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Nano-Loaded Microneedle Patches for Targeted Rheumatoid Arthritis Therapy: A Comprehensive Review

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterised by persistent synovial inflammation, progressive cartilage and bone erosion, and substantial disability. Although disease-modifying antirheumatic drugs (DMARDs), biologics and targeted synthetic agents have transformed outcomes, conventional oral and parenteral routes are limited by systemic toxicity, poor articular bioavailability, first-pass metabolism, frequent dosing and poor patient adherence. Transdermal delivery via microneedle (MN) patches has emerged as a minimally invasive, painless and self-administrable alternative that physically bypasses the stratum corneum barrier. In parallel, nanocarriers—polymeric nanoparticles, micelles, liposomes, lipid nanoparticles, inorganic nanoparticles and biomimetic cell-membrane-coated systems—can exploit the unique inflamed-joint microenvironment (leaky vasculature, activated macrophages over-expressing CD44, folate receptor-β and scavenger receptors, acidic pH, elevated reactive oxygen species and matrix metalloproteinases) to achieve passive and active targeting with stimulus-responsive release. The convergence of these two platforms—nano-loaded microneedle patches—offers a synergistic system in which MNs assist nanocarrier penetration across the skin while the nanocarriers provide controlled, targeted intra-articular and systemic delivery. This review summarises the epidemiology and pathophysiology of RA and the rationale for targeting; surveys MN classification, materials and fabrication; examines nanocarriers and targeting ligands relevant to RA; and critically analyses representative nano-loaded MN systems delivering methotrexate, biologics, peptides and natural products. Characterisation requirements, preclinical efficacy in adjuvant- and collagen-induced arthritis models, and the principal translational, safety, manufacturing and regulatory hurdles are discussed, together with future directions toward clinically deployable, intelligent, on-demand RA therapeutics.

Abbreviations:
RA, rheumatoid arthritis; MN, microneedle; DMARD, disease-modifying antirheumatic drug; csDMARD, conventional synthetic DMARD; bDMARD, biological DMARD; tsDMARD, targeted synthetic DMARD; MTX, methotrexate; TNF, tumour necrosis factor; IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; JAK, Janus kinase; FLS, fibroblast-like synoviocyte; SC, stratum corneum; NP, nanoparticle; PLGA, poly(lactic-co-glycolic acid);

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PLA, polylactic acid; PEG, poly(ethylene glycol); HA, hyaluronic acid; FR-β, folate receptor-β; SR-A, scavenger receptor class A; ROS, reactive oxygen species; MMP, matrix metalloproteinase; EPR, enhanced permeability and retention; ELVIS, extravasation through leaky vasculature and subsequent inflammatory cell-mediated sequestration; AIA, adjuvant-induced arthritis; CIA, collagen-induced arthritis; GLP-1RA, glucagon-like peptide-1 receptor agonist; ISF, interstitial fluid; FDA, Food and Drug Administration; ACR, American College of Rheumatology; EULAR, European Alliance of Associations for Rheumatology.

1. INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder that predominantly targets the synovial joints, producing symmetrical polyarthritis, synovial hyperplasia, pannus formation, and progressive destruction of articular cartilage and subchondral bone [1,2]. Beyond the joints, RA is associated with extra-articular and systemic manifestations affecting the cardiovascular, pulmonary and skeletal systems, and it imposes a considerable burden of pain, functional disability, reduced quality of life and premature mortality [3,4]. The disease affects approximately 0.5–1% of the global adult population, with a marked female predominance and an increasing absolute number of cases worldwide as populations age [5,6].

Contemporary management follows a treat-to-target paradigm in which conventional synthetic DMARDs (csDMARDs)—with methotrexate (MTX) as the anchor drug—are escalated to biological (bDMARDs) and targeted synthetic (tsDMARDs, e.g. Janus kinase inhibitors) agents to achieve remission or low disease activity [7,8]. Despite these advances, the conventional oral and parenteral routes share intrinsic limitations: non-specific systemic distribution and dose-dependent toxicity, hepatic first-pass metabolism, short plasma half-lives, the need for frequent administration, gastrointestinal intolerance, injection-site reactions, needle phobia and consequent poor adherence [8,9]. Critically, because these agents are not selectively delivered to inflamed joints, high systemic doses are required to attain therapeutic articular concentrations, amplifying off-target adverse effects [10,11].

Two technological streams have matured to address these problems. The first is transdermal delivery via microneedle (MN) patches—arrays of micron-scale projections that painlessly and minimally invasively create transient microchannels across the stratum corneum (SC), enabling self-administered delivery of small molecules, peptides, proteins and particulate carriers while avoiding first-pass metabolism and the pain of hypodermic injection [12,13,14]. The second is nanomedicine, in which nanoscale carriers prolong circulation, protect labile cargos, enable controlled release and—by exploiting the distinctive inflamed-joint microenvironment—achieve passive and ligand-mediated active targeting to activated macrophages and synovial tissue [15,16,17]. Individually, each platform has limitations: nanoparticles (NPs) cannot traverse intact SC, while unmodified MNs offer limited control over biodistribution and release kinetics [18].

