. HA-MNs loaded with dual nanocomplexes exhibited several significant features; enabled joint accumulation via the extravasation through leaky vasculature and subsequent inflammatory cell-mediated sequestration (ELVIS) effect and biomimetic delivery assisted by human serum albumin; utilised thioketal-crosslinked fluorinated polyethyleneimine 1.8 K for effective transfection of PUMA (p53 upregulated modulator of apoptosis) plasmids into RA FLS; utilised a pH-responsive release mechanism in human serum albumin-nanocomplex-loaded celastrol to suppress lipopolysaccharide-induced inflammatory responses in RAW264.7 macrophages; demonstrated simultaneous modulation of RA FLS and macrophages to restore synovial homeostasis, significantly attenuating collagen-induced arthritis symptoms, reducing inflammatory infiltration, cartilage damage, and bone erosion. Thus, the proposed HA-MN-assisted delivery of dual nanomedicine, which targets FLS apoptosis and inflammation alleviation, shows great promise for slowing arthritis progression and achieving effective treatment of RA.

3.3. Osteoporosis

Osteoporosis, a metabolic disorder, is defined by reduced bone strength and increased fracture susceptibility, making it a primary contributor to systemic bone pain, deformities, fractures, and mortality among older adults. People with osteoporosis are at heightened risk of fractures, primarily due to factors like glucocorticoid use and inflammatory conditions that lead to a decrease in bone mineral density.[106] Today, the primary goal of treatment is to stop or reduce bone loss and prevent fractures through the use of drugs administered either orally or intravenously, including BPs, parathyroid hormone, and estrogens.[107] However, these medications can have significant side effects. Oral BPs, for instance, may lead

to nausea and gastrointestinal issues such as gastritis, erosive esophagitis, and stomach pain. Intravenous BPs, on the other hand, carry risks including renal damage, atrial fibrillation, mandibular osteonecrosis, and other severe complications. About one-third of patients may experience acute reactions such as fever, joint pain, and muscle soreness following their initial injection.[108] Therefore, it is urgent to seek out a new method to optimise drug administration and natural polymer TDDS seems to be an appropriate way to satisfy it.

Li *et al.*[69] developed a composite, separable MN system featuring a HA base and silk fibroin needle tips for transdermal delivery of sCT for the treatment of osteoporosis. Within 2 minutes, the HA base separated from the tips of the silk fibroin needles, demonstrating the effectiveness of the HA-polyethylene glycol/silk fibroin@sCT MNs in penetrating the stratum corneum. This facilitates the prolonged release of sCT by allowing the SF hydrogel depots to embed into the skin. Therefore, the study of composite separable MN technology holds potential as a long-term, efficient transdermal administration route for sCT in the treatment of osteoporosis, potentially displacing conventional subcutaneous injections. Sultana *et al.* created a MN transdermal patch loaded with precisely designed nanotransfersomes to solve issues with bioavailability.[109] The development of MN patches has proven to be an effective method for transdermal delivery of nanotransfersomes. The effective TDD of nanotransfersomes based on gelatin MN has been demonstrated by the outcomes of both in vitro and *in vivo* investigations. To validate their effectiveness in treating osteoporosis, further preclinical and clinical studies are required on the MN-loaded risedronate sodium and ursolic acid-NTRs developed in our laboratory. Another study introduced a new TDDS for risedronate, a BP used in osteoporosis treatment, utilising a vinyl acetate-dioctyl fumarate copolymer as the foundational material.[110] The release kinetics study, analysed using the Ritger-Peppas model, indicated that the system follows super case II transport dynamics. This suggests a complex transport mechanism primarily governed by the movement of polymer chains. The newly developed risedronate TDDS could potentially serve as an effective alternative for treating osteoporosis.

