

Biodegradable Microneedles for Pain Management in Arthritis Patients

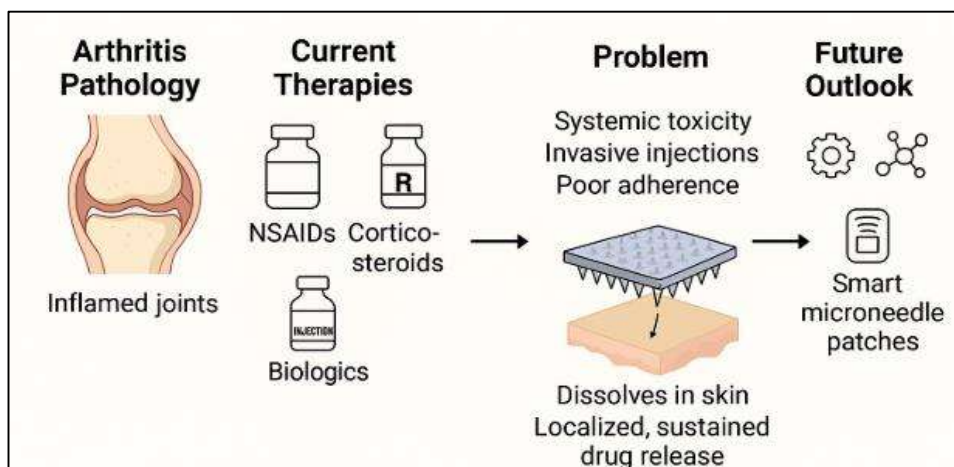
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ABSTRACT: Arthritis, which includes both rheumatoid arthritis (RA) and osteoarthritis (OA), is a long-lasting and debilitating condition characterized by ongoing pain, inflammation, and gradual joint damage. While current treatments like NSAIDs, corticosteroids, DMARDs, biologics, and JAK inhibitors can help manage symptoms and slow down the disease's progression, their long-term use is often hampered by systemic side effects, invasive methods of administration, and issues with patient adherence. Recently, microneedle technology has emerged as a promising, minimally invasive, and patient-friendly option for delivering medication directly through the skin. Among these, biodegradable microneedles (BMNs) are particularly noteworthy because they're crafted from biocompatible materials such as PLGA, hyaluronic acid, and chitosan, which can encapsulate medications and release them in a controlled manner as they dissolve or degrade. Preclinical studies have shown encouraging results, with BMNs effectively delivering NSAIDs, corticosteroids, and anti-TNF biologics to inflamed joints, minimizing toxicity while enhancing therapeutic targeting. However, there are still hurdles to overcome, such as the limited capacity for loading biologics, ensuring the mechanical strength of the microneedles, achieving consistent large-scale production, and navigating the ever-changing regulatory landscape. Looking ahead, innovations like 3D printing, the integration of nanocarriers, and the creation of smart patches powered by AI or IoT could help tackle these challenges. With ongoing advancements, BMNs hold the promise of transitioning from lab research to real-world clinical applications, potentially revolutionizing how we manage arthritis pain and modify the disease.

KEYWORDS: Transdermal delivery, sustained release, biologics, smart drug delivery, Biodegradable microneedles, arthritis therapy, Nanotechnology.



Graphical Abstract

INTRODUCTION

Arthritis is not simply a clinical diagnosis. Arthritis typically refers to a lifelong health condition, often hindering how millions of people move, live independently, and enjoy life. Arthritis has many types, with osteoarthritis (OA) and rheumatoid arthritis (RA), the most common and disabling. Osteoarthritis is referred to as a "wear-and-tear" disease that gradually destroys cartilage and leads to chronic pain, stiffness, and disability (1). Conversely, RA is an autoimmune disease that leads to chronic joint inflammation and damage, with untold years of disability, if untreated. Together, OA and RA represent substantial portions of the global chronic disease burden. Currently, the World Health Organization estimates more than 528 million people live with OA, with numbers

expected to increase with aging populations and increased obesity rates. RA affects slightly less than 1% of adults globally and impacts patients at an age when they are often most productive. This has implications for the patient, their families and healthcare costs (2).