The integration of the two—nano-loaded microneedle patches—is therefore conceptually compelling. The MN array assists nanocarriers in bypassing the SC and depositing them in viable skin, from which targeted nanocarriers can subsequently localise to inflamed joints and release their payload in response to pathological cues, while simultaneously providing sustained release and reduced dosing frequency [18,19,20]. This hybrid strategy has attracted rapidly growing interest, with reported systems delivering MTX, anti-cytokine biologics, peptides, gene therapeutics and bioactive natural products in preclinical models of RA [20,21,22]. This review provides a comprehensive and critical synthesis of the field: it outlines the epidemiology, pathophysiology and targetable features of RA; describes MN classification, materials and manufacture; surveys nanocarriers and targeting ligands relevant to RA; analyses representative nano-loaded MN systems and their characterisation and efficacy; and discusses the translational, safety, manufacturing and regulatory considerations that will determine clinical adoption.

2. Rheumatoid Arthritis: Epidemiology, Pathophysiology, and the Targetable Joint Microenvironment

2.1. Epidemiology and disease burden

RA occurs worldwide with a reported prevalence ranging from approximately 0.24% to 2%, generally higher in industrialised countries and in certain indigenous populations, and consistently two- to three-fold more common in women than in men [5,6,23]. The Global Burden of Disease analyses indicate that, although age-standardised RA mortality has declined over recent decades—reflecting earlier diagnosis and improved therapeutics—the global age-standardised prevalence, the number of prevalent cases and years lived with disability have all risen, and the prevalence is projected to continue increasing toward 2050 [6,24]. Disease onset typically occurs between the fourth and sixth decades, and RA aetiology is multifactorial, integrating genetic susceptibility (notably the shared-epitope HLA-

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DRB1 alleles), environmental and lifestyle exposures (cigarette smoking, periodontal infection, silica and air pollution), hormonal factors and the microbiome [5,23,25].

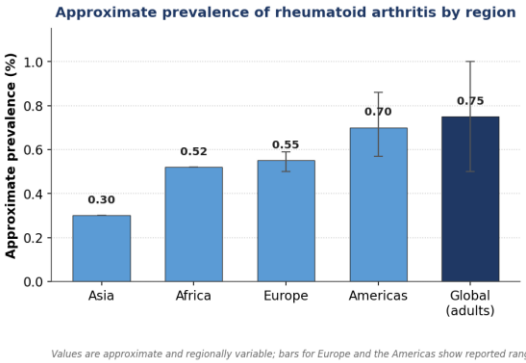

Figure 1. Approximate prevalence of rheumatoid arthritis by region. Reported estimates are regionally variable; the global adult prevalence is generally cited as ~0.5–1% [5,6,23].

2.2. Pathophysiology

RA pathogenesis evolves through a pre-clinical phase of systemic autoimmunity—marked by anti-citrullinated protein antibodies and rheumatoid factor—that precedes clinical synovitis by years [1,26,75,77]. Once established, the rheumatoid synovium becomes a hyperplastic, hypoxic and highly vascularised tissue infiltrated by innate and adaptive immune cells. Activated macrophages, T and B lymphocytes, dendritic cells and neutrophils, together with aggressive, apoptosis-resistant fibroblast-like synoviocytes (FLS), form an invasive pannus that erodes cartilage and bone [1,2,26,79]. A self-amplifying cytokine network—dominated by tumour necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and IL-17—drives inflammation, while receptor activator of nuclear factor-κB ligand (RANKL)-mediated osteoclastogenesis promotes bone resorption [26,27,76]. Synovial macrophages are pivotal: their polarisation toward a pro-inflammatory M1 phenotype sustains cytokine release and oxidative stress, and re-balancing the M1/M2 ratio is a key therapeutic objective [27,28].

2.3. Microenvironmental features exploitable for targeting

Several pathological hallmarks of the inflamed joint can be harnessed for targeted nanocarrier delivery. The neovasculature of the rheumatoid synovium is hyperpermeable and the lymphatic drainage is impaired, producing an "ELVIS" effect (extravasation through leaky vasculature and subsequent inflammatory cell-mediated sequestration), analogous to the EPR effect in tumours, that promotes passive accumulation of long-circulating nanocarriers in inflamed joints [16,17]. Activated synovial macrophages over-express receptors that serve as docking sites for ligand-functionalised carriers, including CD44 (the receptor for hyaluronic acid), folate receptor-β (FR-β), and scavenger receptor class A (SR-A, targetable with dextran sulfate and chondroitin sulfate) [16,28,29]. In addition, the inflamed microenvironment is acidic, hypoxic, and rich in reactive oxygen species (ROS) and matrix metalloproteinases (MMPs); these stimuli are widely exploited to trigger pH-, redox-, ROS- and enzyme-responsive payload release at the disease site [17,28,30]. Collectively, these features underpin the design logic of the targeted nanocarriers discussed in Section 5.

