

Review

Nanoformulation-assisted microneedle transdermal drug delivery system: An innovative platform enhancing rheumatoid arthritis treatment



Yao Wendong^a, Yan Xingxing^a, Xie Xianze^a, Fan Qiaomei^a, Shan Yujun^b, Zhou Shanshan^b, Shi Zheng^{a,b,*}, Xu Hairu^{a,**}

^a The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), Hangzhou 310018, China

^b School of Pharmaceutical Sciences, Zhejiang Chinese Medical University, Hangzhou 310053, China

ARTICLE INFO

Keywords:
Transdermal drug delivery system
Microneedle
Nanoformulation
Rheumatoid arthritis
Nanoformulations combined with MNs

ABSTRACT

A transdermal delivery system offers high bioavailability and favorable patient adherence, constituting an optimal approach for localized administration in rheumatoid arthritis (RA) treatment. However, the stratum corneum (SC) impedes the delivery efficiency of conventional transdermal drug delivery systems. Microneedles (MNs) can temporarily create micropores within the SC, enabling drug distribution via bypassing this barrier and enhancing transdermal delivery effectiveness. Notably, MNs provide a painless method of drug delivery through the skin and may directly modulate inflammation in immune cells by delivering drugs via the lymphatic system during transdermal administration. However, the MN delivery system is not suitable for drugs with low water solubility and stability. Additionally, major concerns exist regarding the safety of using MN delivery for highly cytotoxic drugs, given that it could result in high local drug concentration at the delivery site. While MNs exhibit some degree of targeted delivery to the immune and inflammatory environment, their targeting efficiency remains suboptimal. Nanoformulations have the potential to significantly address the limitations of MNs in RA treatment by improving drug targeting, solubility, stability, and biocompatibility. Therefore, this review provides a concise overview of the advantages, disadvantages, and mechanisms of different types of MNs for RA treatment. It specifically focuses on the application and advantages of combining nanoformulation with MNs for RA treatment and summarizes the current trends in the development of nanoformulations combined with MNs in the field of RA treatment, offering theoretical support for future advancements and clinical applications.

1. Introduction

Rheumatoid arthritis (RA) is a complex systemic autoimmune disease affecting 0.5–1.0 % of the global population [1]. RA manifests clinically with joint swelling, stiffness, and inflammation of the synovial membranes, leading to progressive cartilage and bone destruction [2]. In severe cases, it can cause joint deformities, infections, organ dysfunction, and even mortality [3]. Due to the unclear pathogenesis process, RA remains incurable. Initial treatment typically involves long-term administration of therapeutic drugs, delivered orally or by

intra-articular injection, to manage pain and slow disease progression [4,5]. Examples include nonsteroidal anti-inflammatory drugs (NSAIDs) and methotrexate (MTX). As the disease progresses, treatment may escalate to a combination of disease-modifying antirheumatic drugs (DMARDs) and novel biological agents to target inflammatory factors and immune complexes [6]. Additionally, antibiotics may be used for infections, and high-dose corticosteroids can relieve pain. For critically ill patients, invasive procedures like joint minimally invasive surgery [7], immunosorbent therapy [8], plasma exchange [9], or even stem cell transplantation [6] may be employed to achieve rapid symptom control.

Abbreviations: RA, rheumatoid arthritis; MNs, microneedles; MTX, methotrexate; TDDS, transdermal drug delivery system; SC, stratum corneum; NSAIDs, nonsteroidal anti-inflammatory drugs; NF- κ B, nuclear factor- κ B; JAK/STAT, Janus kinase/signal transduction and transcriptional activator; TNF- α , tumor necrosis factor- α ; IL-1 β , interleukin-1 β ; SLN, solid lipid nanoparticles; PVA, polyvinyl alcohol; HA, hyaluronic acid; PVP, polyvinylpyrrolidone; CMC, carboxymethylcellulose; EN, etanercept; NT, neurotoxin; CS, chondroitin sulfate.

* Corresponding author at: The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), Hangzhou 310018, China.

** Corresponding author.

E-mail addresses: shizheng@zcmu.edu.cn (S. Zheng), eak@163.com (X. Hairu).

<https://doi.org/10.1016/j.biopha.2024.117219>

Received 3 June 2024; Received in revised form 21 July 2024; Accepted 26 July 2024

Available online 30 July 2024

0753-3322/© 2024 The Authors. Published by Elsevier Masson SAS. This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>).

Traditional Chinese medicine approaches [10], such as herbal decoctions, acupuncture, and moxibustion, can be used as complementary therapies alongside medications. However, drug therapy remains the mainstay of RA treatment. Despite some efficacy of traditional therapies and novel biological agents [11], limitations exist: (1) oral medications can cause gastrointestinal side effects and have limited absorption; (2) intra-articular injections suffer from poor patient adherence, increased infection risk, and potential adverse effects on surrounding tissues. These limitations hinder further advancements in RA treatment [12]. Therefore, it is crucial to develop novel drug delivery technologies with superior bioavailability and improved patient adherence to address these shortcomings.

The transdermal drug delivery system (TDDS) is an ideal alternative to conventional delivery methods [13]. TDDS for RA are gaining considerable interest due to their numerous advantages. These systems can bypass gastrointestinal complications and first-pass effects, alleviate injection-related pain, and provide localized action for faster pain relief [14]. In addition, the ease of self-administration further enhances the benefits of this delivery system [15]. As a more adaptable alternative therapy, TDDS is rapidly approaching the efficacy of oral and injection formulations. The transdermal delivery market is projected to reach \$9.6 billion by 2027 [16]. However, the presence of the stratum corneum (SC), the outermost layer of the skin, significantly hinders the effectiveness and efficiency of transdermal drug delivery [17]. Only some lipophilic [18] and small molecule drugs (relative molecular weight < 500) [19] can passively diffuse across the SC to a limited extent. In the context of RA treatment, even extended-release TDDS fail to achieve sustained therapeutic drug levels in the bloodstream, leading to suboptimal therapeutic efficacy [20,21]. The significant barrier posed by the SC restricts the availability of transdermal formulations for RA compared to oral and injectable options. In recent years, several strategies have been explored to enhance transdermal drug absorption, including iontophoresis [22], osmotic promoters [23], electroporation [24], and ultrasound [25]. However, these approaches still face limitations, particularly in delivering macromolecules and drugs with low permeability. Therefore, researchers worldwide are actively researching novel transdermal delivery techniques to overcome these limitations and improve the treatment of RA.

Microneedles (MNs) are minimally invasive devices that can penetrate the stratum corneum [26]. They comprise arrays of needles, typically several hundred micrometers in diameter and ranging from 20 to 2000 μm in height, arranged on a base substrate [27,28]. MNs can permeate the SC without causing significant discomfort to patients. Henry S. utilized MNs for transdermal drug delivery for the first time in 1998 [29]. This innovative approach to drug administration has spurred significant advancements in MN technology within the field of biomedical engineering. Different MN types have been developed to facilitate either direct or indirect drug delivery [17]. In the context of RA treatment, where effective transdermal drug delivery is crucial, MNs offer a valuable solution. They can overcome the challenge faced by traditional transdermal formulations by penetrating the SC without affecting pain receptors [30], thereby significantly improving patient adherence compared to subcutaneous injection. Microneedles have found applications in treating various conditions, including tumors [31], skin diseases [32], diabetes [33], tissue regeneration [34], and others. Furthermore, MNs fabricated with bioresponsive and biosensing materials have enabled painless detection [35] and therapeutic drug monitoring [36]. These advantages position MNs as a superior and more convenient option for treating and managing RA progression compared to other drug delivery methods (Table 1) [37]. However, MNs possess certain inherent limitations, including the inability to precisely target drug delivery and the challenge of delivering drugs with low solubility [30,38]. Considering the characteristics of the RA microenvironment, designing and constructing nanoformulations for RA treatment hold great significance for improving drug efficacy and reducing adverse reactions [39,40]. Nanoformulations have the potential to enhance drug

Table 1

Advantages and disadvantages of MN-based RA treatment compared with conventional RA drug treatment.

Administration	conventional RA drug treatment			MN-based RA treatment Transdermal
	Oral	Injection	Intra-articular injection	
Pain (patient compliance)	++	-	-	++
Absorb	+	++	++	++
Targeting	-	-	++	+
Safety	++	+	-	++

Note: "-" indicates poor quality; "+" indicates good; "++" indicates very good

targeting precision, increase drug solubility and stability, and improve the safety profile of drugs [40], effectively addressing the aforementioned shortcomings of MNs. This paper provides a comprehensive review of the advantages, disadvantages, and mechanisms of MNs in treating RA. It also discusses the classification and use of MNs in RA treatment. We focus particularly on the advantages and application of nanoformulations combined with MNs for RA treatment. We summarize the current development and limitations of nanoformulations combined with MNs in the field of RA treatment (Graphical abstract), with the aim of offering theoretical support for future development and clinical applications.

2. Mechanism of MNs in RA treatment

RA is a chronic inflammatory disease with a complex etiology that remains under investigation. Multiple signaling pathways are known to influence the progression of RA [41]. These pathways include the activation of inflammatory cytokines, nuclear factor- κ B (NF- κ B), Janus kinase/signal transducer and activator of transcription (JAK/STAT), and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt). The primary pathogenic mechanism of RA involves the production of pro-inflammatory factors like tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and IL-6. These factors activate macrophages in inflamed joints, leading to the release of additional inflammatory mediators and the production of matrix metalloproteinases by synovial cells, ultimately exacerbating inflammation [42,43]. One of the most promising mechanisms by which MNs can contribute to RA treatment involves the creation of temporary micropores within the stratum corneum. This allows for the direct delivery of drugs to the dermis or epidermis, significantly enhancing drug penetration and therapeutic availability [44]. Importantly, upon penetrating the epidermis, MNs do not typically come into contact with blood vessels. Consequently, drugs released from MNs are primarily transported via the lymphatic system rather than the bloodstream [18]. The lymphatic system and its associated lymph nodes serve as crucial sites for immune cell development and residence, additionally functioning as transportation hubs for immune cells to reach target organs. Notably, MNs have the potential to deliver drugs directly to immune cells implicated in RA, thereby modulating their activity (Fig. 1) [45,46]. In summary, the proposed primary mechanism by which MNs combined with drug therapy can benefit RA treatment is as follows: MNs are inserted through the SC, creating transient disruptions in the targeted dermal or epidermal layer to facilitate drug delivery. This allows for the controlled, rapid, or sustained release of drugs specifically aimed at regulating relevant signaling pathways and inflammatory factors. Compelling evidence supports the efficacy of using MNs for drug delivery in RA treatment. During RA therapy, drugs are loaded into MNs for targeted delivery to the site of inflammation. MNs effectively penetrate the SC, creating micropores that enable transdermal drug delivery from the epidermis to the dermis [47]. Once within the upper dermis, the drugs disperse and reach the systemic circulation, directly inducing apoptosis in synovial cells. Additionally, MNs can suppress the production of inflammatory

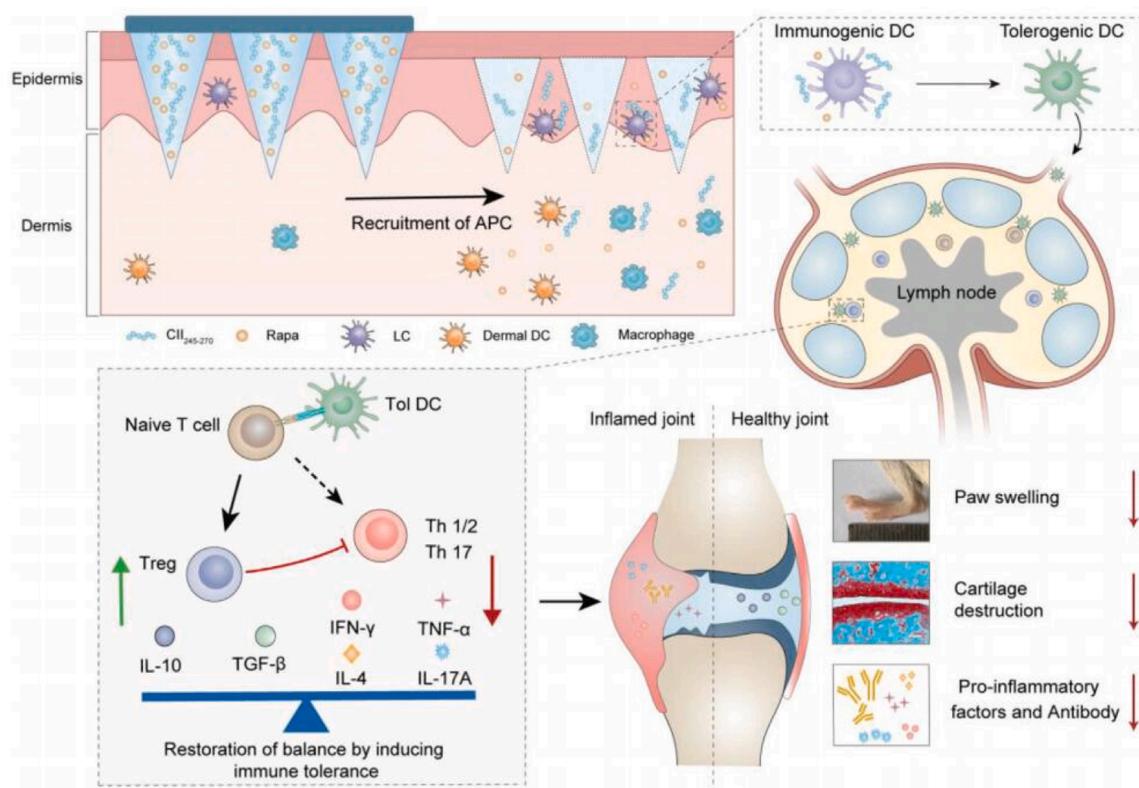


Fig. 1. Schematic illustration of the microneedle-mediated delivery of autoantigen and rapamycin for tolerance induction in RA. The fabricated microneedles successfully delivered autoantigen and rapamycin into the skin and modulated the phenotype of DCs to tolerogenic, which allows further activation of systemic Treg cells and expression of anti-inflammatory mediators, for inhibiting the polarization of Th1/2 and Th17 T cell phenotypes and the expression of inflammatory profiles. Reprinted with permission from ref [46].

mediators like IL-1 and IL-6, inhibit the proliferation of blood vessel cells, and enhance the secretion of adenosine, which further restricts the proliferation of immune cells [48].