As mentioned earlier, although MNs are generally effective and associated with fewer side effects, skin irritation remains a concern, particularly with prolonged drug retention, such as with alendronate. To address this issue, Terutsuki *et al.*[111] developed a porous MN system that uses electroosmosis and gas-propelled technology to enhance drug delivery into the bloodstream. This approach aims to reduce the drug's retention time in the upper dermis, thereby potentially mitigating skin irritation. ROS, generated and released during inflammation by cells like macrophages and neutrophils, are major contributors to skin irritation. Therefore, incorporating antioxidants such as butylhydroxytoluene and selenium could potentially reduce this effect.

3.4. Low back pain

LBP primarily includes encompasses pain in the lower back, lumbosacral region, and hips as its primary symptoms. The prevalence of lumbago is progressively rising and poses a significant health concern. Chronic lower back pain (CLBP) is marked by central sensitisation, and neuropathic pain components, and may result in maladaptive coping mechanisms and depression.[112] Intervertebral disc degeneration is a primary cause of LBP and disability, especially in older adults.[92] Studies suggest that CLBP may progress from localised inflammation and musculoskeletal damage to a more complex condition. This condition involves ongoing anatomical and functional changes in both the peripheral and central nervous systems.[113] Therapeutic options include physical modalities (e.g., exercise therapy), complementary therapies (e.g., acupuncture), and pharmacological interventions (e.g., analgesics, NSAIDs, and corticosteroid injections).[114] Current therapies are effective at managing symptoms but do not alter the disease or address the underlying causes of pain. Managing CLBP remains challenging, with existing treatments often falling short of providing complete relief. Therefore, there is an urgent need to develop new therapeutic approaches to better address LBP. Given the challenges in managing CLBP, medical professionals and researchers are continually exploring new pain management strategies. One such option is the 5% transdermal lidocaine patch, a local anesthetic initially approved by the U.S. Food and Drug Administration in the early 2000s for post-herpetic neuralgia. Due to its reported effectiveness in alleviating pain with minimal side effects, interest has grown in its off-label use for treating CLBP. Several open-label studies have demonstrated that patients using the 5% transdermal lidocaine patch experienced statistically significant reductions in CLBP severity.[115] The alghedon fentanyl transdermal system represents a new generation matrix patch designed for managing moderate to severe chronic pain, offering continuous systemic delivery of fentanyl for up to 72 hours. Alghedon fentanyl transdermal system employs materials commonly used in transdermal treatments for CLBP and is known for its well-established safety profile.[116] Two other randomised, double-blind, multicentre studies have demonstrated the effectiveness of transdermal buprenorphine for patients with moderate to severe CLBP.[117,118] The primary efficacy assessments, which included pain-specific and quality-of-life evaluation tools, consistently indicated that transdermal buprenorphine was more effective than a placebo.[117] The buccal buprenorphine film used in Belbuca™ offers rapid delivery and flexible dosage adjustments across a wider range compared to conventional transdermal buprenorphine systems. Buccal buprenorphine introduces a novel transmucosal technology designed to potentially enhance and expedite buprenorphine absorption. Consequently, buccal buprenorphine represents a significant advancement in addressing moderate to severe pain associated with CLBP.[118] However, the outcomes of long-term research remain uncertain. The adverse events reported in the trials align with the typical side effects listed on medication labels. To effectively inform patients about potential risks, these factors must be carefully considered when making therapeutic decisions.

3.5. Skeletal muscle damage

The extracellular matrix, supporting tissues, and muscle fibres are the main components of skeletal muscles. The