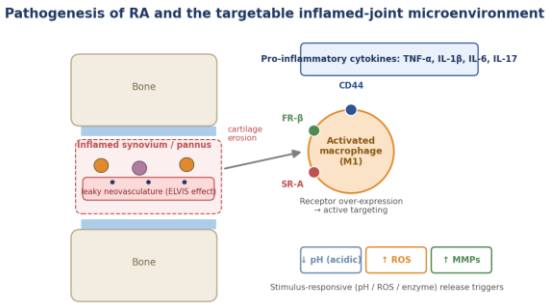

Figure 2. Pathogenesis of rheumatoid arthritis and the targetable inflamed-joint microenvironment. Activated synovial macrophages over-express CD44, folate receptor-β (FR-β) and scavenger receptor class A (SR-A), enabling active targeting, while leaky neovasculature (ELVIS effect), acidic pH, elevated reactive oxygen species (ROS) and matrix metalloproteinases (MMPs) permit passive accumulation and stimulus-responsive release [16,17,28].

3. Current Pharmacotherapy and the Limitations of Conventional Delivery

3.1. The therapeutic armamentarium

The 2021 American College of Rheumatology (ACR) guideline and the 2022 EULAR recommendations endorse a treat-to-target approach centred on early initiation of csDMARDs [7,31]. Methotrexate is the recommended first-line anchor drug for most patients with moderate-to-high disease activity owing to its established efficacy, safety profile, dosing flexibility and low cost; other csDMARDs include leflunomide, sulfasalazine and hydroxychloroquine [7,32]. When csDMARD monotherapy is inadequate, bDMARDs targeting TNF-α (e.g. adalimumab, etanercept, infliximab), IL-6 (tocilizumab), T-cell co-stimulation (abatacept) or B cells (rituximab), or tsDMARDs (the Janus kinase inhibitors tofacitinib, baricitinib and upadacitinib) are added or substituted [7,8,31]. Glucocorticoids remain useful as bridging therapy but their long-term use is discouraged because of osteoporosis, infection and cardiovascular risks [7]. Non-steroidal anti-inflammatory drugs (NSAIDs) provide symptomatic relief without modifying disease progression [9,78].

3.2. Limitations of oral and parenteral delivery

MTX exemplifies the delivery challenge: oral

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bioavailability is variable and saturable, and prolonged systemic exposure causes dose-dependent hepatotoxicity, myelosuppression, gastrointestinal intolerance and pulmonary toxicity, frequently necessitating dose reduction or discontinuation [9,21]. Biologics and peptide therapeutics are macromolecular, susceptible to gastrointestinal degradation, and therefore require subcutaneous or intravenous administration, which is associated with injection-site reactions, needle phobia, cold-chain logistics and high cost [11,33]. Across drug classes, the absence of joint selectivity means that only a small fraction of the administered dose reaches the synovium, while the remainder distributes systemically and contributes to toxicity [10,16]. Intra-articular injection delivers drug locally but is invasive, painful, restricted to accessible joints, impractical for polyarticular disease and limited by rapid clearance from the joint cavity [17]. These constraints provide the rationale for delivery systems that combine route innovation (transdermal MN administration) with targeting and controlled release (nanocarriers).

4. The Skin Barrier and the Rationale for Transdermal Delivery in RA

The skin is the largest organ of the body and an attractive but formidable route for drug delivery. Its principal barrier, the stratum corneum (SC)—a 10–20 μm layer of corneocytes embedded in a lipid matrix—restricts passive transdermal permeation to small (typically <500 Da), moderately lipophilic, low-melting-point molecules, excluding most hydrophilic drugs, peptides, proteins and nanoparticles [34,35,72,83]. Conventional transdermal patches are therefore unsuitable for the macromolecular and particulate therapeutics of greatest interest in RA [13,34].

Transdermal delivery nonetheless offers compelling advantages for a chronic disease such as RA: avoidance of hepatic first-pass metabolism and gastrointestinal degradation, sustained and controllable input, reduced dosing frequency, ease of self-application and termination, and improved adherence relative to injections [13,36]. Microneedles overcome the SC barrier by creating transient, micron-scale aqueous channels into the viable epidermis and superficial dermis—a region rich in dendritic cells and capillaries—without stimulating the deeper dermal nociceptors and blood vessels, so application is essentially painless and bloodless [12,14,34]. This makes MN patches uniquely capable of delivering both small-molecule DMARDs and the macromolecular and nanoparticulate agents that passive patches cannot [13,18,68].