These findings suggest that the therapeutic efficacy of drug-loaded MNs in RA treatment is directly linked to the efficiency of transdermal penetration and the depth of drug delivery. In other words, the morphology of the MNs, including needle length, diameter, and tip sharpness, as well as the applied force, speed, and density of the MN array, all significantly influence the therapeutic outcome. Studies have evaluated the *in vitro* permeation of paeoniflorin using ethosomes and MNs as transdermal delivery systems to penetrate the SC. The study demonstrated that MNs significantly enhanced the permeation of paeoniflorin compared to using ethosomes alone or MNs alone [42]. These studies identified the optimal auxiliary parameters as a needle length of 500 μm, a pressure of 3 N, and an action period of 3 minutes. Notably, the cumulative penetration of paeoniflorin increased with increasing tip length, pressure, and duration time [49]. Therefore, optimizing several aspects of MN design is crucial to enhance the efficacy of MN use, including MN morphology, MN sharpness, application speed and force, as well as MN length and density.

3. Advantages and disadvantages of MNs in RA treatment

The concept of microneedles was first proposed in 1976 as a patch containing an array of microscopic projections attached to a backing layer [15,44]. Upon topical application, these needles are designed to penetrate the stratum corneum, creating microchannels that allow subsequent drug permeation through the skin. As a novel TDDS, the needles of MNs are of a dimension that enables the absorption of topical drugs into the bloodstream via these micropores without causing damage to blood vessels [30]. Therefore, MNs offer a promising alternative

drug delivery approach by creating microchannels in the SC using non-invasive techniques. This significantly enhances drug delivery efficiency, consequently addressing the limitations of conventional transdermal drug delivery that lead to suboptimal treatment results [17]. MNs boast the advantages of superior safety and long-term patient compliance, potentially leading to a substantial reduction in medical expenses, making them an exceptional alternative treatment [50]. Notably, the application of therapeutic drugs with MNs enables localized transdermal distribution, which is impossible with traditional topical delivery methods due to the barrier posed by the SC [51]. In the context of RA, B cells and plasma cells contribute to the production of antibodies that trigger a localized inflammatory response. MNs can potentially deliver therapeutic drugs directly to the synovial membrane, thereby reducing this inflammatory response. MNs offer several advantages that make them particularly attractive for transdermal drug delivery in RA treatment. Firstly, MNs bypass the first-pass effect, leading to a rapid onset of action and improved bioavailability while reducing potential systemic toxicity [52]. This is a crucial benefit considering the chronic nature of RA and the need for long-term therapy [37]. Additionally, MNs facilitate sustained and localized drug release, ensuring consistent plasma drug concentrations for extended durations, thereby reducing the frequency of administration [17,53]. Compared to conventional delivery systems, MNs provide greater control over drug delivery and improved efficacy in RA treatment. These combined advantages make MNs a very promising approach for transdermal drug delivery in RA.

While MNs effectively address the challenge of transdermal drug delivery by overcoming the stratum corneum barrier, their application for RA treatment still faces several significant hurdles. These limitations include the inability of MNs to deliver drugs with poor aqueous solubility or stability, and the lack of precise targeting within the inflamed

RA microenvironment. Addressing these limitations is crucial for the widespread adoption of MNs in RA therapy.

4. Classification and application of MNs in RA treatment

MNs can be classified into several categories, each offering unique functionalities and advantages. Fabrication methods, materials, and drug release mechanisms are the primary criteria for MN classification (Fig. 2). Solid MNs, dissolving MNs, hollow MNs, and hydrogel-forming MNs are all utilized in treating RA (Tables 2,3). These MN variations offer significant advantages in drug delivery, preparation processes, and application. In terms of drug delivery strategies, solid MNs and hollow MNs are employed for indirect transdermal delivery. Dissolving MNs can be directly loaded with drugs for delivery while hydrogel-forming MNs encompass all the aforementioned delivery properties. These MN variations can potentially enhance the transdermal delivery of therapeutic drugs, minimize side effects associated with subcutaneous injection, and achieve anti-inflammatory benefits. Recently, there has been a surge of interest among researchers in MN-based drug delivery systems, making it a prominent area of investigation. The use of MNs in the treatment of RA will be further explored in greater detail.

4.1. Solid MNs

Small-molecule drugs with a relative molecular weight below 500 can passively permeate and be absorbed through the SC. However, when larger doses of these drugs are needed, increased dosage often fails to translate directly into enhanced therapeutic effect. Solid MNs, typically fabricated from materials like silicon, titanium, stainless steel, and ceramics, represent the earliest studied type of drug-free microscale array [54]. Utilizing MNs can enhance the transdermal penetration of drugs and improve their therapeutic efficacy. Solid MNs can be produced through a variety of techniques including electroplating, photochemical etching, micro-grinding, and laser cutting. Additionally, hot stamping and the combination of photolithography and electroforming can also be used to fabricate solid MNs [54,55]. The application of solid MNs relies on a two-step process. First, transient microchannels are formed in the skin. Then, drugs are applied to the preprocessed skin as a solution,

cream, or patch to facilitate absorption by passive diffusion. Lornoxicam, a potent small-molecule non-steroidal anti-inflammatory drug with low water solubility but high permeability, demonstrates unsatisfactory results with conventional administration. However, the use of solid MNs in a transdermal delivery system significantly enhanced the effectiveness of lornoxicam cellulose microbubble gel produced by emulsion solvent diffusion. This approach achieved a 72 % reduction in inflammation within 4 hours, with no adverse side effects such as erythema or irritation observed [56]. Triptolide liposome [57], bee venom gel [58], and paeoniflorin ethosome [49] are all viable options for treating RA by transdermal delivery using solid MNs.

Solid MNs effectively address the challenge of limited transdermal penetration associated with conventional methods. By combining them with established formulations, solid MNs can enhance drug permeation and improve therapeutic efficacy. However, they possess limitations such as the inability to directly load drugs, the potential for residual materials left in the skin, a two-step administration process, and the transient nature of microchannels [59]. These limitations present opportunities for further development and refinement. Despite these challenges, there is significant interest in utilizing solid MNs for RA treatment due to their potential for greater control compared to traditional injectable approaches [60].

4.2. Hollow MNs

The materials used to fabricate hollow MNs are similar to those for solid MNs, primarily ceramics, metals, silicon, and glass. As the name suggests, hollow MNs possess a hollow channel within each needle, enabling the delivery of small volumes of drugs through the skin, akin to a micron-scale syringe. This method is suitable for delivering biologics such as proteins, vaccines, and oligonucleotides. Hollow MNs offer a greater drug loading capacity compared to solid MNs, coated MNs, and dissolving MNs [15,44]. Teriflunomide, the biologically active metabolite of the anti-RA drug leflunomide, exhibits severe side effects on the liver and kidneys when administered systemically. It is also associated with gastrointestinal symptoms like diarrhea and colitis. Several studies have successfully encapsulated teriflunomide into solid lipid nanoparticles (SLNs) for transdermal delivery to RA-affected joints using

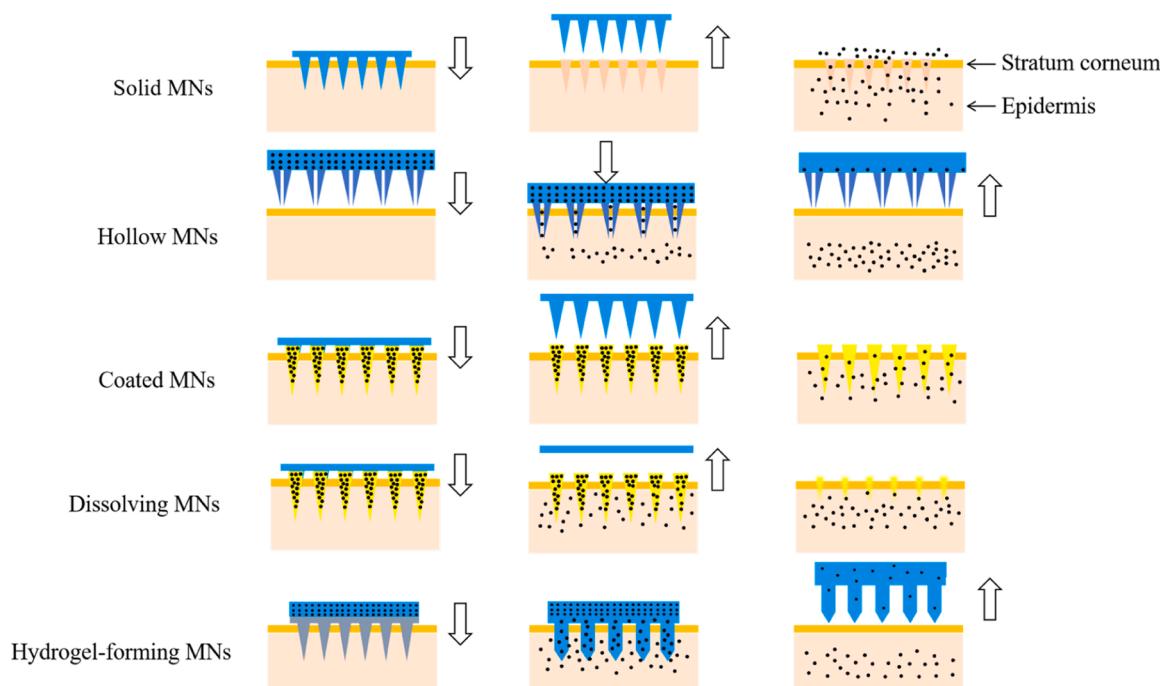


Fig. 2. Classification and mechanism of microneedle in transdermal drug delivery.

Table 2

Classification and treatment efficacy of MNs in the treatment of RA.

Type	Materials	Drugs	Processing Method	Pros/Cons	Application to RA and Efficacy	References
Solid MNs	Stainless steel	Lornoxicam-loaded cellulosic microsponge gel	Electroplating, photochemical etching, micro-grinding, laser cutting, hot stamping, the combination of photolithography and electroforming	① Permeating the SC ② Painless ③ Local administration (1) Lacking drug loading capability (2) The possibility of leaving waste in the skin (3) More complex to administration	The penetration of the drug-carrying gel significantly improved, and inflammation was reduced by 72 % within 4 h	[56]
	Stainless steel	Bee venom gel		Time-dependent of microchannels	Promote the skin permeability of active macromolecules in bee venom gel, reduce the level of NO in the serum of inflammatory rats, and significantly inhibit the occurrence of joint inflammation	[58]
Dissolving MNs	HA	CII peptide autoantigen, rapamycin	Molding, casting, 3D printing	① Excellent biocompatibility, solubility, and permeability ② Painless ③ Local administration ④ High safety ⑤ Sustained release or even controlled drug release (1) Humidity affects mechanical strength (2) Distribution of the drug at the needle tip	The immunized microneedles efficiently recruit antigen-presenting cells and nearly completely eliminate RA symptoms and inflammatory infiltrations.	[46]
	HA	Etanercept			MNs showed good bioequivalence and higher compliance compared with subcutaneous injection	[71]
	PVP, CS, CMC	Neurotoxin			Serum levels of TNF- α and IL-1 β decreased by DMN, the cumulative transdermal rate reached 95.8 %	[30]
	PVA, PVP	Meloxicam			Drug loading up to 98.17 %, Enhanced permeability	[72]
	HA	Artemether			Artemether-loaded DMNs could reverse paw edema painlessly, similar to artemether intramuscular injection.	[74]
	PVP, CS, PVA	Brucine			Serum levels of TNF- α and IL-1 β decreased, and the cumulative transdermal rate reached 95.8 %	[75]
	HA, PVP, PVA	Tocilizumab; Apt1-67			Compared with subcutaneous injection, the DMN was of great advantage in inhibiting bone erosion and alleviating symptoms	[76]
	HA	Melittin			Demonstrating continuous controlled drug release, reducing serum TNF- α , IL-1 β , and IL-6 levels, significantly alleviating ankle joint damage	[77]
	PVA	Tofacitinib			Within 4 h of administration, 95 % of the drug released, 82 % of the drug penetrated, and the histological changes tended to be normal	[78]
Hydrogel-forming MNs	HA	Aptamer targeting DAT6	Molding, casting, 3D printing	① Excellent biocompatibility, solubility, and permeability ② Painless ③ Local administration ④ High safety	Reduced the expression of TNF- α and IL-6, better efficacy than intravenous injection	[83]
	PVA, PVP	Methotrexate		⑤ Sustained release or even controlled drug release (1) Humidity affects mechanical strength (2) Distribution of the drug at the needle tip	Bypassing the SC, delivering variable doses of methotrexate more	[84]

(continued on next page)

Table 2 (continued)

Type	Materials	Drugs	Processing Method	Pros/Cons	Application to RA and Efficacy	References
				(3) Extended micropore healing and increased susceptibility to infection	efficiently, continuous transdermal drug delivery	

Table 3

Nanoformulation-assisted MNs in the treatment of RA and their advantages.

Type	Material	Nanoformulation	Drugs	Advantages	References
Solid MNs	Stainless steel	Ethosome	Paeonin	Having enhanced skin permeability than ethosome itself	[49]
	-	Liposome	Triptolide	Superior safety and enhanced efficacy against RA compared to the original triptolide	[57]
Hollow MNs	Stainless steel	Solid lipid nanoparticles	Teriflunomide	Significantly improved the therapeutic effect of teriflunomide in the treatment of RA with no notable adverse side effects	[61]
	Stainless steel	Emulsomes	Hypericin	Combined with photodynamic therapy, the presented therapeutic platform showed superior joint healing efficacy	[62]
Dissolving MNs	Peach gum, PVA, HA	PLGA nanoparticles	Tetrandrine	Enhanced permeability, effectively improving the inflammatory response of synovial membrane and the formation of neovasculature.	[90]
	PVP	Nanostructured lipid carriers	Aconitine	This preparation can be continuously released to enhance anti-RA efficacy and reduce side effects	[73]
	HA	Bovine serum albumin-modified cerium/manganese oxide nanoparticles	Methotrexate	The innovative approach significantly enhanced drug delivery efficiency, reduced RA inflammation	[109]
	PVP	Folate modified microspheres	Methotrexate	Facilitated sustained and controlled transdermal delivery, mitigating metatarsal edema in arthritic rats.	[115]
	HA	Neutrophil membrane functionalized PLGA nanoparticles	Indomethacin	Provides the ability to bind cytokines and target inflammatory joints.	[116]

hollow MNs. This approach has demonstrated a significant increase in the therapeutic efficacy of RA treatment without causing any notable side effects [61]. Similarly, hypericin emulsomes combined with hollow MNs have shown superior joint healing efficacy compared to other formulations, acting as a non-invasive photodynamic platform for RA treatment [62].