Pain is the essence of arthritis. Pain is an omnipresent, sometimes unpredictable, subjective experience that alters the lives of patients. Pain can result from damage to joints, but is also influenced by an array of overlapping inflamed mediators (e.g., $\text{TNF-}\alpha$, $\text{IL-1}\beta$, prostaglandins, bradykinin), as well as central sensitisations that amplify pain signals in the spine and brain (3). Current therapeutics for pain amelioration, e.g., Non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, opioids, and biologics, provide variable moderate-to-

mild pain relief, but have significant downsides. Long-term NSAID use can lead to serious gastrointestinal bleeding and cardiovascular problems (4). Corticosteroids, when used too much, can lead to systemic toxicity (5) while opioids can induce dependence, tolerance, and decreased quality of life. Even intra-articular injections have many pros and cons; even though they provide local relief, they are invasive, painful procedures, and they have potential risk of infection (6). The state of pain relief remains a barrier to developing an effective, safe, and sustainable strategy for arthritis.

Biodegradable microneedles (BMNs) offer an effective, patient-friendly approach for treating arthritis. They are made using safe materials such as hyaluronic acid, PLGA, and chitosan. This type of microneedle can penetrate the skin and deliver medication to the inflamed joints. Afterward, they dissolve without causing sharp waste (7). Since BMNs can bypass gut and first-pass metabolism, they could improve delivery of NSAIDs, corticosteroids, and biologics while decreasing side effects. Early studies that have used arthritis models appear promising and demonstrate reductions in inflammation and improving mobility (8). Thus, the BMNs are a promising and safer and more sustainable, alternative for pain management.

PATHOPHYSIOLOGY OF ARTHRITIS

ARTHROPATHY AND PAIN

GENESIS:

Arthritis is not a single disease but rather a spectrum of joint disorders that share a common endpoint: inflammation, structural damage, and pain. Among these, rheumatoid arthritis (RA) and osteoarthritis (OA) remain the most significant, both in prevalence and disability burden. These processes are summarized in Figure 1, which highlights the interplay between inflammatory mediators, structural damage, and pain pathways in arthritis pathophysiology.

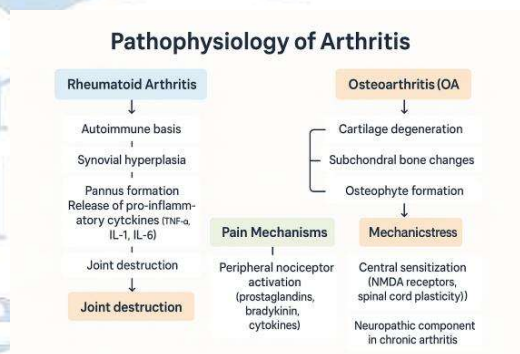


Figure 1. Pathophysiology of Arthritis.

RHEUMATOID ARTHRITIS (RA):

RA is most accurately characterized as an immune attack on the synovium gone awry. Immune cells invade the joint lining and lead to a surge of inflammatory mediators (e.g., TNF-α, IL-1, IL-6), and the synovium

becomes pathologically thickened. Pannus tissue is produced and invades cartilage and bone. Over the course of the disease, these take years to decades, the result is irreversible osteoarthopathy and systemic complications ranging from cardiovascular disease to lung involvement (9,10).

OSTEOARTHRITIS (OA):

OA, once regarded as purely “wear and tear,” is now acknowledged as a dynamic process involving both mechanics and inflammation. Cartilage gradually loses its collagen and proteoglycan matrix, while the underlying bone remodels and develops osteophytes. Mechanical stress, obesity, and ageing accelerate these changes, while chondrocytes themselves release low-grade inflammatory signals that sustain tissue breakdown (11,12). This evolving perspective presents OA not as a passive degenerative condition, but as a whole-joint disease characterised by biochemical and structural interactions (13).