extracellular matrix, which constitutes about 10% of skeletal muscle structure, is crucial for transferring stresses and aiding in muscle fibre healing after injury.[119] Although skeletal muscle has some capacity for self-healing, this regeneration often falls short of complete recovery. Loss of contractile tissue and severe extracellular matrix fibrosis can lead to muscle fibrosis, which impairs muscle composition and functionality, hinders regeneration, and increases the risk of re-injury, ultimately affecting patients' long-term quality of life.[120] The early inflammatory response, which is a preamble for subsequent repair processes, involves attracting inflammatory cells, producing inflammatory cytokines, and removing damaged tissue. This phase is crucial for effective muscle recovery.[121] The actual repair process involves two related and simultaneous actions: the formation of scar tissue in connective tissue and the regeneration of injured muscle fibres. These processes both compete and work together synergistically. Disruption of this delicate balance can lead to excessive fibrosis, often driven by chronic inflammation and high levels of ROS. Pro-fibrotic cytokines, such as muscle inhibitors and transforming growth factor-β1, are more frequently secreted during prolonged inflammation. Although inflammation and ROS are distinct factors in fibrogenesis, they interact and influence each other's effects.[122]

Conventional drug treatments, such as NSAIDs, cyclooxygenase-2 inhibitors, and corticosteroids, are nonspecific and typically target inflammatory pathways. However, long-term NSAID use has been shown to detrimentally impact skeletal muscle regeneration and contractile function, presumably due to their broad effects on the immune system, which plays a central role in the healing process. Given these considerations, this review examines how TDDS can enhance muscle repair and reduce fibrosis in skeletal muscle injuries. To enhance muscle repair, Sousa Filho *et al.*[123] developed a gel containing a quercetin and β-cyclodextrin inclusion complex and evaluated its effects on muscle oxidative indicators in rats, both alone and in combination with transdermal phonophoresis. Their research particularly indicated that the quercetin/β-cyclodextrin gel alone effectively reduced oxidative stress, suggesting that this formulation could be a promising treatment for skeletal muscle injuries without requiring transdermal phonophoresis administration. Integrating carbonised wormwood into the MN patch endowed it with near-infrared light heating capabilities, which improved the efficiency of prostaglandin E2 delivery and enhanced circulation in the injured muscle area. Experimental results show that this photothermal system, modified with carbonised wormwood and loaded with prostaglandin E2, effectively promotes the proliferation and differentiation of muscle stem cells. This advancement has the potential to significantly boost the healing process for skeletal muscle defects.[93] Kong *et al.*[124] presented a novel method involving the conjugation of an antigenic peptide derived from myostatin with low molecular weight HA for transdermal immunotherapy in muscular dystrophy. This HA-peptide conjugate has the potential to act as a self-adjuvanted transdermal vaccine, offering an early intervention for various conditions, including muscular dystrophy. The use of HA-antigenic peptide conjugates in a straightforward transdermal vaccination approach could pave the way for the development of new vaccine strategies. These findings therefore offer insights into current therapeutic approaches and propose new directions for advancing TDDS for treating skeletal muscle damage. However, further development is needed, including evaluating the long-term biological safety of composite TDDS, optimising controlled drug release, and exploring alternative biomaterial encapsulation methods.

4. Various forms and molecular mechanisms of natural polymer-based transdermal drug delivery system for the treatment of musculoskeletal disorders

In recent years, several strategies using natural polymers for TDDS have been developed to enhance the delivery of various drugs for musculoskeletal disorders. This section reviews the progress in natural polymer-based TDDS, focusing on different forms including MNs, nanoparticles, hydrogels, and nanofibres (**Figure 6**).[125-127] MNs, which significantly improve the penetration of therapeutic agents by piercing the stratum corneum and creating hundreds of reversible microchannels in a minimally invasive manner, have been envisioned as a milestone in effective TDDS. In addition, these devices can be used for painless self-administration of injectable formulations, eliminating the need for healthcare professionals.[128] Nanoparticle drug delivery system has the advantages of long drug cycle and controlled release, improving drug solubility and stability, improving efficacy and reducing toxicity.[129] Hydrogels have desirable properties, including biocompatibility, biodegradability, non-toxicity, lack of sensitisation, ease of application and removal, and high water content make them suitable as transdermal drug delivery carriers. The hydration effect exerted by hydrogels on the skin enhances the penetration of therapeutics across the skin, facilitating the transdermal delivery of drugs.[130] Nanofibres have many advantages, in addition to the controlled release of drugs, these systems can improve the solubility and permeability of embedded drugs due to their porous structure and satisfactory surface area/volume ratio.[131]