Due to their unique hollow structure, the fabrication of hollow MNs often requires high-precision manufacturing techniques [63], such as lithography, etching, and microelectromechanical systems (MEMS). Three-dimensional (3D) printing is also emerging as a promising fabrication method. Hollow MNs offer the advantage of controlled drug delivery, allowing for regulation of dosage and release time through the application of external stimuli. Additionally, pressure can be applied to enhance the drug delivery rate for rapid administration purposes [64]. However, these advantages are counterbalanced by challenges associated with the complex manufacturing process and the potential for skin tissue to obstruct the hollow microchannels within the needles.

4.3. Coated MNs

Coated MNs represent an evolution of solid MNs designed to address the complexities associated with the two-step application process. Both solid and coated MNs share substantial overlap in terms of materials and fabrication techniques. The key distinction lies in the addition of a thin layer of therapeutic agent coating the tip surface of coated MNs [65]. Moreover, the application of coated MNs offers a unique advantage: the detachment of the drug coating after administration, enabling rapid separation and delivery of the therapeutic agent [66]. Currently, dip-coating and solvent-casting techniques are the two most prevalent methods for producing coated MNs [44]. Coated MNs are particularly well-suited for vaccine delivery due to the benefits associated with prolonged activity. However, a primary drawback of coated MNs is their limited drug-loading capacity. An increase in the coating thickness can compromise the sharpness of the needle tip and hinder effective skin penetration.

While clinical trials have not yet documented the use of coated MNs in RA treatment, ongoing research and technological advancements

suggest their potential for widespread application in this therapeutic area.

4.4. Dissolving MNs

The development of dissolving MNs has been driven by the potential for complications associated with previously mentioned MN types, such as the presence of sharp waste and the possibility of tip fracture. Dissolving MNs are comprised of biocompatible and biodegradable polymers, including polyvinyl alcohol (PVA), hyaluronic acid (HA), polyvinylpyrrolidone (PVP), carboxymethylcellulose (CMC), dextran, and saccharides [30,67]. These materials dissolve completely upon encountering interstitial fluid in the skin, eliminating the risk of sharp debris and the potential for iatrogenic infection that could arise from reusing MNs [68]. The composition of dissolving MNs can be tailored to achieve sustained drug release lasting for several months [69]. Dissolving MNs are primarily fabricated using molding or casting methods. Maintaining sufficient mechanical strength in the tips throughout the manufacturing process is crucial to ensure effective skin penetration and prevent wasted drug doses [70]. Their exceptional biocompatibility and excellent solubility make dissolving MNs widely used for drug delivery in RA treatment, enabling efficient delivery of therapeutic agents.

Dissolving MNs is a rapidly developing technology with several advantages over traditional injection methods. They offer enhanced safety, simplified control over drug release, and the ability to eliminate potential secondary damage caused by needle reuse as medical waste. Etanercept (EN) is a standard therapeutic approach for treating RA, typically administered via subcutaneous injection in clinical settings. However, this method suffers from drawbacks such as low patient compliance and increased risk of infections. Studies have explored using dissolving MNs fabricated through microfabrication techniques as an alternative transdermal delivery system for EN. This approach demonstrated enhanced skin permeability and promoted skin recovery following application. In a mouse model of RA, dissolving MNs effectively mitigated arthritic symptoms, exhibited favorable bioequivalence, and achieved greater patient adherence compared to traditional injections [71]. These findings suggest that dissolving MNs have the

potential to serve as a viable alternative to subcutaneous injections for EN delivery. Neurotoxin (NT), a key peptide component of cobra venom, possesses anti-inflammatory and immunosuppressive properties. Clinically, it is administered by intramuscular injection. However, its high

molecular weight hinders its routine transdermal delivery. Our research group previously addressed these limitations by developing a novel NT-loaded, two-layer dissolving MN using polyvinylpyrrolidone (PVP) and chondroitin sulfate (CS) fabricated through a 2-step centrifugation

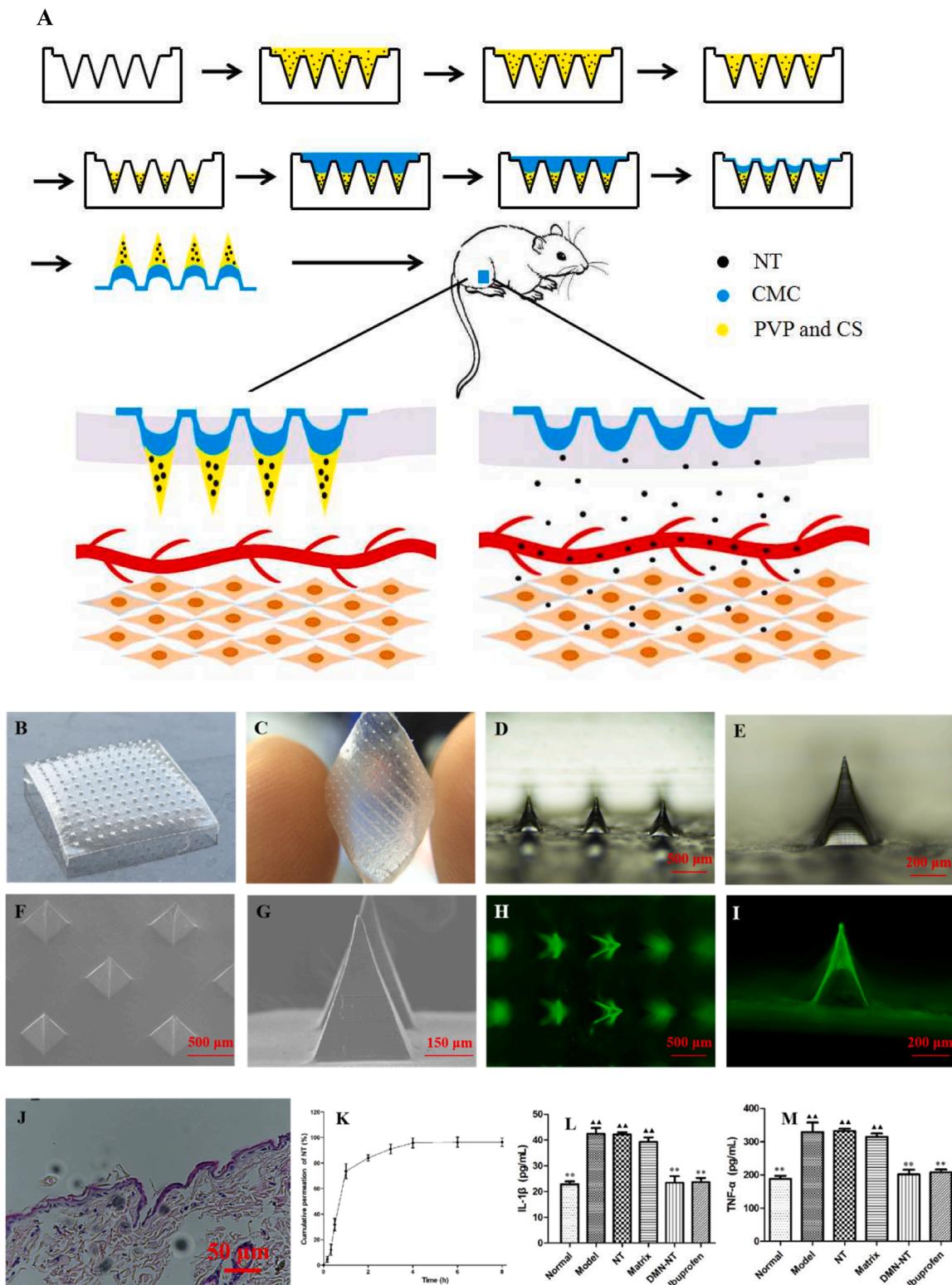


Fig. 3. Preparation of DMN-NT and in vivo drug release mechanism (A). Photographs of whole DMNs (B) and curving DMNs (C). Bright field micrographs of DMNs 40X (D) and 100X (E). Scanning electron micrographs of DMNs 50X (F) and 150X (G). Inverted fluorescent micrographs of DMNs 40X (H) and 100X (I). The depth into the skin of DMNs-NT (J). n vitro transdermal delivery profile of NT from DMNs in rats skin ($n = 8$) (K). IL-1 β (L) and TNF- α (M) in serum of rats in different groups (Compared with model group: * $P<0.05$, ** $P<0.01$; Compared with blank group: ^ $P<0.05$, ^^ $P<0.01$). Reprinted with permission from ref [30].

technique (Fig. 3). This MN design enables sustained delivery of NT for RA treatment. The study demonstrated a significant decrease in serum levels of TNF- α and IL-1 β , along with alleviation of ankle joint injury. The cumulative transdermal delivery rate of NT reached 95.8 % within 4 hours. No adverse reactions were observed following a 15-day administration period. These findings highlight the favorable morphology, mechanical strength, skin permeability, and stability of the NT-loaded MNs, suggesting promising prospects for their use in RA treatment [30]. Furthermore, other anti-inflammatory drugs such as meloxicam (Fig. 4) [72], aconitine [73], artemether [74], brucine [75], tocilizumab [76], melittin [77], and others have been successfully incorporated into dissolving MNs [78]. This innovative approach offers a promising therapeutic option for RA due to its excellent permeability and improved patient adherence. However, a crucial limitation restricting the broader use of dissolving MNs in the field of biomedical engineering is their moisture-dependent mechanical strength. This can lead to low penetration through the SC and uneven drug distribution at the needle tip [79]. Future research efforts should focus on optimizing the polymer composition of dissolving MNs to achieve uniform drug distribution and enhance bioavailability.

4.5. Hydrogel-forming MNs

Hydrogel-forming MNs share similarities with dissolving MNs in their functionality. They penetrate the stratum corneum, release their drug cargo, and eliminate tip waste. However, a key distinction lies in the hydrophilic nature of the hydrogel component. Following penetration of the SC, hydrogel-forming MNs absorb interstitial fluid present between skin cells [80]. This absorption triggers expansion of the MNs, creating channels that facilitate drug delivery into the body. Therefore, selecting materials with desirable biocompatibility and swelling characteristics, such as poly (methyl vinyl ether)/maleic acid, carboxymethyl cellulose (CMC), and branching starch, is crucial [81]. While classified as a subtype of dissolving MNs due to their hydrogel properties, hydrogel-forming MNs offer several advantages [82]. They possess the capability to deliver precise and higher drug payloads, while enabling controlled release at the target site. Exploiting this property, DTA 6, a nucleic acid-targeting aptamer designed to block DEK protein in RA, demonstrated enhanced efficacy when delivered via hydrogel-forming MNs compared to intravenous injection [83]. Additionally, hydrogel-forming MNs facilitated sustained and effective transdermal delivery of methotrexate at varying doses by leveraging the progressive and controlled release properties of the hydrogel [84]. These findings highlight the specific advantages of hydrogel-forming MNs in improving drug encapsulation and controlling release profiles.

Hydrogel-forming MNs are primarily composed of polymeric materials with excellent water-swelling properties and biocompatibility. These materials are designed to be completely degraded within the skin tissue after application. However, the expansion of hydrogel-forming MNs can hinder complete micropore closure, potentially extending the healing process and increasing susceptibility to infection. Nonetheless, hydrogel-forming MNs offer a significant advantage over other MN types. They enable enhanced drug loading by manipulating the micro-channel network within the hydrogel and facilitate controlled drug release by altering the crosslinking density of the polymer matrix. These features position hydrogel-forming MNs as a promising platform for delivering RA treatment drugs, potentially achieving sustained and controlled release profiles in future research endeavors.

5. Advantages of nanoformulations combined with MNs for the treatment of RA

Extensive research has explored the use of nanoformulations to facilitate the delivery of a wide range of drugs. These nanoformulations offer advantages that can be leveraged by microneedles to broaden the spectrum of deliverable drugs, improve therapeutic efficacy in RA

treatment, and impart unique *in vivo* properties to the drug delivery system. The combination of nanoformulations with MNs as a drug delivery platform presents significant benefits. The enhancements offered by nanoformulations to MNs can be broadly categorized as follows: (1) enhancing drug solubility, (2) increasing drug permeability, (3) enhancing drug stability, (4) augmenting biosecurity, (5) controlling drug release, and (6) achieving targeted drugs delivery.

5.1. Enhancing drug solubility

Drug efficacy is highly dependent on achieving a specific concentration within the bloodstream. Drugs with superior water solubility generally exhibit improved pharmacokinetic properties, making solubility enhancement a critical factor in drug development [85,86]. While traditional MN delivery offers limited improvement in drug solubility and bioavailability [75], nanoformulations excel in enhancing these parameters, addressing a key challenge in MN-based drug delivery. Combining nanoformulations, which significantly improve drug solubility, with MNs leads to a greater accumulation of drugs in the dermis through transdermal delivery [87,88]. This approach facilitates deeper skin penetration, specifically targeting the joint area, and demonstrates improved bioavailability. Triptolide, a hydrophobic (water-insoluble) pharmaceutical compound derived from botanical sources, exhibits significant efficacy in RA treatment [89]. Encapsulating triptolide within liposomes significantly augmented its therapeutic efficacy against RA when delivered transdermally using solid MNs. This approach also considerably extended the drug's duration of action within the body [57]. Similarly, tetrrandrine-loaded nanoparticles [90] and aconitine-loaded nanostructured lipid carriers [73] enhanced the therapeutic impact against RA when delivered transdermally via MNs.