PAIN MECHANISMS:

What makes arthritis especially disabling is the persistent and complex nature of pain.

- On the peripheral side, pain is driven by sensitization of nociceptors to prostaglandins, bradykinin, and cytokines released in the inflamed joint (14).

- At the central level, the nervous system begins to “remember” pain. Neurons in the spinal cord become overly excitable, NMDA receptors increase, and normal inhibitory pathways weaken. This process, called central sensitisation, makes pain signals stronger even after inflammation subsides (15).
- Over time, some patients also develop a neuropathic component. They may experience burning or shooting pain due to nerve damage and adverse interactions between the nervous and immune systems (16).

PAIN MANAGEMENT IN ARTHRITIS MECHANISMS OF ACTION (MOA):

Arthritis pain is rarely straightforward; it stems from a complex interplay of inflammation, mechanical strain on the joints, and nerve-related changes, creating a persistent and often unpredictable burden. For this reason, no single drug class can address all dimensions of the disease. Instead, clinicians rely on a palette of pharmacological options - each acting at different checkpoints of the pain and inflammation cascade, and each carrying its own benefits and trade-offs. These mechanisms are summarised in Figure 2.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS):

NSAIDs are still the first port of call in arthritis therapy. By blocking cyclooxygenase (COX-1 and COX-2) enzymes, they suppress prostaglandin production, reducing peripheral sensitization, swelling, and stiffness (17). Their rapid symptom relief explains their popularity, but prolonged use comes at a price - gastrointestinal bleeding and cardiovascular risks remain major concerns, especially with selective COX-2 inhibitors like celecoxib and etoricoxib (18).

CORTICOSTEROIDS:

Corticosteroids provide almost immediate relief by shutting down the NF- κ B pathway, silencing pro-inflammatory cytokines (TNF- α , IL-1, and IL-6), and preventing immune cells from flooding the joint (19). When injected directly into joints, they deliver fast results, but repeated use risks joint damage, osteoporosis, adrenal suppression, and metabolic side effects (20). Thus, they are powerful but best reserved for short-term interventions.

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS) AND BIOLOGICS:

Unlike NSAIDs or steroids, DMARDs work at the root of the disease process. Methotrexate remains the gold standard, calming immune overactivity by suppressing T-cell function (21). Biologic DMARDs—including anti-TNF agents (adalimumab, infliximab, etanercept) and IL-6 inhibitors (tocilizumab)—take precision a step further, directly neutralizing the cytokines that fuel synovial destruction (22). These therapies have revolutionized RA outcomes, but they require injections or infusions and carry an increased risk of infection.

OPIOIDS:

Opioids, like tramadol or morphine, work centrally by activating μ -opioid receptors in the brain and spinal cord, dampening the transmission of pain signals (23). However, they do not address the inflammatory basis of arthritis and are associated with tolerance, dependency, and opioid-induced hyperalgesia. For these reasons, guidelines now restrict opioids to last-line therapy in severe, refractory cases (24).

NOVEL AGENTS: JAK INHIBITORS:

The newest entrants in the arthritis treatment arsenal are Janus kinase (JAK) inhibitors—oral molecules such as tofacitinib, baricitinib, and upadacitinib. By disrupting the JAK-STAT pathway, they

prevent cytokine-driven signalling at its source (25). Convenient and highly effective, they are often viewed as oral alternatives to biologics. However, their long-term safety profile is still under scrutiny, with warnings about infection risk, thrombosis, and even malignancy (26).