5. Microneedle Technology: Classification, Materials and Fabrication

Microneedles are micron-scale structures (typically 25–2000 μm in length) arranged as arrays on a backing to form a patch [12,37]. They are conventionally grouped into five principal types according to their mechanism of drug delivery: solid, coated, hollow, dissolving and hydrogel-forming MNs; hybrid and stimulus-responsive designs are increasingly reported [37,38,39,71,81].

5.1. Microneedle types

Solid MNs employ a two-step "poke-and-patch" approach: the array pierces the skin to create microchannels, is removed, and a drug formulation is then applied for diffusion through the pores; they are mechanically robust but offer limited dose control [37,40]. Coated MNs ("coat-and-poke") carry a thin drug layer on solid needle surfaces deposited by dip-, spray- or inkjet-coating; drug loading is constrained by coating thickness and uniformity [40,41,80]. Hollow MNs ("poke-and-flow") contain bores through which liquid formulations are infused under pressure, enabling higher and adjustable doses but risking bore blockage and leakage [37,41]. Dissolving MNs are fabricated from water-soluble or biodegradable polymers in which the drug or nanocarrier is encapsulated; upon insertion the matrix dissolves in interstitial fluid, releasing the cargo and leaving no sharps waste—features that, together with high drug-loading capacity and simple low-cost micromoulding, have made them the most widely studied type [40,42,84]. Hydrogel-forming MNs comprise swellable crosslinked polymer arrays that imbibe interstitial fluid, swell and release drug from an attached reservoir while remaining intact for clean removal; they also enable interstitial fluid sampling for diagnostics [38,39,43,70]. Table 1 summarises the comparative attributes of these types.

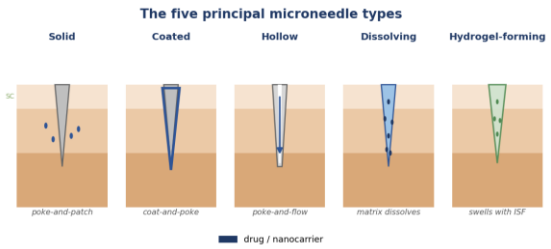

Figure 3. Schematic of the five principal microneedle types and their delivery mechanisms across the skin (SC, stratum corneum) [37,40,42].

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Table 1. Comparison of the principal microneedle types relevant to nano-loaded patch design.

MN type	Mechanism	Drug loading	Key features / limitations
Solid	Poke-and-patch; pierce, remove, then apply formulation	Low; via micropores	Robust; simple; poor dose control and efficiency [37,40]
Coated	Coat-and-poke; drug coated on needle surface	Low–moderate	Rapid release; limited by coating thickness/uniformity [40,41]
Hollow	Poke-and-flow; pressure-driven infusion	High, adjustable	Liquid/bolus or infusion; risk of bore blockage, leakage [37,41]
Dissolving	Polymer matrix dissolves in skin, releasing cargo	High	No sharps waste; high loading; most studied; ideal for NPs [40,42]
Hydrogel-forming	Swells with interstitial fluid; drug from reservoir	High (reservoir)	Clean removal; sustained release; ISF sampling [38,39,43]

5.2. Materials

MN performance depends critically on the choice of material, which must combine sufficient mechanical strength for SC penetration with biocompatibility and—for dissolving and hydrogel systems—appropriate dissolution or swelling behaviour [37,44]. Solid and hollow MNs have been fabricated from silicon, metals (stainless steel, titanium), ceramics and rigid polymers, while dissolving and hydrogel MNs employ water-soluble or biodegradable materials including poly(vinyl alcohol), poly(vinylpyrrolidone), hyaluronic acid, chondroitin sulfate, carboxymethylcellulose, sodium alginate, chitosan, dextran, sugars (sucrose, trehalose, maltose) and biodegradable polyesters such as PLGA and PLA [42,44,45]. Many of these polymers double as nanoparticle matrices or targeting ligands—hyaluronic acid, for example, both forms the MN body and serves as a CD44-targeting ligand—allowing elegant single-material designs [20,21,82].