4.1. Microneedles based on natural polymers

MNs, mounted on a support base, are an array of needle-like projections ranging from 10 to 2000 μm in height. By applying external pressure, MNs penetrate the stratum corneum, enabling the direct delivery of therapeutics into the deeper skin layers. MNs are a highly promising method for natural polymer-based TDDS due to their ability to effectively breach the stratum corneum while minimising interaction with the dermal nerve system, resulting in painless drug administration[13,132] (**Figure 7**). Natural polymers offer excellent biocompatibility and high degradability, which minimise skin irritation during administration. Their low production costs and superior swelling properties make certain natural polymers ideal materials for fabricating MNs.[133]

Hydrogel MNs are a foundational element of TDDS, composed of swellable natural polymers that form a robust

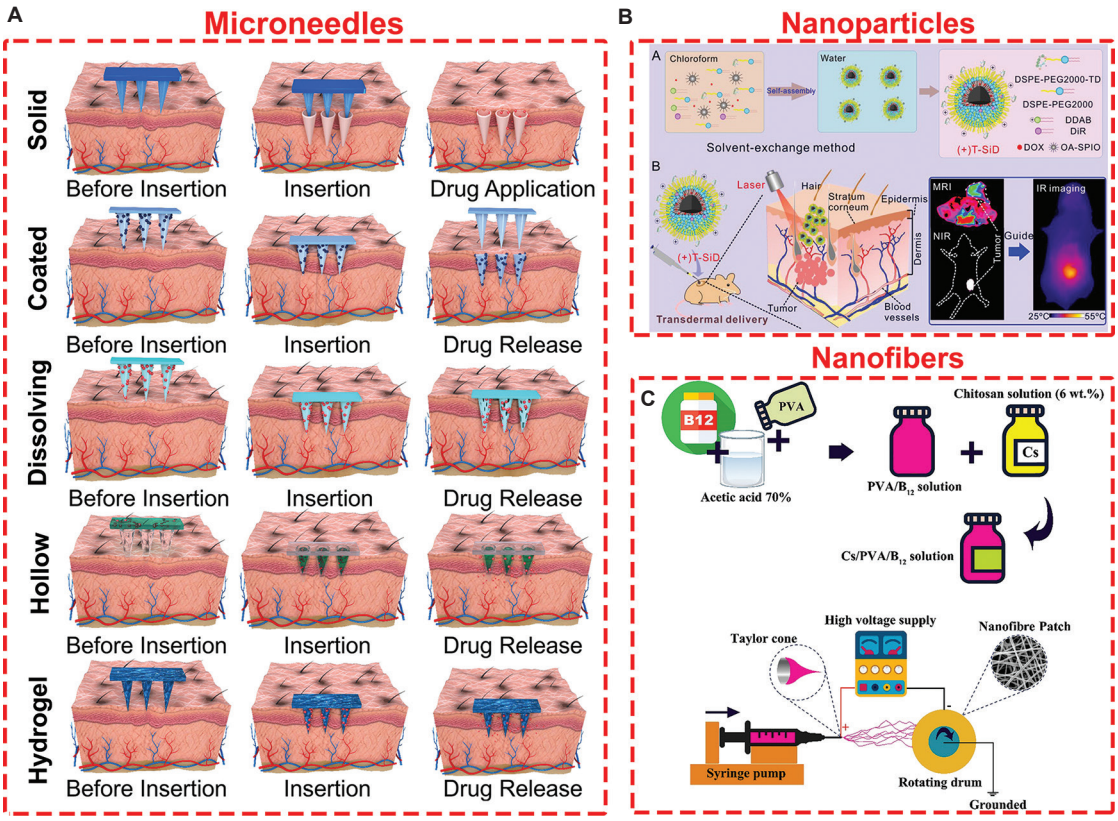

Figure 6. Schematic Illustration of the the forms and molecular mechanism of natural polymer TDDS for musculoskeletal disorders. (A) Microneedles. Reprinted from Zhang *et al.*[125] Copyright 2021 Acta Materialia Inc. (B) Nanoparticles. Reprinted from Yekrang *et al.*[126] Copyright 2023 Elsevier B.V. (C) Nanofibres. Reprinted from Guo *et al.*[127]