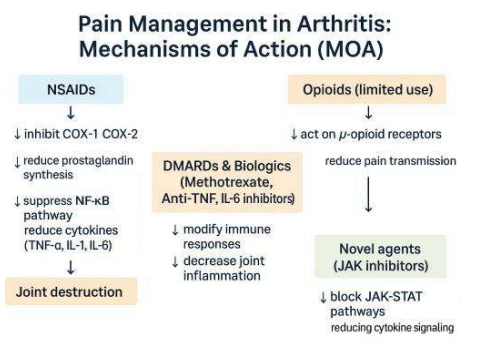


Figure 2. Pain Management in Arthritis: Mechanisms of Action (MOA).

MICRONEEDLE TECHNOLOGY

BASICS

Microneedles (MNs) are reshaping the way we think about transdermal drug delivery. Unlike traditional oral or injectable routes, which are often associated with systemic side effects or needle phobia, MNs painlessly pierce the stratum corneum—the skin’s toughest barrier—to create microscopic channels. These tiny portals allow drugs to reach deeper tissues without causing bleeding or nerve stimulation. Due to their minimally invasive nature, ease of use, and patient-friendly design, MNs are emerging as a particularly attractive option

for chronic conditions, such as arthritis, where long-term treatment compliance is crucial. Representative market or clinical examples are summarised in Table 1.

TYPES OF MICRONEEDLES:

Microneedles are not a one-size-fits-all technology; they come in several forms, each designed to address specific therapeutic needs:

- Solid microneedles act as skin perforators, forming microchannels through which a drug-loaded patch can later diffuse—a method often called the “poke and patch” strategy.
- Hollow microneedles resemble miniature syringes with tiny bores that actively inject liquid formulations directly into the dermis.
- Coated microneedles deliver medication rapidly, as the drug is applied onto the surface of the needle and dissolves once inserted.
- Dissolving microneedles are made entirely of water-soluble polymers, encapsulating the drug within their matrix. They dissolve completely inside the skin, releasing their payload in a controlled manner.
- Biodegradable microneedles take this concept a step further, using polymers

that degrade naturally in the skin. These not only ensure the safe elimination of the device but also provide the possibility of sustained or timed drug release, making them especially relevant for arthritis management (2728).

MATERIALS USED:

The material composition of MNs determines their strength, dissolution profile, and biocompatibility. Biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), hyaluronic acid (HA), chitosan, polyvinylpyrrolidone (PVP), and carboxymethyl cellulose (CMC) are commonly used because they are safe, versatile, and capable of carrying both small molecules and biologics. Among them, hyaluronic acid is of special interest for arthritis applications, not only because of its excellent safety profile but also due to its natural role in joint lubrication and cartilage support (29). To ensure adequate skin penetration, these polymers are often combined with synthetic materials that

provide additional mechanical strength and structural stability.

FABRICATION METHODS:

The success of microneedles lies in the precision of their design, and several fabrication methods have been developed to achieve this (Table 1):

- Micromolding or casting is the most common, where drug-polymer mixtures are poured into microstructured molds to form needle arrays.
- Lithography and etching, techniques borrowed from microelectronics, allow the creation of sharp, highly reproducible microneedle geometries.
- 3D printing and additive manufacturing are bringing a new dimension of flexibility, enabling personalized microneedle designs tailored to individual patient needs (30).
- Electro-drawing and droplet-born air blowing represent newer, mold-free approaches that cut down on production time and costs.

Table 1. Overview of Microneedle Technology: Types, Materials, Fabrication, and Market Examples