5.2. Increasing permeability

An ideal transdermal formulation should efficiently permeate the SC, facilitate deeper penetration into the skin to deliver drugs effectively and ensure no injury to underlying tissues [91]. MNs effectively penetrate the SC to deliver drugs, while nanoformulations offer distinct advantages in permeating cell membranes. Additionally, some nanoformulations can enhance drug penetration by optimizing their composition and materials, thereby facilitating drug diffusion [92]. Combining the characteristics of MNs with nanoformulations may effectively enhance drug permeability by capitalizing on their synergistic effects. For instance, the combination of tetrrandrine-loaded PLGA nanoparticles with dissolving MNs for transdermal delivery significantly increased their penetration capacity, resulting in a notable improvement in the inflammatory response of the synovial membrane and the formation of neovascular pannus (Fig. 5) [90].

5.3. Enhancing drug stability

Many drugs are limited by their inadequate stability, posing challenges in achieving therapeutic applications [52]. Large molecule drugs, such as polypeptides, proteins, antibodies, and nucleic acids, are highly susceptible to denaturation due to temperature, humidity, and light exposure. As a consequence, their storage and transportation requirements are stringent. Additionally, certain drugs are readily metabolized or hydrolyzed by enzymes within the body, resulting in reduced bioavailability and diminished efficacy. Therefore, enhancing the transdermal delivery of these drugs through various formulation techniques holds immense importance [93]. MNs have demonstrated some success in improving the stability of certain drugs. For example, studies have shown that enalapril [71], melittin [77], and NT [30] all exhibited notable stability when loaded into MNs. While the stability of NT was enhanced for one month following transdermal delivery via MNs, a quantifiable 3 % decrease in the amount present was observed after three months [30]. These findings suggest that adjustments to

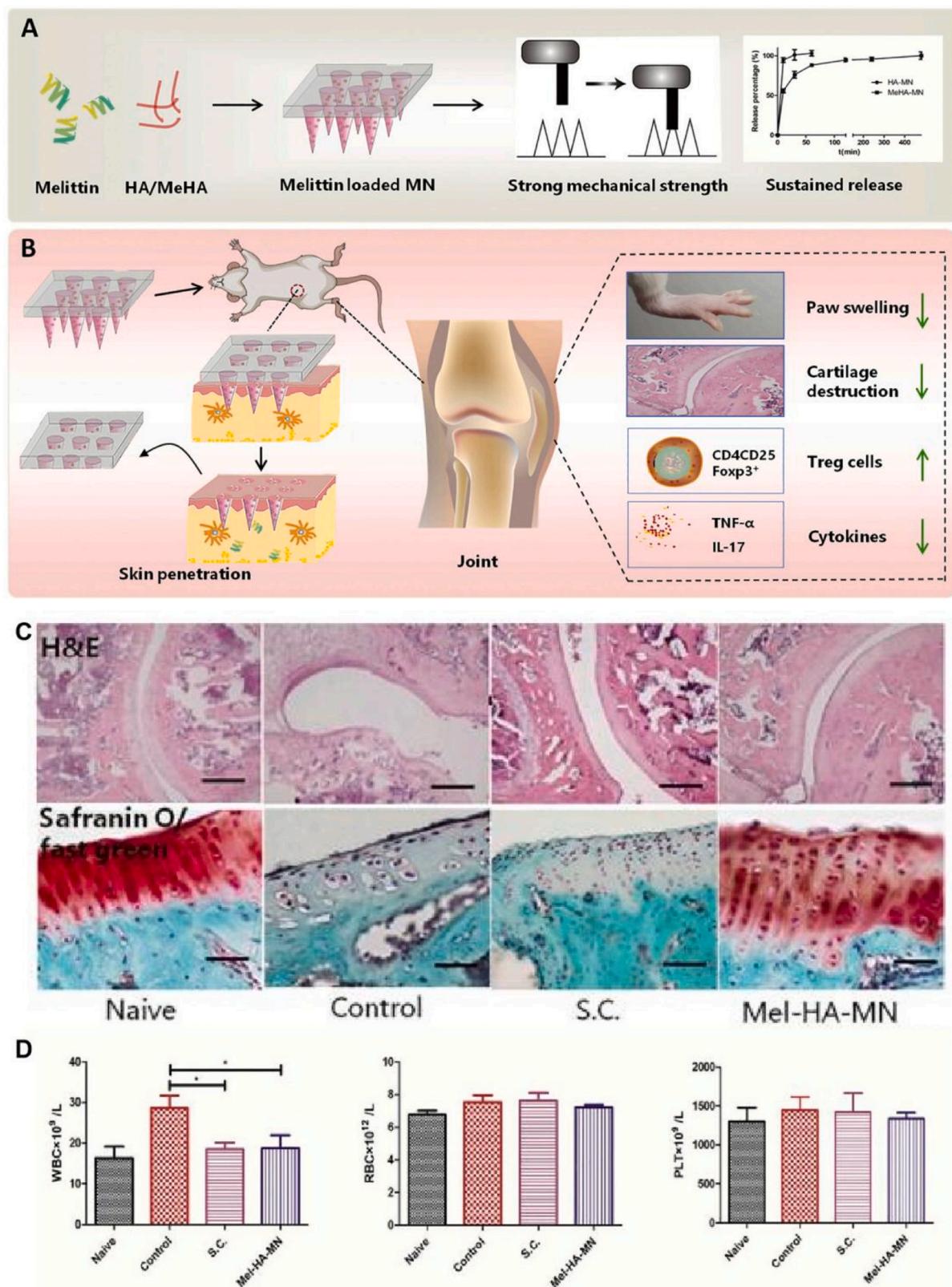


Fig. 4. Scheme of microneedle-mediated delivery of melittin for RA treatment and therapeutic potency of Mel-HA-MN in rat AIA model. (A): Fabrication of microneedles and characterization of mechanical strength and release behavior. (B): The fabricated microneedles successfully delivered melittin into the skin and inhibited RA progression, as shown by results in histological, paw swelling, and levels of pro-inflammatory cytokines and Treg cells. (C): H&E and Safranin O/fast green stain images of paws. a: cartilage destruction, b: cell infiltration. Scale bar: 1000 μm (upper) and 250 μm (lower). (D): Hematologic parameters on day 22 including WBC, RBC and Platelets. Bars represent mean \pm SEM, n=6. *P<0.05. HA: hyaluronic acid, MN: microneedles, MeHA: methacrylate modified hyaluronic acid, Treg: CD4 regulatory T cells. Reprinted with permission from ref [77].

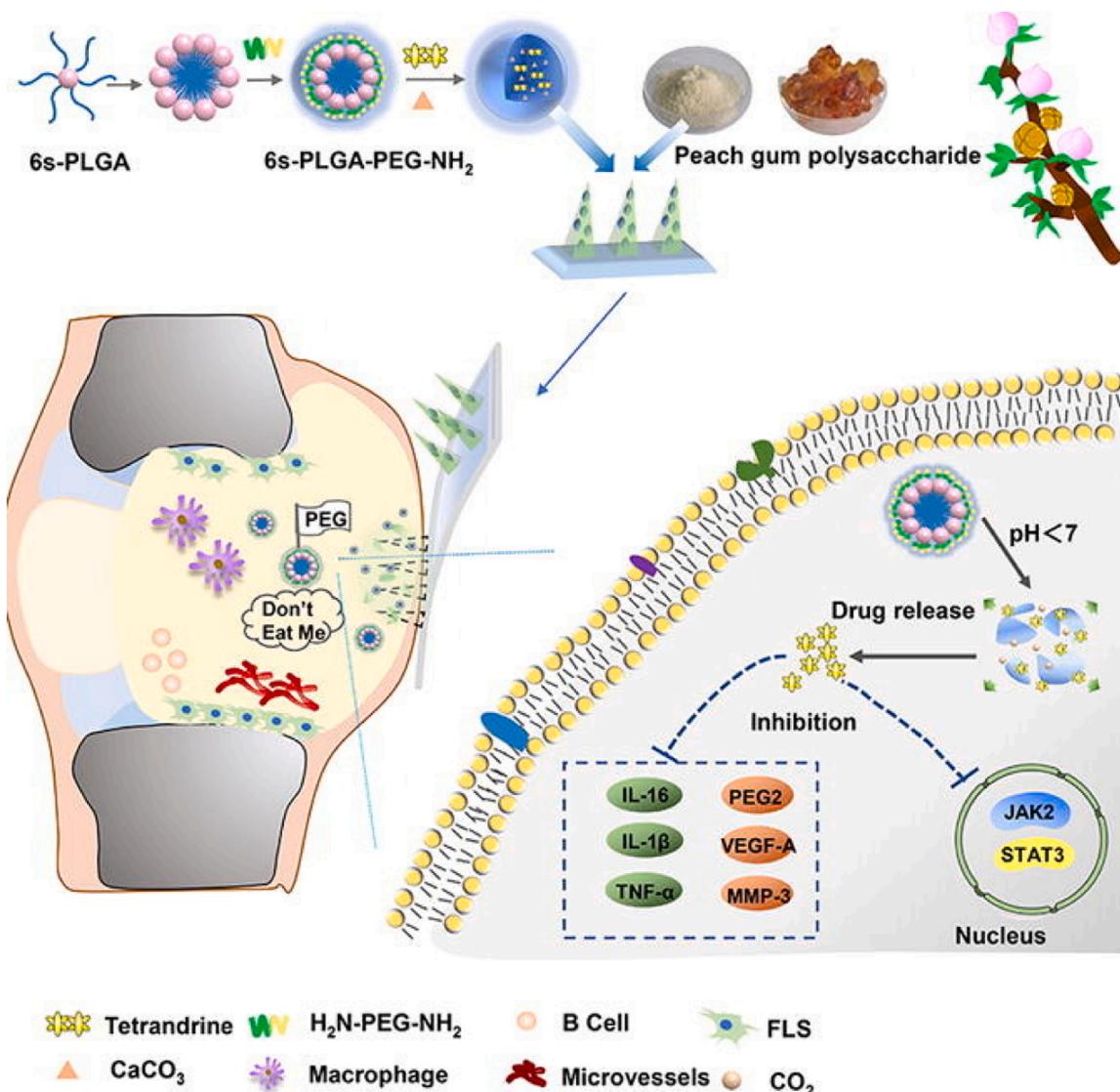


Fig. 5. PEGylated star-shaped PLGA, which hybridized with calcium carbonate to form nanoparticles [6 s-NPs (CaCO_3)] with immune stealth and acid-responsive properties, increased the loading of tetrandrine (Tet). Then, the nanoparticles were integrated into peach gum-fabricated dissolving microneedles for transdermal delivery. The delivery system increased synovial uptake of Tet with stealth escape from phagocytes and inflammatory acidity-triggered release, improving regulation of the VEGF, JAK2/p-JAK2, and STAT3/p-STAT3 pathways in RA. FLS: fibroblast-like synoviocytes. Reprinted with permission from ref [90].

material composition and preparation methods may further enhance drug stability within MNs. However, more development is necessary. Researchers have explored the use of nanoformulations as drug carriers, recognizing their potential to significantly enhance drug stability when combined with MNs. Dual protection offered by PLGA nanoparticles and MNs allowed ovalbumin to be stored in a normal environment for 10 weeks without significantly changing its pharmacological properties [94]. Similarly, a COVID-19 nanovaccine loaded into separable MNs can be stored at room temperature for 30 days[95]. Therefore, nanoformulation-assisted microneedles provide superior protection for transdermal delivery of drugs with poor stability compared to using MNs alone.

5.4. Augmenting biosecurity

The inherent drug release profile of MNs can lead to a temporary period of high drug concentration within the dermis [96]. However, some anti-RA drugs, such as methotrexate and triptolide, exhibit significant cytotoxicity. When these drugs accumulate in the dermis at high concentrations, they can cause localized safety concerns at the

administration site. Encapsulating or loading drugs within nanoformulations can prevent them from directly contacting surrounding tissues. Examples include triptolide-loaded liposomes [57] and methotrexate-encapsulated microspheres [97]. Moreover, the drug reservoir formed by aconitine-loaded nanostructured lipid carriers integrated with dissolving MNs effectively mitigated aconitine-induced arrhythmia [73]. Limiting direct tissue exposure improves the biocompatibility of the combined drug delivery system comprised of nanoformulations and MNs.

5.5. Controlling drug release

MNs facilitate drug delivery to the subcutaneous tissue, where the drugs can be gradually released into the lymphatic circulation [18]. Additionally, MNs can be used for passive control over drug release by incorporating multiple drugs within the same patch, potentially optimizing therapeutic effects or preventing unwanted interactions [98]. This approach offers clear advantages in terms of sustained and controlled drug release. For rapid drug release, strategies such as rapidly dissolving coatings on MNs [99] or the incorporation of fast-acting

excipients, such as NaHCO_3 [100] can be employed. MNs have demonstrated the ability to achieve controlled release for certain conditions, such as regulating blood sugar levels in diabetes [101,102]. However, achieving controlled release for RA treatment remains a challenge. Nanoformulations, when combined with MNs, offer the potential for more precise control over drug release, extended *in vivo* circulation times, and even responsive release triggered by the pathological environment of RA [103,104]. These formulations can be specifically engineered to react to key pathological features of RA, including low pH [105], excessive production of matrix metalloproteinases [106], and the presence of an inflammatory milieu [107,108]. For instance, tetrandrine-loaded PLGA nanoparticles formulated with calcium carbonate as an acid-responsive trigger were delivered transdermally via MNs. Upon reaching the low pH environment of RA joints, the calcium carbonate dissolves, compromising the structural integrity of the PLGA nanoparticles and facilitating the release of tetrandrine (Fig. 5) [90]. Similarly, cerium/manganese oxide nanoparticles delivered transdermally via MNs can respond to reactive oxygen species (ROS) present in the inflammatory milieu of RA, leading to the release of methotrexate (Fig. 6) [109]. Beyond responding to endogenous factors, certain physical factors like magnetic fields [110], ultrasound [111], and photothermal effects [112] can also be used to control the release of nanoformulations applied externally to the joint. While these approaches offer more localized targeting, most require additional devices, limiting patient independence. In conclusion, the combination of nanoformulations with MNs holds significant promise for controlled drug delivery in RA treatment. This approach can significantly enhance the development of clinically viable applications for managing this chronic condition.