Abbreviations: DDAB: Dimethyldioc-tadecylammonium bromide; DiR: 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindotricarbocyanine iodide; DOX: Doxorubicin; DSPE: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine; IR: Infrared; MRI: Magnetic resonance imaging; OA-SPIO: Oleic acid-super-paramagnetic iron oxide nanoparticles; PEG2000: Polyethylene glycol 2000; PVA: Polyvinyl alcohol; TD: Transdermal enhanced peptide; T-SiD: Transdermal nanoplatform based on superparamagnetic iron oxide core and doxorubicin.

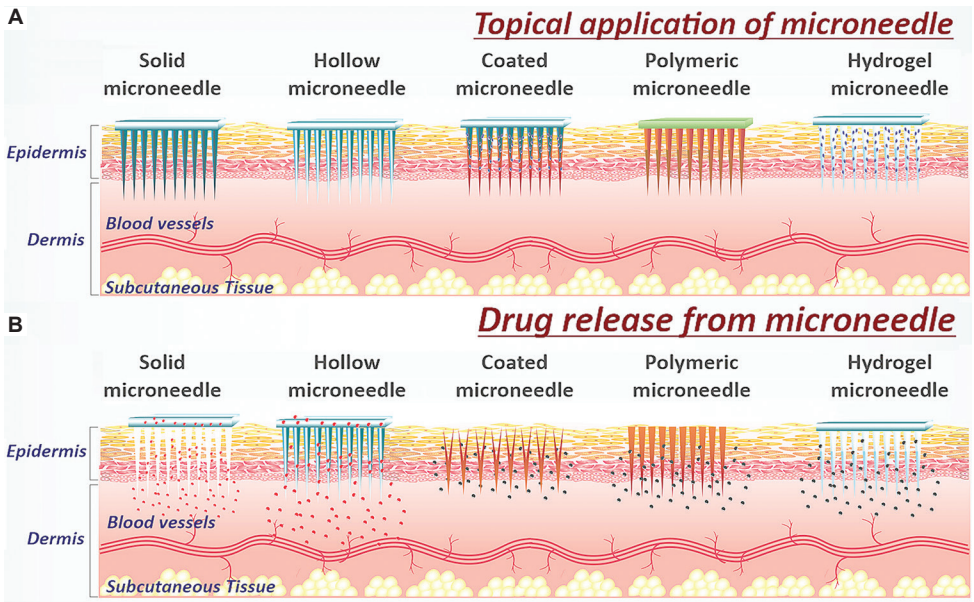

Figure 7. Different types of microneedles in terms of penetration and drug release. The topical application of microneedles (A) and drug release from microneedles (B). Reprinted from Phatale *et al.*[132] Copyright 2022 Elsevier B.V.

three-dimensional network structure (**Figure 8A**).[33] These crosslinked hydrogels are insoluble in water but capable of swelling in aqueous environments. Hydrogel MNs are easy to fabricate and feature a unique drug reservoir or extensive network, allowing for high drug-loading capacity. Cao *et al.*[134] pioneered a HA-based hydrogel MN platform designed to