Type of Microneedle	Common Materials	Fabrication Methods	Examples / Applications

Solid Microneedles	Silicon, stainless steel, titanium, PMMA	Lithography, etching, laser cutting	Early prototypes for vaccines; some cosmetic skin patches.
Hollow Microneedles	Metals (stainless steel, titanium), glass, polymers (PLGA)	Micro-drilling, lithography, laser ablation	BD Soluvia® (used for influenza vaccines); Insulin delivery prototypes.
Coated Microneedles	Stainless steel, silicon, biodegradable polymers (PVP, CMC)	Dip-coating, spray-coating, inkjet printing	Zosano Pharma's ZP Patch® (zolmitriptan for migraine, under trials).
Dissolving Microneedles	Hyaluronic acid, PVP, CMC, maltose	Micromolding, casting, 3D printing	MicronJet® (NanoPass Technologies) for vaccines; cosmetic HA microneedle patches widely marketed in Asia.
Biodegradable Microneedles	PLGA, chitosan, hyaluronic acid, silk fibroin	Micromolding, electro-drawing, additive manufacturing	Emerging in preclinical/clinical studies for arthritis, insulin, and contraceptive delivery (no fully approved market product yet).

BIODEGRADABLE MICRONEEDLES IN ARTHRITIS MANAGEMENT

The use of biodegradable microneedles (BMNs) in arthritis management is a breakthrough in transdermal drug delivery.

Unlike the traditional drugs that are orally consumed or injected, BMNs directly deliver drugs at the inflammatory site. It has a superior therapeutic effect and reduces the likelihood of systemic adverse effects.

DRUG CANDIDATES:

A vast array of drugs has been examined for delivery using biodegradable microneedles (BMNs) in the treatment of arthritis.

- NSAIDs (diclofenac, indomethacin): Delivery from biodegradable polymers allows controlled locoregional release with decreased gastrointestinal and cardiovascular risk associated with orally taken NSAIDs (31).
- Corticosteroids (e.g., dexamethasone, triamcinolone): BMNs can deliver precise doses intra-dermally or periarticularly, minimising systemic exposure and long-term metabolic side effects (32).
- It is challenging to administer biologics in the form of anti-TNF drugs like etanercept and adalimumab through conventional transdermal methods due to the bulky mass of the molecule. Biodegradable microneedles of the PLGA or hyaluronic acid type are promising in this regard and also possess the ability of localised drug release with the preservation of the sensitive protein in a stable conformational state (33).

MECHANISM OF DRUG RELEASE:

Biodegradable microneedles (BMNs) are designed from polymers that degrade slowly after puncture of the skin, such as PLGA, hyaluronic acid, or chitosan. Drug

delivery is accomplished through two mechanisms of release. In water-soluble systems of hyaluronic acid microneedles, the matrix quickly dissolves and the drug is released in a period of minutes to hours. In other polymers like PLGA, the degradation is slower and the gradual release of the drug is seen in the range of days or even weeks (34). Such fine-tuning of the release is of particular benefit in long-standing chronic diseases like arthritis, where prolonged therapeutic levels at the inflammatory site are obligatory

TARGETED AND LOCALIZED DELIVERY:

Biodegradable microneedles (BMNs) can deliver directly to inflamed joints or inflammation in surrounding tissues, which is one of the major advantages of BMMN systems. Targeting the site of the disease will minimize the amount of drug delivered systemically, therefore avoiding many of the adverse events associated with standard therapies (e.g., gastrointestinal upset due to NSAIDs, metabolic side effects of corticosteroids, or general immunosuppression associated with biologics). The evidence from preclinical studies supports this benefit; the local application of BMNs with diclofenac and anti-TNF biologic-based agents resulted in greater pain reduction and improved control

of inflammation compared to standard oral or injectable applications (3536). Ultimately, BMNs combine the safety of biodegradable polymers, a minimally invasive method of application, and the therapeutic benefit of sustained localised release. If BMNs can be successfully

translated into a clinically appropriate device, it may represent a significant change in how arthritis pain and disease progression are managed. A summary of drug candidates, modes of release, and representative results is presented in Table 2.