5.3. Fabrication methods

The dominant fabrication route for dissolving and hydrogel MNs is micromoulding, in which a polymer/drug solution is cast into a microstructured (commonly polydimethylsiloxane) mould under vacuum or centrifugation and dried; this method is simple, scalable and well suited to encapsulating thermolabile cargos and nanocarriers under mild conditions [42,44]. Solid and master moulds are produced by photolithography, micromachining, laser ablation or etching, while additive approaches—notably two-photon polymerisation and other three-dimensional printing techniques—permit precise, customisable needle geometries [37,46,73]. Drawing lithography, droplet-born air blowing and atomised spraying have also been used to form needles directly. Multilayer and bubble/effervescent designs concentrate the drug or nanocarrier in the needle tips to maximise delivery efficiency and minimise waste in the baseplate [21,47]. The choice of method governs needle sharpness, aspect ratio, mechanical strength, reproducibility and ultimately manufacturability at scale.

6. Nanocarriers for Rheumatoid Arthritis: Types and Targeting Strategies

Nanocarriers improve the therapeutic index of antirheumatic drugs by protecting cargos from degradation, prolonging circulation, controlling release, increasing solubility of hydrophobic agents, and enabling passive and active targeting to inflamed joints [15,16,17,74]. The principal classes investigated for RA are summarised in Table 2.

6.1. Classes of nanocarrier

Polymeric nanoparticles—most commonly PLGA, PLA, chitosan and their PEGylated derivatives—offer tunable size, high stability and sustained, biodegradable release, and have been used to encapsulate MTX, glucocorticoids, celastrol and nucleic acids [16,48,49]. Polymeric micelles, self-assembled from amphiphilic block copolymers such as methoxy-PEG-PLA, solubilise poorly water-soluble drugs within their hydrophobic core and are readily surface-functionalised for targeting [21,50]. Liposomes and other lipid-based carriers (solid lipid nanoparticles, nanostructured lipid carriers) provide excellent biocompatibility and can be decorated with ligands such as folate, dextran sulfate or chondroitin sulfate to address receptors on activated macrophages [29,51,52]. Inorganic and enzyme-mimetic nanoparticles—including cerium- and manganese-based nanozymes, mesoporous silica and gold—combine drug delivery with intrinsic ROS-scavenging or imaging capability [33,53]. Biomimetic, cell-membrane-coated nanoparticles cloaked in macrophage or neutrophil membranes evade immune clearance, neutralise inflammatory cytokines and home to inflamed tissue, representing a sophisticated targeting strategy increasingly paired with MN delivery [22,54].

6.2. Passive and active targeting

Passive targeting relies on the ELVIS/EPR-like accumulation of appropriately sized (typically 20–200 nm), long-circulating, often PEGylated nanocarriers within the hyperpermeable inflamed synovium [16,17]. Active targeting superimposes molecular recognition: hyaluronic acid and anti-CD44 ligands, folate and anti-FR-β ligands, and dextran sulfate or chondroitin sulfate (SR-A) direct carriers to activated macrophages, while peptides

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such as the type II collagen-binding sequence WYRGRL target cartilage extracellular matrix [20,28,29]. Such functionalisation increases synovial accumulation, enhances cellular uptake and reduces off-target exposure relative to non-targeted carriers [16,28,69].

6.3. Stimulus-responsive release

The acidic pH, elevated ROS, hypoxia, glutathione redox imbalance and MMP over-expression of the inflamed joint are widely exploited as endogenous triggers for site-specific payload release. pH-sensitive linkers and polymers, ROS- and redox-cleavable bonds (e.g. thioketal, disulfide), and MMP-cleavable peptide spacers have all been engineered into RA nanocarriers to confine drug release to the disease microenvironment, thereby maximising local efficacy and limiting systemic toxicity [17,28,30,54]. Exogenous triggers—light, ultrasound, magnetic fields and heat—offer additional on-demand control and are emerging in intelligent MN platforms [55,56].

Table 2. Representative nanocarrier classes used for rheumatoid arthritis and their salient features.

Nanocarrier	Representative examples for RA	Advantages
Polymeric NPs	PLGA/PLA, chitosan, PEGylated NPs carrying MTX, celastrol, glucocorticoids, siRNA [16,48,49]	Tunable size; sustained biodegradable release; high stability
Polymeric micelles	mPEG-PLA micelles for MTX; dextran sulfate prodrug micelles for celastrol [21,30,50]	Solubilise hydrophobic drugs; easy ligand functionalisation
Liposomes / lipid NPs	Folate-, dextran sulfate-, chondroitin sulfate-decorated liposomes; NLCs [29,51,52]	Biocompatible; flexible surface modification; co-loading
Inorganic / nanozymes	Cerium–manganese oxide, mesoporous silica, gold NPs [33,53]	Intrinsic ROS scavenging; theranostic potential
Biomimetic membrane-coated	Macrophage- or neutrophil-membrane-coated NPs [22,54]	Immune evasion; cytokine neutralisation; inflammation homing