5.6. Achieving targeted drugs delivery

MN-based transdermal delivery offers a valuable approach for localized drug administration, achieving high drug concentrations at the target site [44,113]. Nanoformulations further enhance localization by selectively accumulating *via* targeting moieties, resulting in reduced distribution to healthy tissues and improved drug specificity [114]. The synergy between these two delivery systems presents a promising strategy for reducing toxicity and side effects associated with RA treatment. Studies have demonstrated the effectiveness of this combined approach. For example, folate-modified methotrexate-loaded microspheres delivered transdermally via MNs achieved sustained and targeted drug delivery, effectively mitigating RA symptoms in rats [115]. Beyond folate, nanoformulations can be engineered for comparable targeting effects using RA-specific antibodies and peptides. A particularly novel therapeutic strategy involves biomimetic nanoparticles designed to target RA inflammation. These nanoparticles can be coated with membranes derived from neutrophils (NeuM) [116], macrophages [117], and regulatory fibroblast-like synoviocytes [118]. Following local transdermal delivery via dissolving MNs, NeuM-functionalized PLGA nanoparticles demonstrated enhanced cytokine binding and inflammatory joint tropism (Fig. 7) [116]. In conclusion, the combination of MNs with targeted nanoformulations offers a compelling formulation strategy for specific anti-RA drugs that require reduced toxicity, minimized side effects, or targeted delivery to the inflamed joint site. (Table 4)

6. Summary and prospect

RA is a chronic autoimmune disease characterized by inflammation and destruction of joint structures. Current RA management focuses on alleviating inflammation and preventing bone and cartilage degradation. Transdermal drug delivery, a method for delivering drugs through the skin, has emerged as a promising therapeutic approach, particularly for localized treatments. However, the SC, the outermost layer of the skin, presents a significant barrier to transdermal drug delivery [30,

131]. Several strategies have been developed to overcome this barrier and enhance drug penetration [24], including chemical approaches (such as liposomes [132], ethosomes [133], solid lipid nanoparticles [134], microemulsions [135]) and physical methods (such as MNs, electroporation [136], sonophoresis [137]). Among these, microneedles have emerged as a relatively efficient and well-tolerated approach for promoting drug permeation. MN technology has advanced significantly in recent years, demonstrating promise for transdermal drug delivery in RA treatment. MNs can deliver a variety of drugs for RA, including small molecules like methotrexate [84] and lornoxicam [56]), as well as large molecules like neurotoxins [30] and etanercept [71]). Regardless of the drug size, the mechanism of action remains similar. MNs create temporary microchannels within the SC, facilitating the delivery of drugs to the deeper layers of the skin (dermis) or even the epidermis [45]. This process enhances drug permeation, improves drug utilization within the target tissue, and ultimately helps suppress the formation and release of inflammatory mediators, thereby achieving therapeutic goals in RA. A key advantage of MN technology is its ability to deliver drugs effectively with minimal pain. Phase II and III clinical trials have demonstrated the safety of MN use in humans [51], suggesting that MNs have the potential to become a prevalent approach for treating RA in the future.

Microneedles have been extensively explored for RA treatment, but limitations remain. The therapeutic efficacy of MNs can be hindered by the physicochemical properties of drugs. To achieve a more intelligent, effective, and convenient MN delivery system, successful integration with nanoformulations is necessary. Nanoformulations can improve drug stability, solubility, and permeability, addressing certain shortcomings of MNs. Combining the controlled release and targeted delivery capabilities of nanoformulations with MNs further enhances their potential as a treatment modality for RA. However, several key challenges must be addressed before the clinical application of the nanoformulation-MN hybrid delivery system: 1. Biological Understanding: The mechanisms behind nanoformulation transdermal delivery, transport, retention, and clearance *via* MNs remain unclear. Additionally, the relationship between MN size, preparation material, nanoparticle size, and charge requires further investigation. 2. Long-Term Stability: While initial studies have shown promising stability, long-term and accelerated stability data are crucial for industrial-scale manufacturing. Further research is needed on the stability of nanoformulations during atomization and drying, and the selection of appropriate lyoprotectants for coated or dissolving MNs. 3. Drug Loading Capacity: MNs often suffer from low drug loading capacity, limiting their suitability for high-dose drugs. Nanoformulations themselves also occupy space, further restricting drug loading within the combined system. Optimization strategies are needed to improve overall drug loading capacity. 4. Safety Evaluation: Extensive research has established the safety of MNs applied to the skin, focusing on micropore formation and infection risk. However, long-term safety data for the combined MN-nanoformulation system is lacking. 5. Clinical Translation: Current pharmacodynamic assessments primarily rely on animal models, with limited clinical data available. Acceptance of MN and nanoformulation-based drug delivery among patients must also be addressed. 6. Individualized Treatment: Skin characteristics vary significantly across age, gender, and ethnicity. Certain medical conditions can also impact skin properties. Therefore, dosage and MN dimensions need to be tailored to individual patients. Rheumatoid arthritis is an autoimmune and inflammatory disease. The skin, a multifunctional organ, plays a crucial role in regulating inflammation, immune response, and angiogenesis through its unique immunological properties [138]. Disruption of the local microenvironment leads to the activation of dermal dendritic cells beneath the SC, triggering a cascade of immune responses [139]. Further investigation is required to explore the potential of MNs and nanoformulations in impeding RA progression by potentially enhancing local blood circulation and stimulating the immune system. Overall, the combination of nanoformulations and MNs offers a promising approach for transdermal drug delivery in RA

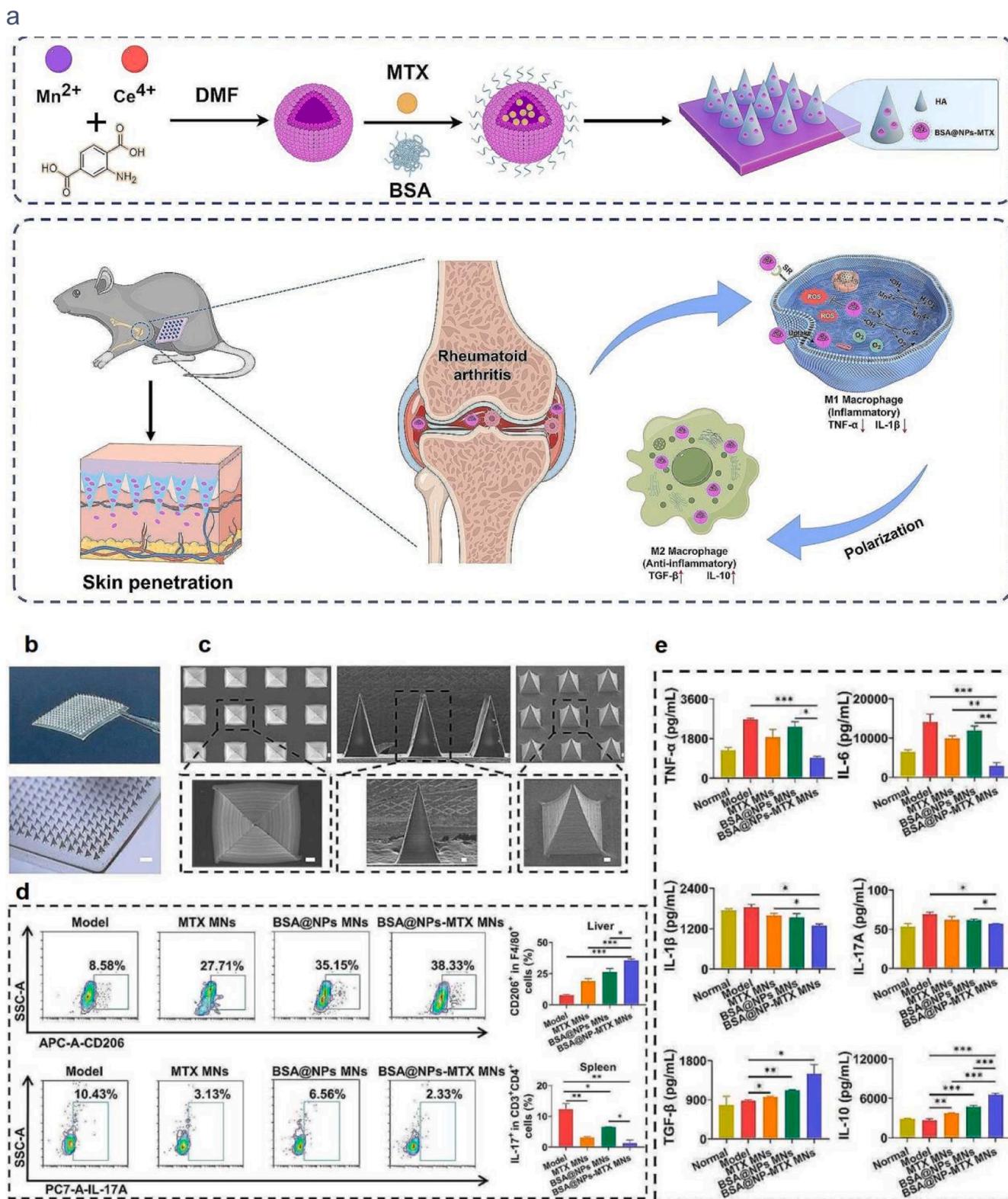
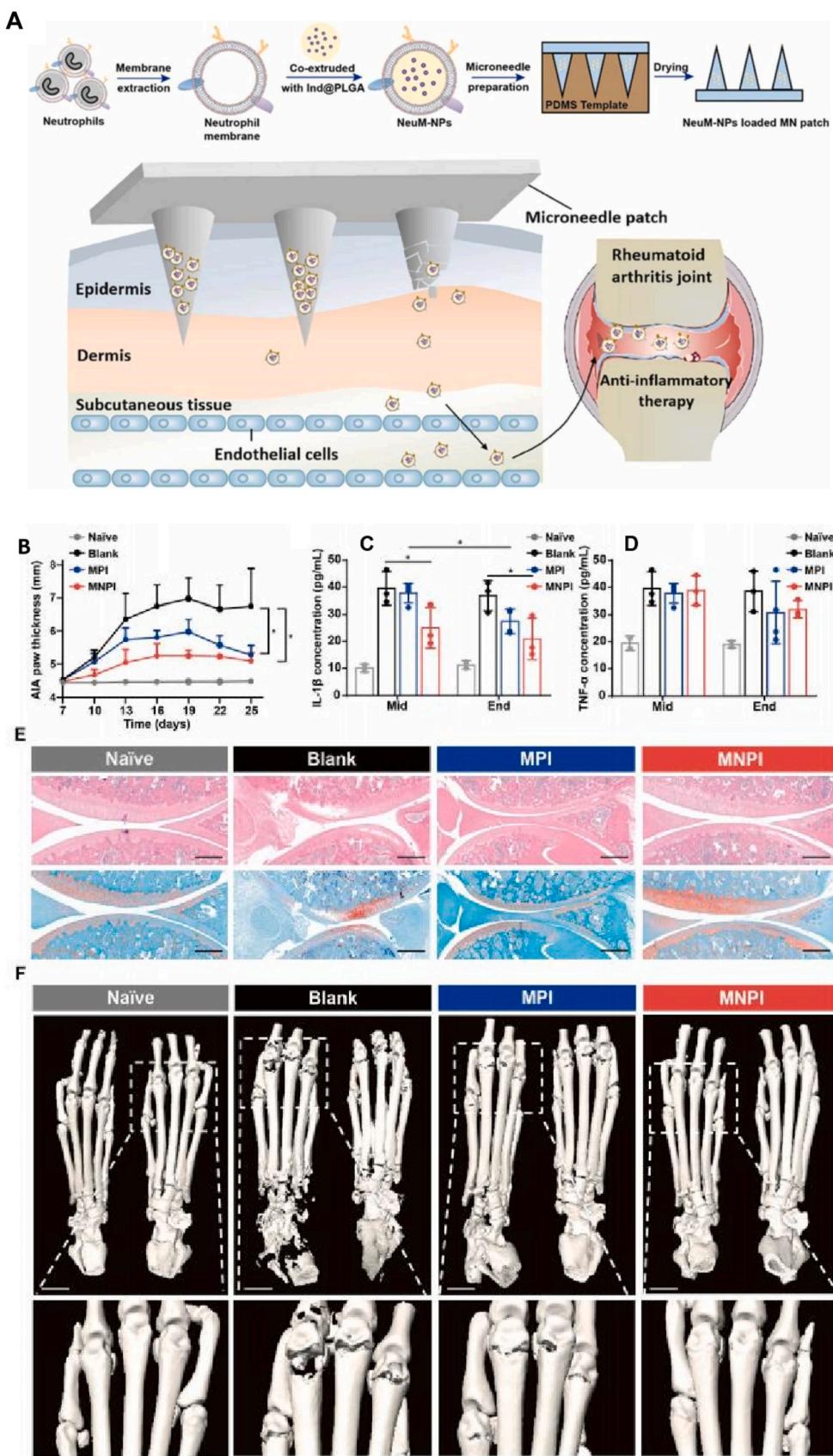


Fig. 6. Schematic illustration of BSA@NPs-MTX preparation and corresponding therapeutic mechanism in RA treatment (a). (a) was created by Figdraw. Digital images (b) of HA/PVP MNs. Scale bar: 1 mm. (c) SEM images of side elevation at low and high magnification, vertical view of MNs at low and high magnification. Scale bar: 100 μ m. Flow cytometry (d) showed the percentage of $F4/80^+$ $CD206^+$ M2 in $F4/80^+$ macrophages in liver and $CD3^+$ $CD4^+$ $IL-17 A^+$ Th17 in spleen of CIA mice after different treatments. ELISA measured cytokines levels (e) in the serum of mice after different treatments. Data were expressed as the mean \pm SEM ($n = 6$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). Reprinted with permission from ref [109].