Table 2. Biodegradable Microneedles in Arthritis Management: Drug Candidates, Mechanisms, and Examples

Drug Candidate	Mechanism of Release	Examples / Studies
NSAIDs (e.g., Diclofenac, Indomethacin)	Dissolution of HA-based MNs or PLGA degradation for sustained release	Diclofenac-loaded HA MNs showed effective local delivery and reduced systemic toxicity in RA animal models.
Corticosteroids (e.g., Dexamethasone, Triamcinolone)	Controlled release via PLGA/chitosan MN degradation	Dexamethasone-embedded PLGA MNs demonstrated prolonged anti-inflammatory effect in preclinical arthritis models.
Biologics (Anti-TNF agents: Etanercept, Adalimumab)	Sustained release via biodegradable polymer degradation (PLGA, HA composites)	Anti-TNF mAb-loaded MNs achieved long-term joint inflammation control in murine arthritis models.
Combination Therapy (NSAID + Biologic or Steroid)	Dual release from layered/double-compartment MNs	Smart MN patches co-delivering methotrexate and anti-TNF showed synergistic effects in RA therapy (37).

ADVANTAGES OVER CONVENTIONAL THERAPIES:

For a long time now, individuals with arthritis have relied on pills, injections, and infusions to mitigate pain and inflammation. These methods have their advantages, however, they are often accompanied by side effects, infrequent adherence, and long-term issues with patient acceptance. A more patient-friendly alternative with fewer inconveniences and side effects is Biodegradable Microneedles (BMNs).

Because they permit a greater degree of mobility when compared to traditional injections, microneedles BMNs are a game-changer for individuals who are constantly on the go. BMNs are beneficial microneedles because they do not stimulate pain receptors and, therefore, do not have the same damaging impact on freely accessible blood vessels or nerves on the outer layers of the skin as traditional injections (38).

BMNs also enhance drugs' bioavailability, and facilitate controlled drug release. Microneedles can deliver drugs that will reach therapeutic levels without being affected by the digestive tract and the first-pass liver metabolism. This increases the bioavailability of drugs delivered via microneedles. Biomaterials can also modify

bioavailability, examples being PLGA and hyaluronic acid. Certain biomaterials can potentially be used in BMNs, to control the release of drugs over hours and days, thus avoiding the peaks and valleys associated with orally or injection administered medications only (39).

BMNs also have some practical advantages. Because BMNs dissolve completely within the skin, there are no sharp waste products and a very low risk of infection or accidental re-use. Being similar to a patch, BMNs are easy to apply to skin, leading to favourable patient acceptance and the possibility of self-administration in the home. These features are important and may improve overall treatment outcomes and quality of life. This is especially important for chronic health conditions, such as arthritis and compliance may be important barriers for treatment (40).

RECENT ADVANCES & CASE

STUDIES:

What was once regarded as advanced technology is swiftly becoming a reality. BMNs loaded with anti-inflammatory agents like diclofenac and dexamethasone have, in preclinical studies, shown remarkable effectiveness in reducing joint inflammation compared to bolus doses or injections, all while remaining systemically non-toxic (41). Furthermore, biologic

treatments such as anti-TNF antibody therapies have been delivered via BMN patches in animal studies, offering prolonged control of joint inflammation and the activity of many inflammatory cytokines (42).

Technological progress continues to support the development of stimuli-responsive microneedles that “sense” inflammation and release drugs at the right time and in the designated area. For example, microneedles that respond to reactive oxygen species (ROS) release biologics at inflamed tissues, thereby reducing waste of biologics and side effects related to inflammation (43).

The development of combination microneedle therapies is among the most

fascinating innovations in this field. Researchers are creating Dual-loaded Biodegradable Microneedles (BMNs) that also release nonsteroidal anti-inflammatory drugs (NSAIDs) to provide rapid pain relief while delivering biologics or corticosteroids for prolonged disease management. Some designs also combine standard drugs with natural anti-inflammatory compounds, such as curcumin and resveratrol, thus offering a dual action against inflammation and joint destruction (44). These innovations emphasise that BMNs are not a new concept; instead, they represent a multifunctional, practical platform capable of transforming arthritis treatment.