7. Nano-Loaded Microneedle Patches: The Combined Platform

7.1. Rationale for synergy

Nanocarriers and microneedles are functionally complementary. Intact SC excludes nanoparticles from passive transdermal entry, so the MN array serves as the enabling vehicle that physically deposits nanocarriers into viable skin; conversely, the nanocarrier endows the system with controlled release, protection of labile drugs and active joint targeting that bare MNs lack [18,19]. In a nano-loaded MN patch, nanoparticles are encapsulated within the dissolving or hydrogel needle matrix (or coated onto/loaded into hollow needles); upon application the needles dissolve or swell, liberating intact nanocarriers locally, which then either act regionally or enter the lymphatic and systemic circulation to reach inflamed joints, where stimulus-responsive mechanisms release the payload [18,20,22]. The result is a minimally invasive, self-administrable, sustained and targeted delivery system—precisely the profile required for a chronic, polyarticular disease such as RA [19,20].

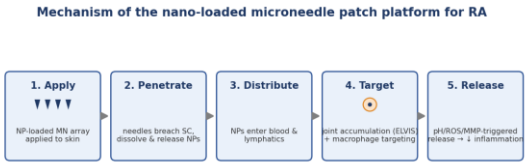

Figure 4. Mechanism of the nano-loaded microneedle patch platform for rheumatoid arthritis: application and skin penetration, nanocarrier release, systemic/lymphatic distribution, passive and active joint targeting, and stimulus-responsive drug release [18,20,22].

7.2. Design configurations

Several architectures have been reported. In the simplest, pre-formed drug-loaded nanocarriers are dispersed throughout a dissolving polymer and cast into needles. Tip-loaded and multilayer designs concentrate the nanocarrier in the needle tips to improve delivery efficiency and reduce baseplate waste [21,47]. In situ-forming systems incorporate amphiphilic polymers that self-assemble into nanomicelles only after the needle dissolves in skin interstitial fluid, combining high loading with on-site nanocarrier generation [21]. Active and stimuli-responsive patches add propulsion or triggering elements: effervescent/bubble-generating layers that accelerate and deepen delivery, and ROS-, pH- or near-infrared-responsive components that gate release [47,55,56]. Cartilage- and macrophage-targeting ligands (WYRGRL peptide, hyaluronic acid, folate, dextran sulfate) and biomimetic membrane coatings are frequently integrated to confer joint specificity [20,22,29].

7.3. Representative systems for RA

A growing body of preclinical work demonstrates the feasibility of nano-loaded MN patches in RA models. In an in situ nanomicelle-generating dissolving MN patch, methoxy-PEG-PLA and hyaluronic acid were used to form both the needles and nanomicelles; upon skin insertion the needles dissolved and generated MTX-loaded, CD44-targeting nanomicelles that accumulated in activated macrophages and suppressed disease progression without treatment-related toxicity [21]. A separate dissolving MN patch delivering MTX significantly increased transdermal permeation relative to a cream, reduced paw swelling and downregulated

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TNF-α and IL-1β, slowing RA progression in adjuvant-induced arthritis (AIA) rats and outperforming intragastric administration at equivalent doses [9]. Cartilage-targeting silk-fibroin nanoparticles functionalised with the WYRGRL peptide and loaded with glucagon-like peptide-1 receptor agonists (GLP-1RAs) were incorporated into dissolving MNs, enabling painless transdermal delivery, suppression of chondrocyte ferroptosis via the cGAS–STING pathway and induction of macrophage M2 polarisation [20].

Biomimetic strategies have also been combined with MNs: neutrophil-membrane-encapsulated NSAID-loaded polymeric nanoparticles delivered from a degradable biopolymer MN patch provided dual anti-inflammatory action and local transdermal delivery in RA [22]. Acid-responsive PEGylated branched-PLGA nanoparticles integrated into dissolving MNs enhanced local arthritis treatment through microenvironment-triggered release [57], and MNs loaded with cerium–manganese oxide nanozyme particles targeted synovial macrophages while scavenging ROS [53]. Polymeric MNs have additionally been used to deliver the peptide melittin transdermally for RA [58], and nanostructured-lipid-carrier-loaded dissolving MNs achieved controlled local administration of the natural product aconitine [59]. Active MN patches incorporating spontaneous bubble generation have further enhanced delivery efficiency and therapeutic outcomes in RA models [47]. Representative systems are compiled in Table 3.

Table 3. Representative nano-loaded microneedle systems investigated for rheumatoid arthritis (preclinical).