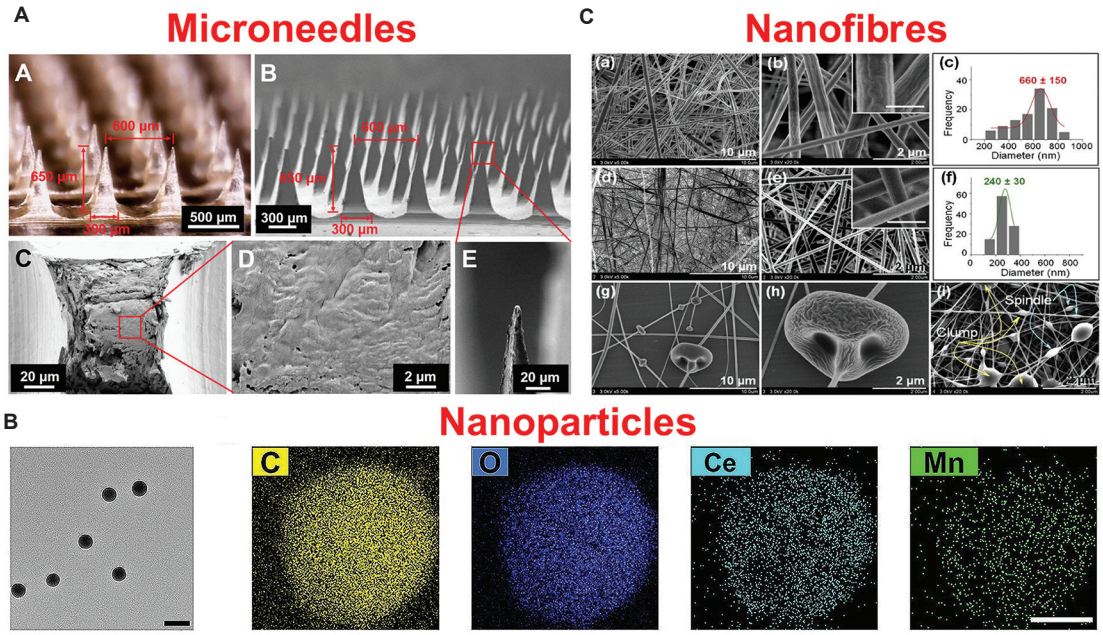

Figure 8. Representative scanning electron microscope images of microneedles, nanofibres and nanoparticles. (A) Scanning electron microscope images of 3-aminophenylboronic acid-modified alginate/hyaluronic acid microneedles arrays, fracture surface and tips. Reprinted from Yu *et al.*[33] Copyright 2017 Elsevier B.V. (B) Transmission electron microscope and scanning electron microscope images of nanoparticles and corresponding elemental mapping images of C, O, Ce and Mn of nanoparticles. Scale bar: 50 nm. Reprinted from Xia *et al.*[85] (C) Scanning electron microscope images of ketoprofen-loaded cellulose acetate nanofibres prepared using a single electrospinning process. Scale bar: 500 nm. Reprinted from Yu *et al.*[140] Copyright 2012 Elsevier Ltd. Copyright Elsevier.
Abbreviations: C: Carbon; Ce: Cerium; Mn: Manganese; O: Oxygen.

deliver chemically modified aptamers for RA therapy. They further developed a hydrogel MN tailored for the transdermal delivery of DNA binding protein DEK-targeting aptamer 6 (DTA6). This MN system maintains its structural integrity upon absorbing the aptamer solution, effectively penetrates the skin, and facilitates the rapid release of DTA6 into the dermis. The DTA6-loaded hydrogel MNs significantly reduce inflammation and protect joints from cartilage and bone erosion in collagen-induced arthritis mice. Based on patient reports, hollow MNs are better tolerated than subcutaneous injections due to their shorter needle length. Abd-El-Azim *et al.*[135] demonstrated the transdermal delivery of teriflunomide encapsulated in solid lipid nanoparticles using hollow MNs to directly administer the therapeutic agent into arthritic joints. This approach presents a promising, user-friendly, and minimally invasive method for effectively treating RA. In the future, such innovative combination systems could provide painless and self-administered alternatives to the invasive intra-articular injections currently in use.