Table 3. Case Studies of Biodegradable Microneedles in Arthritis Therapy

Drug(s)	Material / Type	Outcome
Diclofenac	HA dissolving MNs	Reduced joint inflammation, low systemic toxicity
Dexamethasone	PLGA biodegradable MNs	Prolonged anti-inflammatory effect
Anti-TNF antibody	PLGA–HA composite MNs	Long-term suppression of synovial inflammation
Methotrexate + Anti-TNF	Layered PLGA MNs	Synergistic pain & inflammation control

Curcumin + Diclofenac	Chitosan/PLGA MNs	Enhanced antioxidant & anti-inflammatory effect
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CHALLENGES AND LIMITATIONS

Although biodegradable microneedles (BMNs) have potential for arthritic treatment, significant issues must be resolved before they can be generally accepted in clinical settings. Perhaps the most pressing challenge is the loading of drugs, especially for large molecules such as monoclonal antibodies. Due to their intricate configurations and vulnerability to environmental factors, the stability of their encapsulation within microneedles (MN) is often inadequate, which limits the dose that can be delivered (45).

In addition, the dermal microneedles exhibit limited mechanical strength and lower penetrating dependability. Biodegradable and biocompatible polymers, such as hyaluronic acid and chitosan, are often too weak to ensure reliable skin penetration, which is essential for the complete and consistent delivery of medication; this also increases the risk of microneedle fracture (46).

Scaling up from laboratory prototypes to reproducible, large-scale manufacturing is another barrier. Techniques like Micromolding and 3D printing work well at

the research scale, but translating them into cost-effective industrial processes with batch-to-batch reliability requires further innovation (47).

Finally, regulatory hurdles and patient acceptance add layers of complexity. Regulatory frameworks for microneedle-based devices, especially biodegradable systems that act as both a device and a drug delivery system, are still evolving. Patient acceptance, though generally favorable due to painless application, may still be influenced by cultural perceptions of skin piercing and uncertainty about long-term safety (48).

FUTURE PERSPECTIVES

The future of BMNs in arthritis therapy lies in technological integration and personalisation. 3D printing and additive manufacturing are expected to make microneedle patches customizable, tailoring patch design, needle length, and drug loading to the individual needs of arthritis patients (49).

The convergence of nanotechnology and BMNs offers exciting opportunities. Embedding nanocarriers such as liposomes, dendrimers, or hydrogel nanoparticles into

biodegradable microneedles can protect fragile biologics, prolong release, and enable stimuli-responsive delivery triggered by pH, enzymes, or local inflammation (50).

In parallel, BMNs are being reimagined as “smart patches” that integrate biosensors, wireless connectivity, and AI-driven analytics. Such systems could monitor local biomarkers of inflammation and deliver therapy in real time, transforming arthritis management into a closed-loop, patient-centered model (51).

Finally, the clinical translation and global market potential of BMNs will depend on coordinated efforts between researchers, industry, and regulators. With increasing demand for minimally invasive and patient-friendly therapies, biodegradable microneedles could progress from experimental platforms to mainstream clinical solutions for arthritis in the near future (52).

CONCLUSION

Biodegradable microneedles represent a breakthrough in arthritis management, bridging the gap between efficacy, safety, and patient convenience. By enabling localized, sustained release of anti-inflammatory agents and biologics, they overcome many drawbacks of oral and

injectable therapies, including systemic toxicity, poor adherence, and invasive delivery routes. Their versatility in design and material selection allows fine-tuning for different drugs and therapeutic regimens. While significant progress has been made, key barriers such as drug loading limitations, mechanical strength optimization, large-scale manufacturing, and regulatory approval must be addressed before widespread adoption. The future lies in synergistic innovations—3D printing for personalization, nanotechnology for improved payload stability, and AI/IoT integration for smart, responsive therapy. If these advancements align with regulatory acceptance and patient trust, biodegradable microneedles have the potential to revolutionize arthritis care by offering a safe, effective, and patient-centered solution for long-term pain relief and disease control.

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