(caption on next page)

Fig. 7. (A) Preparation and delivery of NeuM encapsulated NPs by degradable polymer microneedle patch for RA therapy. Microneedle patch promotes the transdermal absorption of NSAIDs, while surface modification by NeuM enhances the inflammatory joint targeting and cytokine adsorption. Anti-inflammatory treatment of NeuM-Ind@PLGA NPs loaded MN patch in the rat model of adjuvant-induced arthritis (AIA); (B) Paw thickness of rat AIA model; change of concentration profiles of IL-1 β (C) and TNF- α (D) in the serum of AIA rats treated with different groups; (E) representative images of H&E staining (upper row) and safranine O/ fast green (lower row) staining on knee sections of various treatment groups from AIA rats (scale bars, 500 μ m); (F) representative micro-CT images of various treatment groups from AIA mice (scale bars, 4 mm). MPI: indomethacin @PLGA-microneedle; MNPI: NeuM-indomethacin@PLGA-microneedle. Reprinted with permission from ref [116].

Table 4
RA targeting ligands and targeting mechanism.

Ligands	Targeting mechanism	References
Folate	Targeting activation of highly expressed folate receptors on the surface of macrophages, especially β	[115,119]
CD134	Targeting activated CD4 $^{+}$ T cells	[120]
CD22	Targeting activated B cells	[121]
HAP-1	Targeting the hyperplastic synovial lining layer	[122]
ART-1; ART-2	Targeting synovial endothelial cells	[123,124]
RGD; iRGD	Targeting the avb3 receptor on neovascular endothelial cells	[125,126]
hyaluronic acid	Targeting overexpressed CD44 in activated cells within the synovial membrane	[127]
Sialic acid	Targeting the L-selectin on the surface of neutrophils	[128]
Ascorbic acid	Targeting the microenvironment of oxidative stress in RA	[129]
Mannose	Targeting the C-type lectin receptors on the surface of macrophages and regulating macrophage polarization	[130]

treatment. Persistent research efforts focused on overcoming the identified challenges hold the potential for significant advancements in RA therapy.

Authors' contributions

Shi Zheng and Xu Hairu conceived and designed the project. Yao Wendong, Yan Xingxing, Xie Xianze, Fan Qiaomei, Shan Yujun, and Zhou Shanshan were in charge of literature investigation. Yao Wendong wrote the original manuscript. Shi Zheng, Xu Hairu, and Yan Xingxing assisted in revising the manuscript. All authors reviewed and approved the final manuscript.

CRediT authorship contribution statement

Wendong Yao: Writing – review & editing, Writing – original draft, Visualization, Investigation. **Yan Xingxing:** Writing – review & editing, Investigation. **Xie Xianze:** Investigation. **Xu Hairu:** Writing – review & editing, Conceptualization. **Fan Qiaomei:** Investigation. **Shan Yujun:** Investigation. **Zhou Shanshan:** Investigation. **Zheng Shi:** Writing – review & editing, Conceptualization.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Data availability

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

Acknowledgments

This study was financially supported by the Science and Technology in Zhejiang Province Chinese Medicine Program (2024ZR080, 2024ZF075, 2022ZA060) and Hospital Pharmacy Scientific Research Project of Zhejiang Pharmaceutical Association (2019ZYY23,

2023ZYY25). We thank Home for Researchers editorial team (www.home-for-researchers.com) for language editing service.

References

- [1] J. Smolen, D. Aletaha, A. Barton, G. Burmester, P. Emery, G. Firestein, A. Kavanaugh, I. McInnes, D. Solomon, V. Strand, K. Yamamoto, Rheumatoid arthritis, *Nature reviews, Dis. Prim.* 4 (2018) 18001.
- [2] D. Pappas, T. Blachley, S. Zlotnick, J. Best, K. Emeanuru, J. Kremer, Methotrexate discontinuation and dose decreases after therapy with tocilizumab: results from the corrona rheumatoid arthritis registry, *Rheumatol. Ther.* 7 (2) (2020) 357–369.
- [3] M. Feldmann, S. Maini, Role of cytokines in rheumatoid arthritis: an education in pathophysiology and therapeutics, *Immunol. Rev.* 223 (2008) 7–19.
- [4] A. van der Helm-van Mil, R. Knevel, G. Cavet, T. Huizinga, D. Haney, An evaluation of molecular and clinical remission in rheumatoid arthritis by assessing radiographic progression, *Rheumatol.* 52 (5) (2013) 839–846.
- [5] I. Tarner, U. Müller-Ladner, Drug delivery systems for the treatment of rheumatoid arthritis, *Expert Opin. Drug Deliv.* 5 (9) (2008) 1027–1037.
- [6] P. Prasad, S. Verma, Surbhi, N. Ganguly, V. Chaturvedi, S. Mittal, Rheumatoid arthritis: advances in treatment strategies, *Mol. Cell. Biochem.* 478 (1) (2023) 69–88.
- [7] M. Del Core, D. Koehler, Elbow arthritis, *J. Hand Surg.* 48 (6) (2023) 603–611.
- [8] F. Cheng, T. Su, Y. Liu, S. Zhou, J. Qi, W. Guo, G. Zhu, Targeting Lymph Nodes for Systemic Immunosuppression Using Cell-Free-DNA-Scavenging And cGAS-Inhibiting Nanomedicine-In-Hydrogel for Rheumatoid Arthritis Immunotherapy, *Adv. Sci.* 10 (26) (2023) e2302575.
- [9] L. Shi, F. Hu, C. Xu, H. Zhu, D. Qie, C. Yuan, Y. Tao, H. Liu, Plasma exchange successfully treated macrophage activation syndrome in rheumatoid factor-positive polyarticular juvenile idiopathic arthritis with co-existing pneumonia, *Int. J. Rheum. Dis.* 21 (5) (2018) 1142–1145.
- [10] Y. Liang, M. Liu, Y. Cheng, X. Wang, W. Wang, Prevention and treatment of rheumatoid arthritis through traditional Chinese medicine: role of the gut microbiota, *Front. Immunol.* 14 (2023) 1233994.
- [11] Y. Qin, G. Wu, J. Jin, H. Wang, J. Zhang, L. Liu, H. Zhao, J. Wang, X. Yang, A fully human connective tissue growth factor blocking monoclonal antibody ameliorates experimental rheumatoid arthritis through inhibiting angiogenesis, *BMC Biotechnol.* 23 (1) (2023) 6.
- [12] X. Liu, W. Pei, Y. Wu, F. Ren, S. Yang, X. Wang, Transdermal delivery of triptolide-phospholipid complex to treat rheumatoid arthritis, *Drug Deliv.* 28 (1) (2021) 2127–2136.
- [13] W. Zhu, T. Wei, Y. Xu, Q. Jin, Y. Chao, J. Lu, J. Xu, J. Zhu, X. Yan, M. Chen, Q. Chen, Z. Liu, Non-invasive transdermal delivery of biomacromolecules with fluorocarbon-modified chitosan for melanoma immunotherapy and viral vaccines, *Nat. Commun.* 15 (1) (2024) 820.
- [14] P. Sampathkumar, Injection safety in the United States: miles to go? *Mayo Clin. Proc.* 95 (2) (2020) 216–217.
- [15] J. Yang, X. Liu, Y. Fu, Y. Song, Recent advances of microneedles for biomedical applications: drug delivery and beyond, *Acta pharmaceutica Sinica, B* 9 (3) (2019) 469–483.
- [16] F. Sabbagh, B. Kim, Recent advances in polymeric transdermal drug delivery systems, *J. Control. Release Off. J. Control. Release Soc.* 341 (2022) 132–146.
- [17] T. Waghray, G. Singhvi, S. Dubey, M. Pandey, G. Gupta, M. Singh, K. Dua, Microneedles: a smart approach and increasing potential for transdermal drug delivery system, *Biomed. Pharmacother. = Biomedecine Pharmacother.* 109 (2019) 1249–1258.
- [18] A. Sabri, Y. Kim, M. Marlow, D. Scull, J. Segal, A. Banga, L. Kagan, J. Lee, Intradermal and transdermal drug delivery using microneedles - fabrication, performance evaluation and application to lymphatic delivery, *Adv. Drug Deliv. Rev.* 153 (2020) 195–215.
- [19] J. Bos, M. Meinardi, The 500 Dalton rule for the skin penetration of chemical compounds and drugs, *Exp. Dermatol.* 9 (3) (2000) 165–169.
- [20] S. Chandrasekhar, L. Iyer, J. Panchal, E. Topp, J. Cannon, V. Ranade, Microarrays and microneedle arrays for delivery of peptides, proteins, vaccines and other applications, *Expert Opin. Drug Deliv.* 10 (8) (2013) 1155–1170.
- [21] J. Pielenhofer, J. Sohl, M. Windbergs, P. Langguth, M. Radsak, Current progress in particle-based systems for transdermal vaccine delivery, *Front. Immunol.* 11 (2020) 266.
- [22] R. Yang, O. Okonkwo, D. Zurakowski, D. Kohane, Synergy between chemical permeation enhancers and drug permeation across the tympanic membrane, *J. Control. Release: Off. J. Control. Release Soc.* 289 (2018) 94–101.
- [23] H. Wang, Q. Shao, Y. Zhang, J. Ding, M. Yang, L. Yang, W. Wang, P. Cui, Z. Dai, L. Ma, Preparation and evaluation of liposomes containing ethanol and propylene glycol as carriers for nicotine, *Curr. Drug Deliv.* 21 (2) (2024) 249–260.