4.2. Nanoparticles based on natural polymers

In general, natural polymer-based nanocarriers have superior biocompatibility and safety than their synthetic counterparts. With the advancement of pharmacology, the emergence of nanocarriers has demonstrated substantial advantages in the field of natural polymer TDD.[19,125] Nanocarriers typically consist of hydrophobic cores and hydrophilic shells, and could potentially address challenges like poor drug solubility in clinical applications and improve the loading efficiency of hydrophilic drugs (**Figure 8B**).[85] When used in natural polymer-based TDDS, these nanocarriers also enhance drug stability and prolong circulation in the body, thereby optimising drug efficacy.[53] Moreover, surface functionalisation of nanocarriers or the use of specific materials to trigger drug release in response to particular stimuli can further enhance their transdermal efficiency and targeting capabilities. Mechanisms for achieving this include: (1) adjusting the particle size of the nanocarrier to facilitate drug penetration; (2) developing drug reservoirs to enhance drug concentration gradients; and (3) improving interaction with the skin to improve the efficiency of natural polymer-based TDD.[136,137] Li *et al.*[138] presented a straightforward and viable approach for TDD using mesoporous silica nanoparticles incorporated into deep eutectic solvent hydrogels to achieve topical treatment of RA. Initially, the nanoparticles were engineered within an arginine–citric acid deep eutectic solvent and subsequently incorporated into a carbomer hydrogel matrix. The deep eutectic solvent-mesoporous silica nanoparticle hydrogel network was robustly integrated through extensive intramolecular hydrogen bonding between hydrogen bond donors and acceptors. This study presents a new approach for applying rigid nanoparticles to the skin, enabling controlled drug delivery and absorption. This method shows promise for providing synergistic benefits in the management of RA.

4.3. Nanofibres based on natural polymers

A class of biological nanocarriers known as nanofibres is distinguished by their length and diameter at the micrometer scale. Compared to other carriers, nanofibres offer a higher surface area-to-volume ratio and enhanced porosity. These

features enable quicker loading of hydrophobic drugs and provide controlled, sustained release of hydrophilic drugs.[139] Appropriate adhesion qualities also provide significant benefits for natural polymer TDD applications. Controlling the drug release rate during nanofibre manufacture is mostly dependent on adjusting the porosity, diameter, and drug-to-polymer ratio[19,126,140] (**Figure 8C**).

Like other nanocarriers, nanofibres improve drug deposition on the skin due to their superior adhesion, while their significant hydrating effect enhances deeper transdermal drug penetration. Teng *et al.*[141] demonstrated that lappaconitine trifluoroacetate and polyvinyl alcohol can be electrospun together to create composite polyvinyl alcohol/lappaconitine trifluoroacetate nanofibrous membranes with sustained release properties. In a mouse model of pain induced by acetic acid, the transdermal delivery of lappaconitine trifluoroacetate via these nanofibrous membranes effectively controlled drug release and alleviated pain. These results suggest that synthetic lappaconitine trifluoroacetate has promising analgesic effects, indicating that these transdermal membranes have the potential to be transformed into effective analgesic patches in the near future. Elshabrawy *et al.*[142] devised a transdermal platform using nanomaterials, employing a combination of advanced techniques such as three-dimensional printing, electrospinning, and electrospraying. The potential of the platform for treating RA in a rat model was later assessed. The patches are composed of a composite layer of electrospun and electrosprayed polyvinyl alcohol nanofibres or nanoparticles conjugated with diclofenac, supported by a layer of electrospun polycaprolactone nanofibres. Moreover, a three-dimensional-printed sodium alginate-based hydrogel infused with rosuvastatin-loaded core-shell lipid nanocapsules and sodium hyaluronate is featured in the patches. Positive results from these trials suggest that the effectiveness of these novel triple-layered transdermal patches for RA treatment in animal models could be significant. However, further research is needed to thoroughly evaluate their efficacy before they can be advanced to clinical trials.