Nanocarrier / drug	MN type	Targeting / trigger	Model	Key outcome [ref]
mPEG-PLA/HA nanomicelles; MTX	Dissolving (in situ-forming)	CD44 / activated macrophages	RA model	Reduced disease progression; no treatment-related toxicity [21]
Polymer matrix; MTX	Dissolving	Local skin depot	AIA rats	↓ paw swelling, TNF-α, IL-1β; > intragastric dosing [9]
Silk-fibroin NPs; GLP-1RAs	Dissolving	WYRGRL peptide / cartilage	RA model	Inhibited chondrocyte ferroptosis; M2 polarisation [20]
Neutrophil-membrane NPs; NSAID	Degradable biopolymer	Inflammation homing	RA model	Dual anti-inflammatory; effective local delivery [22]
PEGylated branched-PLGA NPs	Dissolving	Acid-responsive release	Arthritis model	Enhanced local treatment via pH trigger [57]
Cerium–manganese oxide nanozyme	Microneedle array	Macrophage / ROS scavenging	RA model	Macrophage targeting; oxidative-stress relief [53]
Polymeric carrier; melittin	Polymeric MN	Local transdermal	RA model	Effective transdermal peptide delivery [58]

7.4. Therapeutic payloads

The platform has accommodated a broad therapeutic range. Small-molecule csDMARDs—above all MTX—remain the most studied, benefiting from reduced systemic toxicity when delivered via targeted nano-loaded MNs [9,21]. Anti-inflammatory NSAIDs and corticosteroids have been delivered for symptomatic control, including patient-friendly fast-dissolving MN patches of meloxicam [60] and acid-responsive nanoparticle systems [57]. Macromolecular biologics and peptides—etanercept, melittin and GLP-1RAs—exploit the MN route to bypass gastrointestinal degradation and injection [20,58,61]. Gene therapeutics (e.g. TNF-α-silencing siRNA in biomimetic carriers) and nanozymes address the cytokine network and oxidative stress directly [53,54]. Finally, bioactive natural products such as celastrol, aconitine and others, often poorly soluble and systemically toxic, are strong candidates for nanocarrier-in-MN delivery [30,59].

8. Characterisation, Quality Attributes and Preclinical Evaluation

Rigorous physicochemical and biological characterisation is essential to establish the quality, safety and performance of nano-loaded MN patches. Standard assessments fall into nanocarrier-level and patch-level domains.

8.1. Nanocarrier characterisation

Encapsulated nanocarriers are characterised for particle size and size distribution (dynamic light scattering), surface charge (zeta potential), morphology (transmission and scanning electron microscopy), drug-loading and encapsulation efficiency, colloidal stability and—where relevant—ligand conjugation density and stimulus-responsive behaviour [16,21,49]. Maintaining nanocarrier integrity and size after incorporation into, and release from, the needle matrix is a critical quality attribute, since aggregation or degradation during fabrication or storage can abolish targeting and controlled-release functions [18,21].

8.2. Microneedle patch characterisation

Patch evaluation encompasses needle morphology and array geometry (optical and electron microscopy), mechanical strength and fracture force (texture analysis), skin-insertion capability and penetration depth (typically assessed in excised skin or skin-mimicking films with staining, optical coherence tomography or histology), dissolution or swelling kinetics, drug content and content

uniformity, in vitro drug release, and ex vivo transdermal permeation across animal or human skin in Franz diffusion cells [9,40,42]. Insertion efficiency and mechanical robustness must be balanced against rapid in-skin dissolution for dissolving systems, while moisture sensitivity and storage stability are important practical attributes [42,49].

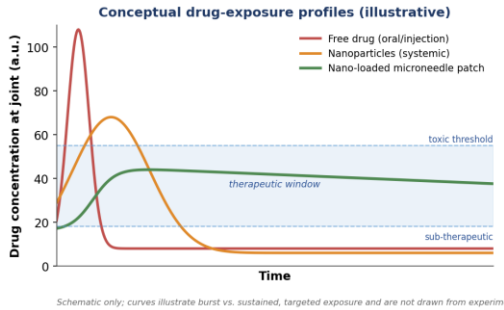

Figure 5. Conceptual comparison of drug-exposure profiles at the joint for free drug, systemically administered nanoparticles, and a nano-loaded microneedle patch. The schematic illustrates the shift from a high, transient burst toward sustained, targeted exposure within the therapeutic window; curves are illustrative and not drawn from experimental data.

8.3. Preclinical efficacy and safety models

In vivo efficacy is most commonly evaluated in rodent models that recapitulate RA pathology—principally adjuvant-induced arthritis (AIA) and collagen-induced arthritis (CIA). Outcome measures include paw and joint swelling, arthritis index, body weight, serum and synovial pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), histopathological assessment of synovial inflammation, cartilage erosion and bone destruction (including micro-computed tomography), and pharmacokinetic and biodistribution studies confirming preferential joint accumulation [9,20,21]. Reported nano-loaded MN systems consistently demonstrate enhanced transdermal permeation, increased synovial drug accumulation, superior anti-inflammatory and chondroprotective efficacy, and reduced systemic toxicity relative to free drug administered orally or by injection [9,20,21,22]. Local skin tolerability—erythema, oedema, recovery of microchannels and absence of infection—and systemic safety (hepatic, renal and haematological parameters) are routinely assessed and have generally been favourable in short-term studies [9,42].