- [24] V. Phatale, K. Vaiphei, S. Jha, D. Patil, M. Agrawal, A. Alexander, Overcoming skin barriers through advanced transdermal drug delivery approaches, *J. Control. Release Off. J. Control. Release Soc.* 351 (2022) 361–380.
- [25] B. Polat, D. Hart, R. Langer, D. Blankscheit, Ultrasound-mediated transdermal drug delivery: mechanisms, scope, and emerging trends, *J. Control. Release Off. J. Control. Release Soc.* 152 (3) (2011) 330–348.
- [26] J. Yang, J. Yang, X. Gong, Y. Zheng, S. Yi, Y. Cheng, Y. Li, B. Liu, X. Xie, C. Yi, L. Jiang, Recent progress in microneedles-mediated diagnosis, therapy, and theranostic systems, *Adv. Healthc. Mater.* 11 (10) (2022) e2102547.
- [27] R. Donnelly, E. Larrañeta, Microarray patches: potentially useful delivery systems for long-acting nanosuspensions, *Drug Discov. Today* 23 (5) (2018) 1026–1033.
- [28] X. Chen, L. Wang, H. Yu, C. Li, J. Feng, F. Haq, A. Khan, R. Khan, Preparation, properties and challenges of the microneedles-based insulin delivery system, *J. Control. Release Off. J. Control. Release Soc.* 288 (2018) 173–188.
- [29] S. Henry, D. McAllister, M. Allen, M. Prausnitz, Microfabricated microneedles: a novel approach to transdermal drug delivery, *J. Pharm. Sci.* 87 (8) (1998) 922–925.
- [30] W. Yao, C. Tao, J. Zou, H. Zheng, J. Zhu, Z. Zhu, J. Zhu, L. Liu, F. Li, X. Song, Flexible two-layer dissolving and safing microneedle transdermal of neurotoxin: a biocomfortable attempt to treat Rheumatoid Arthritis, *Int. J. Pharm.* 563 (2019) 91–100.
- [31] M. Xiang, C. Yang, L. Zhang, S. Wang, Y. Ren, M. Gou, Dissolving microneedles for transdermal drug delivery in cancer immunotherapy, *J. Mater. Chem. B* 12 (24) (2024) 5812–5822.
- [32] X. Dai, A. Permana, M. Li, Habibie, M. Nur Amir, K. Peng, C. Zhang, H. Dai, A. Paredes, L. Vora, R. Donnelly, Calcipotriol nanosuspension-loaded trilayer dissolving microneedle patches for the treatment of psoriasis: in vitro delivery and in vivo antipsoriatic activity studies, *Mol. Pharm.* 21 (6) (2024) 2813–2827.
- [33] M. Starlin Chellathurai, S. Mahmood, Z. Mohamed Sofian, C. Wan Hee, R. Sundarapandian, H. Ahamed, C. Kandasamy, A. Hilles, N. Hashim, A. Janakiraman, Biodegradable polymeric insulin microneedles - a design and materials perspective review, *Drug Deliv.* 31 (1) (2024) 2296350.
- [34] W. Duan, K. Xu, S. Huang, Y. Gao, Y. Guo, Q. Shen, Q. Wei, W. Zheng, Q. Hu, J. Shen, Nanomaterials-incorporated polymeric microneedles for wound healing applications, *Int. J. Pharm.* 659 (2024) 124247.
- [35] L. Wang, Y. Wang, X. Wu, P. Wang, X. Luo, S. Lv, Advances in microneedles for transdermal diagnostics and sensing applications, *Mikrochim. Acta* 191 (7) (2024) 406.
- [36] Y. Hu, Z. Pan, M. De Bock, T. Tan, Y. Wang, Y. Shi, N. Yan, A. Yetisen, A wearable microneedle patch incorporating reversible FRET-based hydrogel sensors for continuous glucose monitoring, *Biosens. Bioelectron.* 262 (2024) 116542.
- [37] P. Guo, C. Huang, Q. Yang, G. Zhong, J. Zhang, M. Qiu, R. Zeng, K. Gou, C. Zhang, Y. Qu, Advances in formulations of microneedle system for rheumatoid arthritis treatment, *Int. J. Nanomed.* 18 (2023) 7759–7784.
- [38] B. Gowda, M. Ahmed, A. Sahebkar, Y. Riadi, R. Shukla, P. Kesharwani, Stimuli-responsive microneedles as a transdermal drug delivery system: a demand-supply strategy, *Biomacromolecules* 23 (4) (2022) 1519–1544.
- [39] A. Radu, S. Bungau, Nanomedical approaches in the realm of rheumatoid arthritis, *Ageing Res. Rev.* 87 (2023) 101927.
- [40] Y. Han, S. Huang, Nanomedicine is more than a supporting role in rheumatoid arthritis therapy, *J. Control. Release: Off. J. Control. Release Soc.* 356 (2023) 142–161.
- [41] S. Liu, H. Ma, H. Zhang, C. Deng, P. Xin, Recent advances on signaling pathways and their inhibitors in rheumatoid arthritis, *Clin. Immunol.* 230 (2021) 108793.
- [42] S. Gorantla, G. Gorantla, R. Saha, G. Singhvi, CD44 receptor-targeted novel drug delivery strategies for rheumatoid arthritis therapy, *Expert Opin. Drug Deliv.* 18 (11) (2021) 1553–1557.
- [43] A. Alunno, F. Carubbi, R. Giacomelli, R. Gerli, Cytokines in the pathogenesis of rheumatoid arthritis: new players and therapeutic targets, *BMC Rheumatol.* 1 (2017) 3.
- [44] X. Liang, Y. Li, J. Zhang, H. Bai, S. Sun, Q. Zhang, J. Yang, R. Wang, Application of microneedle-assisted percutaneous drug delivery system in treatment of rheumatoid arthritis: a review, *Zhongguo Zhong yao za zhi = Zhongguo zhongyao zazhi = China J. Chin. Mater. Med.* 48 (1) (2023) 13–21.
- [45] A. Permana, F. Nainu, K. Moffatt, E. Larrañeta, R. Donnelly, Recent advances in combination of microneedles and nanomedicines for lymphatic-targeted drug delivery, *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* 13 (3) (2021) e1690.
- [46] Y. Zhao, X. Chen, P. He, X. Wang, Y. Xu, R. Hu, Y. Ou, Z. Zhang, Z. Zhang, G. Du, X. Sun, Transdermal microneedles alleviated rheumatoid arthritis by inducing immune tolerance via skin-resident antigen presenting cells, *Small* (2023) e2307366.
- [47] A. Guillot, A. Cordeiro, R. Donnelly, M. Montesinos, T. Garrigues, A. Melero, Microneedle-based delivery: an overview of current applications and trends, *Pharmaceutics* 12 (6) (2020).
- [48] S. Darwish, W. El-Bakly, H. Arafa, E. El-Demerdash, Targeting TNF- α and NF- κ B activation by bee venom: role in suppressing adjuvant induced arthritis and methotrexate hepatotoxicity in rats, *PloS One* 8 (11) (2013) e79284.
- [49] Y. Cui, Y. Mo, Q. Zhang, W. Tian, Y. Xue, J. Bai, S. Du, Microneedle-Assisted Percutaneous Delivery of Paeoniflorin-loaded Ethosomes, *Molecules* 23 (12) (2018).
- [50] Y. Zhang, J. Yu, A. Kahkoska, J. Wang, J. Buse, Z. Gu, Advances in transdermal insulin delivery, *Adv. Drug Deliv. Rev.* 139 (2019) 51–70.
- [51] K. Ahmed Saeed Al-Japairai, S. Mahmood, S. Hamed Almurisi, J. Reddy Venugopal, A. Rebhi Hilles, M. Azmama, S. Raman, Current trends in polymer microneedle for transdermal drug delivery, *Int. J. Pharm.* 587 (2020) 119673.
- [52] A. Vargason, A. Anselmo, S. Mitragotri, The evolution of commercial drug delivery technologies, *Nat. Biomed. Eng.* 5 (9) (2021) 951–967.
- [53] S. Gorantla, G. Singhvi, V. Rapalli, T. Waghule, S. Dubey, R. Saha, Targeted drug-delivery systems in the treatment of rheumatoid arthritis: recent advancement and clinical status, *Ther. Deliv.* 11 (4) (2020) 269–284.
- [54] Z. Faraji Rad, P. Prewett, G. Davies, An overview of microneedle applications, materials, and fabrication methods, *Beilstein J. Nanotechnol.* 12 (2021) 1034–1046.
- [55] J. Wang, Z. Lu, R. Cai, H. Zheng, J. Yu, Y. Zhang, Z. Gu, Microneedle-based transdermal detection and sensing devices, *Lab a chip* 23 (5) (2023) 869–887.
- [56] Y. He, K. Majid, M. Maqbool, T. Hussain, A. Yousaf, I. Khan, Y. Mehmood, A. Aleem, M. Arshad, A. Younus, J. Nirwan, M. Ghori, S. Rizvi, Y. Shahzad, Formulation and characterization of lornoxicam-loaded cellulose-microsponge gel for possible applications in arthritis, *Saudi Pharm. J. SPJ Off. Publ. Saudi Pharm. Soc.* 28 (8) (2020) 994–1003.
- [57] G. Chen, B. Hao, D. Ju, M. Liu, H. Zhao, Z. Du, J. Xia, Pharmacokinetic and pharmacodynamic study of triptolide-loaded liposome hydrogel patch under microneedles on rats with collagen-induced arthritis, *Acta Pharm. Sin. B* 5 (6) (2015) 569–576.
- [58] M. Zhao, J. Bai, Y. Lu, S. Du, K. Shang, P. Li, L. Yang, B. Dong, N. Tan, Anti-arthritis effects of microneedling with bee venom gel, *J. Tradit. Chin. Med. Sci.* 3 (04) (2016) 256–262.
- [59] R. Al-Kasabeh, A. Brady, A. Courtenay, E. Larrañeta, M. McCrudden, D. O’Kane, S. Liggett, R. Donnelly, Evaluation of the clinical impact of repeat application of hydrogel-forming microneedle array patches, *Drug Deliv. Transl. Res.* 10 (3) (2020) 690–705.
- [60] C. Wu, J. Cheng, W. Li, L. Yang, H. Dong, X. Zhang, Programmable polymeric microneedles for combined chemotherapy and antioxidant treatment of rheumatoid, *Arthritis ACS Appl. Mater. Interfaces* 13 (46) (2021) 55559–55568.
- [61] H. Abd-El-Azim, H. Abbas, N. El Sayed, A. Fayed, M. Zewail, Non-invasive management of rheumatoid arthritis using hollow microneedles as a tool for transdermal delivery of teriflunomide loaded solid lipid nanoparticles, *Int. J. Pharm.* 644 (2023) 123334.
- [62] H. Abd-El-Azim, H. Abbas, N. El Sayed, M. Mousa, H. Elbardisy, M. Zewail, Hypericin emulsomes combined with hollow microneedles as a non-invasive photodynamic platform for rheumatoid arthritis treatment, *Int. J. Pharm.* 653 (2024) 123876.
- [63] S. Bhatnagar, P.R. Gadeela, P. Thathireddy, V.V.K. Venuganti, Microneedle-based drug delivery: materials of construction, *J. Chem. Sci.* 131 (9) (2019) 1–28.
- [64] Z. Ahmad, E. Stride, M. Edirisinha, Novel preparation of transdermal drug-delivery patches and functional wound healing materials, *J. Drug Target.* 17 (9) (2009) 724–729.
- [65] K. Cheung, D. Das, Microneedles for drug delivery: trends and progress, *Drug Deliv.* 23 (7) (2016) 2338–2354.
- [66] D. Zhu, Q. Wang, X. Liu, X. Guo, Rapidly separating microneedles for transdermal drug delivery, *Acta Biomater.* 41 (2016) 312–319.
- [67] E. Yalcintas, D. Ackerman, E. Korkmaz, C. Telmer, J. Jarvik, P. Campbell, M. Bruchez, O. Ozdoganlar, Analysis of in vitro cytotoxicity of carbohydrate-based materials used for dissolvable microneedle arrays, *Pharm. Res.* 37 (3) (2020) 33.
- [68] K. Koh, Y. Liu, S. Lim, X. Loh, L. Kang, C. Lim, K. Phua, Formulation, characterization and evaluation of mRNA-loaded dissolvable polymeric microneedles (RNAPatch), *Sci. Rep.* 8 (1) (2018) 11842.
- [69] W. Li, J. Tang, R. Terry, S. Li, A. Brunie, R. Callahan, R. Noel, C. Rodríguez, S. Schwendeman, M. Prausnitz, Long-acting reversible contraception by effervescent microneedle patch, *Sci. Adv.* 5 (11) (2019) eaaw8145.
- [70] A. Rodgers, M. McCrudden, E. Vincente-Perez, A. Dubois, R. Ingram, E. Larrañeta, A. Kisseneppenig, R. Donnelly, Design and characterisation of a dissolving microneedle patch for intradermal vaccination with heat-inactivated bacteria: a proof of concept study, *Int. J. Pharm.* 549 (2018) 87–95.
- [71] J. Cao, N. Zhang, Z. Wang, J. Su, J. Yang, J. Han, Y. Zhao, Microneedle-assisted transdermal delivery of etanercept for rheumatoid arthritis treatment, *Pharmaceutics* 11 (5) (2019).
- [72] S. Amodwala, P. Kumar, H. Thakkar, Statistically optimized fast dissolving microneedle transdermal patch of meloxicam: a patient friendly approach to manage arthritis, *Eur. J. Pharm. Sci. Off. J. Eur. Fed. Pharm. Sci.* 104 (2017) 114–123.
- [73] T. Guo, N. Cheng, J. Zhao, X. Hou, Y. Zhang, N. Feng, Novel nanostructured lipid carriers-loaded dissolving microneedles for controlled local administration of aconitine, *Int. J. Pharm.* 572 (2019) 118741.
- [74] Y. Qiu, C. Li, S. Zhang, G. Yang, M. He, Y. Gao, Systemic delivery of artemether by dissolving microneedles, *Int. J. Pharm.* 508 (2016) 1–9.
- [75] X. Song, Y. Wang, H. Chen, Y. Jin, Z. Wang, Y. Lu, Y. Wang, Dosage-efficacy relationship and pharmacodynamics validation of brucine dissolving microneedles against rheumatoid arthritis, *J. Drug Deliv. Sci. Technol.* 63 (2021) 1773.
- [76] M. An, M. Shi, J. Su, Y. Wei, R. Luo, P. Sun, Y. Zhao, Dual-drug loaded separable microneedles for efficient rheumatoid arthritis therapy, *Pharmaceutics* 14 (7) (2022) 1518.
- [77] G. Du, P. He, J. Zhao, C. He, M. Jiang, Z. Zhang, Z. Zhang, X. Sun, Polymeric microneedle-mediated transdermal delivery of melittin for rheumatoid arthritis treatment, *J. Control. Release Off. J. Control. Release Soc.* 336 (2021) 537–548.
- [78] Y. Li, Y. Sun, S. Wei, L. Zhang, S. Zong, Development and evaluation of tofacitinib transdermal system for the treatment of rheumatoid arthritis in rats, *Drug Dev. Ind. Pharm.* 47 (6) (2021) 878–886.