5. Challenges and future perspectives of natural polymer transdermal drug delivery system

Natural polymers offer numerous advantages over their synthetic counterparts due to their ready availability from living organisms, cost-effectiveness, and their potential for chemical modification. The natural polymer-based TDDS enables precise delivery of therapeutic directly to targeted lesions through the skin. This approach not only improves the effectiveness of the drug but also reduces its toxic impact on healthy tissues by avoiding first-pass metabolism.[143] Recent advancements are centred on innovative materials engineered for controlled drug release. These materials have unique macroscopic and microscopic structures as well as distinct chemical properties, allowing for effective utilisation of the polymers' sensitivity and reactivity.[144]

Despite the many advantages of TDDS, certain limitations remain. A major concern is the potential for skin irritation upon application. Although natural polymer-based TDDS has shown promising progress in preclinical studies, further research is needed for broader clinical adoption. The complex purification processes required for natural polymers increase costs significantly, and there is a lack of comprehensive research on their mechanisms for facilitating drug delivery through the skin. Similarly, variations in individual skin attributes—whether normal or pathological—can lead to differing rates of polymer degradation, which may cause premature drug release and adverse effects on healthy tissues. Consequently, the effectiveness of natural polymer-based TDDS in achieving superior therapeutic outcomes compared to traditional methods for treating musculoskeletal diseases involving deep bone and joint tissues remains uncertain.

The future trajectory of natural polymer-based TDDS hinges on the development of intelligent wearable platforms integrating diagnostic and drug delivery functionalities. The overarching objective is to achieve precise, on-demand drug delivery while reducing toxic effects on normal tissues, ensuring deep tissue penetration. Future research should prioritise achieving reproducibility in the preparation of natural polymer-based TDDS, as this is essential for any successful application. It is crucial to design these systems with controllable degradation rates to accommodate the diverse nature of patient skin. Enhancing drug penetration for various musculoskeletal disorders is vital, with a focus on precise targeting and intelligent drug release mechanisms. Interdisciplinary advancements are pushing the development of closed-loop wearable natural polymer TDDS systems, which integrate targeted drug delivery, biosensing, and artificial intelligence technologies. These advanced systems aim to deliver drugs precisely to target sites and release them as needed, paving the way for personalised medicine. While the synthesis and investigation of new polymer combinations will further expand the landscape of drug delivery methodologies, it will simultaneously necessitate a comprehensive understanding of their chemical compositions and physical structure and properties. Increasingly, scientists and engineers are also prioritising environmental sustainability in polymer composite manufacturing, emphasising the use of ecologically safe ingredients and processes throughout the product lifecycle, from synthesis to disposal. In recent years, active enhancement technology has also been developed and widely used. Using them to deliver drugs penetrates the skin more easily and faster. The application of active enhancement techniques is expanding to include magnetophoresis, iontophoresis, electroporation, and ultrasound, which are lacking in this review.

6. Conclusions

Natural polymer-based TDDS is a highly safe and well-tolerated therapeutic approach with significant potential for treating musculoskeletal disorders. It has emerged as a key component of advanced drug delivery systems, offering prolonged bioactivity that reduces dosing frequency and helps to minimise potential side effects. In addition to the outstanding biocompatibility and biodegradability, natural polymers reduce the risks associated with introducing external carrier materials to the skin and normal tissues. Exciting prospects

in polymer-based drug delivery include reaction systems that enable precise drug targeting and controlled drug levels at the therapeutic site. The current challenges and prospects for polymer-based TDDS provide insights into therapeutic approaches for musculoskeletal disorders and propose new directions for advancements in this field.

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Author contributions
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Ethics approval and consent to participate
Not applicable.
Consent for publication
Not applicable.
Availability of data
Not applicable.

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