9. Translational Challenges, Safety, Manufacturing and Regulatory Considerations

Despite compelling preclinical results, the clinical translation of nano-loaded MN patches faces multiple inter-related barriers [62,63].

9.1. Manufacturing and scale-up

Reproducible, high-throughput production of MN arrays containing uniformly distributed, intact nanocarriers is technically demanding. Challenges include batch-to-batch consistency of drug and nanoparticle loading, preservation of needle geometry and mechanical strength, the additional complexity and cost of sterile or aseptic processing, and the absence of standardised quality-control assays for MN products [62,63]. Continuous, automatable processes and robust in-process controls are required to move from laboratory micromoulding to commercial manufacture [63,64].

9.2. Stability, dosing and biological variability

Nano-loaded patches must remain physically and chemically stable across shelf life, with nanocarriers retaining size, loading and function; polymeric and protein cargos are particularly sensitive to moisture and temperature [42,63]. Achieving precise, reproducible dose delivery is complicated by inter-individual variability in skin thickness, hydration and application force, which affect insertion depth and the fraction of dose deposited [12,62]. For a polyarticular systemic disease, the relative contributions of local versus systemic exposure, and the achievable doses for high-dose biologics, require careful definition [11,18].

9.3. Safety and nanotoxicology

Repeated application raises questions of local skin irritation, sensitisation and infection risk at microchannels, as well as the long-term fate, accumulation and potential immunogenicity of biodegradable polymers and nanomaterials [62,65]. Biocompatible, well-characterised materials and thorough nanotoxicological evaluation are prerequisites for chronic use [44,65].

9.4. Regulatory landscape

MN-nanoparticle combination products sit at the intersection of drug, device and nanomedicine regulatory frameworks, and dedicated, harmonised guidance remains limited; this regulatory ambiguity slows development and approval [62,63]. Clear definitions of critical quality attributes, standardised characterisation and sterility requirements, and combination-product classification pathways would substantially de-risk translation [63,64]. To date, MN technologies for other indications have advanced into clinical testing, providing a template, but no nano-loaded MN product for RA has yet reached the clinic [62,66]. Patient and prescriber acceptability, cost-effectiveness relative to established biologics, and demonstration of meaningful clinical benefit in well-designed trials remain decisive [62,66].

10. Current Status and Future Perspectives

Research on nano-loaded MN patches for RA is expanding rapidly but remains largely preclinical.

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Future progress is likely to centre on several converging directions. Intelligent, stimulus-responsive and closed-loop patches—integrating inflammation-triggered (ROS, pH, MMP) and externally actuated (near-infrared, ultrasound, electrical, gas-propelled) release—promise on-demand, self-regulating therapy matched to disease flares [55,56,67]. Biomimetic cell-membrane-coated nanocarriers and precision ligand engineering (CD44, FR-β, SR-A and cartilage-binding peptides) will refine joint and macrophage selectivity, while gene therapeutics, nanozymes and combination payloads address the disease at multiple nodes simultaneously [22,53,54]. Theranostic patches that combine therapy with interstitial-fluid biomarker sampling could enable disease monitoring alongside treatment [39,43]. Realising this potential will require advances in scalable, GMP-compatible manufacturing, long-term safety and stability data, standardised characterisation, clearer regulatory pathways, and ultimately rigorous clinical trials demonstrating efficacy, safety and patient acceptability relative to current standards of care [62,63,66].

11. CONCLUSION

Rheumatoid arthritis continues to demand therapies that deliver drugs selectively to inflamed joints while minimising systemic toxicity and the burden of frequent injections. Nano-loaded microneedle patches unite two complementary technologies: microneedles surmount the stratum corneum to enable minimally invasive, painless, self-administered delivery, and nanocarriers provide protection, controlled release and passive and active targeting that exploit the distinctive inflamed-joint microenvironment. Preclinical studies delivering methotrexate, biologics, peptides, gene therapeutics, nanozymes and natural products consistently report enhanced transdermal permeation, increased synovial accumulation, superior anti-inflammatory and chondroprotective efficacy, and reduced systemic toxicity compared with conventional routes. Significant translational hurdles—scalable sterile manufacturing, stability, dosing reproducibility, nanotoxicology and an underdeveloped regulatory framework—must nevertheless be overcome before clinical adoption. With continued progress in intelligent design, materials science and regulatory science, nano-loaded microneedle patches represent a promising and patient-centred platform for the targeted, controlled and convenient treatment of rheumatoid arthritis.

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