- [79] K. Ita, Dissolving microneedles for transdermal drug delivery: advances and challenges, *Biomed. Pharmacother. = Biomedecine Pharmacother.* 93 (2017) 1116–1127.
- [80] A. Sivaraman, A. Banga, Novel in situ forming hydrogel microneedles for transdermal drug delivery, *Drug Deliv. Transl. Res.* 7 (1) (2017) 16–26.
- [81] A. Tucak, M. Sirbubalo, L. Hindija, O. Rahić, J. Hadžiabdić, K. Muhamedagić, A. Čekić, E. Vranić, Microneedles: characteristics, materials, production methods and commercial development, *Micromachines* 11 (11) (2020) 961.
- [82] J. Turner, L. White, P. Estrela, H. Leese, Hydrogel-forming microneedles: current advancements and future trends, *Macromol. Biosci.* 21 (2) (2021) e2000307.
- [83] J. Cao, J. Su, M. An, Y. Yang, Y. Zhang, J. Zuo, N. Zhang, Y. Zhao, Novel DEK-targeting aptamer delivered by a hydrogel microneedle attenuates collagen-induced arthritis, *Mol. Pharm.* 18 (1) (2021) 305–316.
- [84] I.A. Tekko, G. Chen, J. Domínguez-Robles, R.R.S. Thakur, I.M.N. Hamdan, L. Vora, E. Larrañeta, J.C. McElroy, H.O. McCarthy, M. Rooney, R.F. Donnelly, Development and characterisation of novel poly (vinyl alcohol)/poly (vinyl pyrrolidone)-based hydrogel-forming microneedle arrays for enhanced and sustained transdermal delivery of methotrexate, *Int. J. Pharm.* 586 (prepublis) (2020) 119580.
- [85] F. Noa, D. Arik, Solubility-enabling formulations for oral delivery of lipophilic drugs: considering the solubility-permeability interplay for accelerated formulation development, *Expert Opin. Drug Deliv.* 21 (2023) 13–29.
- [86] P. Tran, J. Park, Application of supercritical fluid technology for solid dispersion to enhance solubility and bioavailability of poorly water-soluble drugs, *Int. J. Pharm.* 610 (2021) 121247.
- [87] A. Permana, A. Paredes, F. Volpe-Zanutto, Q. Anjani, E. Utomo, R. Donnelly, Dissolving microneedle-mediated dermal delivery of itraconazole nanocrystals for improved treatment of cutaneous candidiasis, *Eur. J. Pharm. Biopharm. Off. J. Arb. Fur Pharm. Verfahrt. e.V.* 154 (2020) 50–61.
- [88] S. Abdelghany, I. Tekko, L. Vora, E. Larrañeta, A. Permana, R. Donnelly, Nanosuspension-based dissolving microneedle arrays for intradermal delivery of curcumin, *Pharmaceutics* 11 (7) (2019) 308–321.
- [89] R. Guo, X. Zhang, D. Yan, Y. Yu, Y. Wang, H. Geng, Y. Wu, Y. Liu, L. Kong, X. Li, Folate-modified triptolide liposomes target activated macrophages for safe rheumatoid arthritis therapy, *Biomater. Sci.* 10 (2) (2022) 499–513.
- [90] H. Hongmei, R. Hang, R. Shuyao, P. Lixia, J. Qian, W. Tong, H. Xiaolin, X. Hao, W. Youjie, F. Nianping, Z. Yongtai, Acid-responsive PEGylated branching PLGA nanoparticles integrated into dissolving microneedles enhance local treatment of arthritis, *Chem. Eng. J.* 431 (P2) (2022) 134196.
- [91] M. Prausnitz, R. Langer, Transdermal drug delivery, *Nat. Biotechnol.* 26 (11) (2008) 1261–1268.
- [92] W.Y. Wang, P.C.L. Hui, E. Wat, F.S.F. Ng, C.W. Kan, C.B.S. Lau, P.C. Leung, Enhanced transdermal permeability via constructing the porous structure of poloxamer-based hydrogel, *Polymers* 8 (11) (2016).
- [93] R. Neupane, S. Boddu, M. Abou-Dahech, R. Bachu, D. Terrero, R. Babu, A. Tiwari, Transdermal delivery of chemotherapeutics: strategies, requirements, and opportunities, *Pharmaceutics* 13 (7) (2021).
- [94] M. Leone, J. Mönkkäre, J. Bouwstra, G. Kersten, Dissolving microneedle patches for dermal vaccination, *Pharm. Res.* 34 (11) (2017) 2223–2240.
- [95] Y. Yin, W. Su, J. Zhang, W. Huang, X. Li, H. Ma, M. Tan, H. Song, G. Cao, S. Yu, D. Yu, J.H. Jeong, X. Zhao, H. Li, G. Nie, H. Wang, Separable microneedle patch to protect and deliver DNA nanovaccines against COVID-19, *ACS Nano* 15 (9) (2021) 14347–14359.
- [96] P. Zhao, Z. Li, Z. Ling, Y. Zheng, H. Chang, Efficient loading and sustained delivery of methotrexate using a tip-swelling microneedle array patch for psoriasis treatment, *ACS Biomater. Sci. Eng.* 10 (2) (2024) 921–931.
- [97] P. Shende, M. Salunke, Transepidermal microneedles for co-administration of folic acid with methotrexate in the treatment of rheumatoid arthritis, *Biomed. Phys. Eng. Express* 5 (2) (2019) 25023.
- [98] S. Khan, A. Hasan, F. Attar, M. Babadei, H. Zeinabad, M. Salehi, M. Alizadeh, M. Hassan, H. Derakhshankhah, M. Hamblin, Q. Bai, M. Sharifi, M. Falahati, T. Ten Hagen, Diagnostic and drug release systems based on microneedle arrays in breast cancer therapy, *J. Control. Release Off. J. Control. Release Soc.* 338 (2021) 341–357.
- [99] D. Zhu, X. Zhang, C. Shen, Y. Cui, X. Guo, The maximum possible amount of drug in rapidly separating microneedles, *Drug Deliv. Transl. Res.* 9 (6) (2019) 1133–1142.
- [100] J. Tao, B. Wang, Y. Dong, X. Chen, S. Li, T. Jiang, X. Zhao, Photothermal and acid-responsive fucoidan-CuS bubble pump microneedles for combined CDT/PTT/CT treatment of melanoma, *ACS Appl. Mater. Interfaces* 15 (34) (2023) 40267–40279.
- [101] W. Chen, R. Tian, C. Xu, B. Yung, G. Wang, Y. Liu, Q. Ni, F. Zhang, Z. Zhou, J. Wang, G. Niu, Y. Ma, L. Fu, X. Chen, Microneedle-array patches loaded with dual mineralized protein/peptide particles for type 2 diabetes therapy, *Nat. Commun.* 8 (1) (2017) 1777.
- [102] Y. Fu, P. Liu, M. Chen, T. Jin, H. Wu, M. Hei, C. Wang, Y. Xu, X. Qian, W. Zhu, On-demand transdermal insulin delivery system for type 1 diabetes therapy with no hypoglycemia risks, *J. Colloid Interface Sci.* 605 (2022) 582–591.
- [103] S. Mangalathilam, N. Rejinold, A. Nair, V. Lakshmanan, S. Nair, R. Jayakumar, Curcumin loaded chitin nanogels for skin cancer treatment via the transdermal route, *Nanoscale* 4 (1) (2012) 239–250.
- [104] F.-Q. Luo, G. Chen, W. Xu, D. Zhou, J.-X. Li, Y.-C. Huang, R. Lin, Z. Gu, J.-Z. Du, Microneedle-array patch with pH-sensitive formulation for glucose-responsive insulin delivery, *Nano Res.* 14 (8) (2021) 1–8.
- [105] Y. Liu, J. Jin, H. Xu, C. Wang, Y. Yang, Y. Zhao, H. Han, T. Hou, G. Yang, L. Zhang, Y. Wang, W. Zhang, Q. Liang, Construction of a pH-responsive, ultralow-dose triptolide nanomedicine for safe rheumatoid arthritis therapy, *Acta Biomater.* 121 (2021) 541–553.
- [106] N. Li, Y. Qiao, L. Xue, S. Xu, N. Zhang, Targeted and MMP-2/9 responsive peptides for the treatment of rheumatoid arthritis, *Int. J. Pharm.* 569 (2019) 118625.
- [107] Y. Dou, C. Li, L. Li, J. Guo, J. Zhang, Bioresponsive drug delivery systems for the treatment of inflammatory diseases, *J. Control. Release Off. J. Control. Release Soc.* 327 (2020) 641–666.
- [108] N. Ahamed, A. Prabhakar, S. Mehta, E. Singh, E. Bhatia, S. Sharma, R. Banerjee, Trigger-responsive engineered-nanocarriers and image-guided theranostics for rheumatoid arthritis, *Nanoscale* 12 (24) (2020) 12673–12697.
- [109] T. Xia, Y. Zhu, K. Li, K. Hao, Y. Chai, H. Jiang, C. Lou, J. Yu, W. Yang, J. Wang, J. Deng, Z. Wang, Microneedles loaded with cerium-manganese oxide nanoparticles for targeting macrophages in the treatment of rheumatoid arthritis, *J. Nanobiotechnol.* 22 (1) (2024) 103.
- [110] Y. Liu, F. Cao, B. Sun, J. Bellanti, S. Zheng, Magnetic nanoparticles: a new diagnostic and treatment platform for rheumatoid arthritis, *J. Leukoc. Biol.* 109 (2) (2021) 415–424.
- [111] R. Guo, L. Wang, J. Huang, H. Pang, L. Wang, B. Zhu, Y. Tang, L. Ma, L. Qiu, Ultrasound-targeted microbubble destruction-mediated cell-mimetic nanodrugs for treating rheumatoid, Arthritis, *ACS Biomater. Sci. Eng.* 9 (6) (2023) 3670–3679.
- [112] X. Fu, Y. Song, X. Feng, Z. Liu, W. Gao, H. Song, Q. Zhang, Synergistic chemotherapy/PTT/oxygen enrichment by multifunctional liposomal polydopamine nanoparticles for rheumatoid arthritis treatment, *Asian J. Pharm. Sci.* 19 (1) (2024) 100885.
- [113] Y. Xu, M. Zhao, J. Cao, T. Fang, J. Zhang, Y. Zhen, F. Wu, X. Yu, Y. Liu, J. Li, D. Wang, Applications and recent advances in transdermal drug delivery systems for the treatment of rheumatoid arthritis, *Acta Pharm. Sin. B* 13 (11) (2023) 4417–4441.
- [114] N. Zhang, Y. Wu, W. Xu, Z. Li, L. Wang, Synergic fabrication of multifunctional liposomes nanocomposites for improved radiofrequency ablation combination for liver metastasis cancer therapy, *Drug Deliv.* 29 (1) (2022) 506–518.
- [115] P. Shende, M. Salunke, Transepidermal microneedles for co-administration of folic acid with methotrexate in the treatment of rheumatoid arthritis, *Biomed. Phys. Eng. Express* 5 (2) (2019).
- [116] L. Yixuan, C. Yang, D. Ronghui, Q. Hao, L. Nan, Q. Yuting, C. Hanqing, W. Yaohua, W. Zeming, S. Qing, Q. Wenyi, S. Jian, C. Long, W. Yuguang, N. Guangjun, Z. Ruifang, Delivery of neutrophil membrane encapsulated non-steroidal anti-inflammatory drugs by degradable biopolymer microneedle patch for rheumatoid arthritis therapy, *Nano Today* 49 (2023) 101791.
- [117] Y. Wu, S. Wan, S. Yang, H. Hu, C. Zhang, J. Lai, J. Zhou, W. Chen, X. Tang, J. Luo, X. Zhou, L. Yu, L. Wang, A. Wu, Q. Fan, J. Wu, Macrophage cell membrane-based nanoparticles: a new promising biomimetic platform for targeted delivery and treatment, *J. Nanobiotechnol.* 20 (1) (2022) 542.
- [118] Y. Liu, P. Rao, H. Qian, Y. Shi, S. Chen, J. Lan, D. Mu, R. Chen, X. Zhang, C. Deng, G. Liu, G. Shi, Regulatory fibroblast-like synoviocytes cell membrane coated nanoparticles: a novel targeted therapy for rheumatoid arthritis, *Adv. Sci.* 10 (4) (2023) e2204998.
- [119] Y. Yang, L. Guo, Z. Wang, P. Liu, X. Liu, J. Ding, W. Zhou, Targeted silver nanoparticles for rheumatoid arthritis therapy via macrophage apoptosis and Re-polarization, *Biomaterials* 264 (2021) 120390.
- [120] E.P. Boot, G.A. Koning, G. Storm, J.P. Wagenaar-Hilbers, W. van Eden, L. A. Everse, M.H. Wauben, CD134 as target for specific drug delivery to auto-aggressive CD4+ T cells in adjuvant arthritis, *Arthritis Res Ther.* 7 (3) (2005) R604–R615.
- [121] K.J. Bednar, C.M. Nycholat, T.S. Rao, J.C. Paulson, W.P. Fung-Leung, M. S. Macauley, Exploiting CD22 To selectively tolerize autoantibody producing B-cells in rheumatoid arthritis, *ACS Chem. Biol.* 14 (4) (2019) 644–654.
- [122] S. Meng, Z. Song, Z. Tang, X. Yang, Y. Xiao, H. Guo, K. Zhou, M. Du, Y.Z. Zhu, X. Wang, Surface-decorated nanoliposomal leonurine targets activated fibroblast-like synoviocytes for efficient rheumatoid arthritis therapy, *Biomater. Sci.* 11 (21) (2023) 7099–7113.
- [123] R.R. Meka, S.H. Venkatesha, K.D. Moudgil, Peptide-directed liposomal delivery improves the therapeutic index of an immunomodulatory cytokine in controlling autoimmune arthritis, *J. Control Release* 286 (2018) 279–288.
- [124] R.R. Meka, S.H. Venkatesha, B. Acharya, K.D. Moudgil, Peptide-targeted liposomal delivery of dexamethasone for arthritis therapy, *Nanomed.* 14 (11) (2019) 1455–1469.
- [125] H. Wu, Y. He, H. Wu, M. Zhou, Z. Xu, R. Xiong, F. Yan, H. Liu, Near-infrared fluorescence imaging-guided focused ultrasound-mediated therapy against Rheumatoid Arthritis by MTX-ICG-loaded iRGD-modified echogenic liposomes, *Theranostics* 10 (22) (2020) 10092–10105.
- [126] Y. Wang, Z. Liu, T. Li, L. Chen, J. Lyu, C. Li, Y. Lin, N. Hao, M. Zhou, Z. Zhong, Enhanced therapeutic effect of RGD-modified polymeric micelles loaded with low-dose methotrexate and nimesulide on rheumatoid arthritis, *Theranostics* 9 (3) (2019) 708–720.
- [127] R. Heo, J.S. Park, H.J. Jang, S.H. Kim, J.M. Shin, Y.D. Suh, J.H. Jeong, D.G. Jo, J. H. Park, Hyaluronan nanoparticles bearing γ -secretase inhibitor: in vivo therapeutic effects on rheumatoid arthritis, *J. Control Release* 192 (2014) 295–300.
- [128] X. Lai, S. Wang, M. Hu, Y. Sun, M. Chen, M. Liu, G. Li, Y. Deng, Dual targeting single arrow: Neutrophil-targeted sialic acid-modified nanoplateform for treating comorbid tumors and rheumatoid arthritis, *Int. J. Pharm.* 607 (2021) 121022.
- [129] M. Li, G. Wang, Y. Yan, M. Jiang, Z. Wang, Z. Zhang, X. Wu, H. Zeng, Triptolide and l-ascorbate palmitate co-loaded micelles for combination therapy of

- rheumatoid arthritis and side effect attenuation, *Drug Deliv.* 29 (1) (2022) 2751–2758.
- [130] L. Yang, Y. Sha, Y. Wei, H. Fang, J. Jiang, L. Yin, Z. Zhong, F. Meng, Mannose-mediated nanodelivery of methotrexate to macrophages augments rheumatoid arthritis therapy, *Biomater. Sci.* 11 (6) (2023) 2211–2220.
- [131] M. Ashtikar, K. Nagarsekar, A. Fahr, Transdermal delivery from liposomal formulations - Evolution of the technology over the last three decades, *J. Control. Release: Off. J. Control. Release Soc.* 242 (2016) 126–140.
- [132] E. Silva, L. Barreiros, M. Segundo, S. Costa Lima, S. Reis, Cellular interactions of a lipid-based nanocarrier model with human keratinocytes: Unravelling transport mechanisms, *Acta Biomater.* 53 (2017) 439–449.
- [133] L. Yang, L. Wu, D. Wu, D. Shi, T. Wang, X. Zhu, Mechanism of transdermal permeation promotion of lipophilic drugs by ethosomes, *Int. J. Nanomed.* 12 (2017) 3357–3364.
- [134] L. Peng, W. Wei, Y. Shan, Y. Chong, L. Yu, J. Gao, Sustained release of piroxicam from solid lipid nanoparticle as an effective anti-inflammatory therapeutics in vivo, *Drug Dev. Ind. Pharm.* 43 (1) (2017) 55–66.
- [135] A. Dogrul, S. Arslan, F. Tirnaksiz, Water/oil type microemulsion systems containing lidocaine hydrochloride: in vitro and in vivo evaluation, *J. Microencapsul.* 31 (5) (2014) 448–460.
- [136] H. Nguyen, A. Banga, Electrically and ultrasonically enhanced transdermal delivery of methotrexate, *Pharmaceutics* 10 (3) (2018).
- [137] S. Gaikwad, A. Zanje, J. Somwanshi, Advancements in transdermal drug delivery: a comprehensive review of physical penetration enhancement techniques, *Int. J. Pharm.* 652 (2024) 123856.
- [138] A. Matejuk, Skin immunity, *Arch. Immunol. Et. Ther. Exp.* 66 (1) (2018) 45–54.
- [139] J. Zhao, P. He, M. Jiang, C. He, Y. Zhao, Z. Zhang, Z. Zhang, G. Du, X. Sun, Transdermally delivered tolerogenic nanoparticles induced effective immune tolerance for asthma treatment, *J. Control. Release Off. J. Control. Release Soc.* 366 (2024) 637–649.