Available online on 15.09.2026 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Review Article

# Nanomedicine Approaches for Rheumatoid Arthritis (RA): Targeted Therapy and Controlled Drug Release

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## Article Info:

Article History:

Received 03 July 2026
Reviewed 27 July 2026
Accepted 30 Aug 2026
Published 15 Sep 2026

Cite this article as:

Swami P, Kesharwani AS, Nanomedicine Approaches for Rheumatoid Arthritis (RA): Targeted Therapy and Controlled Drug Release, Journal of Drug Delivery and Therapeutics. 2026; 16(9):299-317 *DOI:* https://doi.org/10.22270/jddt.v16i9.7990

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## Abstract

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder characterized by persistent synovial inflammation, progressive cartilage degradation, bone erosion, and joint deformity, ultimately leading to functional disability and reduced quality of life. Despite significant advances in disease management, conventional therapeutic approaches, including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional disease-modifying antirheumatic drugs (DMARDs), biologic agents, and Janus kinase (JAK) inhibitors, are frequently associated with limited tissue specificity, poor pharmacokinetic profiles, systemic adverse effects, and variable patient responses. These limitations have driven the development of nanomedicine-based drug delivery systems that offer enhanced targeting capabilities, improved drug stability, prolonged circulation time, and controlled drug release at inflamed joints. This review comprehensively summarizes recent advances in nanomedicine approaches for rheumatoid arthritis, with particular emphasis on targeted therapy and controlled drug release strategies. The review discusses the design principles and therapeutic potential of various nanocarriers, including liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles, nanostructured lipid carriers, polymeric micelles, metallic nanoparticles, mesoporous silica nanoparticles, hydrogels, and extracellular vesicle-based systems. It further explores passive and active targeting mechanisms, stimuli-responsive drug release platforms, and nanocarrier-mediated delivery of anti-inflammatory agents, biologics, nucleic acids, and emerging therapeutics. Recent preclinical and clinical developments demonstrating improved therapeutic efficacy, reduced systemic toxicity, enhanced bioavailability, and modulation of inflammatory pathways are critically evaluated. Furthermore, the review highlights current challenges related to biological barriers, long-term biosafety, large-scale manufacturing, regulatory approval, and clinical translation while discussing emerging trends such as biomimetic nanocarriers, artificial intelligence-assisted nanomedicine design, precision medicine, and multifunctional theranostic platforms. Overall, advanced nanomedicine represents a promising strategy for improving the safety, efficacy, and personalization of rheumatoid arthritis treatment and holds significant potential for transforming future clinical management of this debilitating autoimmune disease.

**Keywords:** Rheumatoid arthritis; Nanomedicine; Targeted drug delivery; Controlled drug release; Nanocarriers.

## 1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune inflammatory disease characterized by persistent synovial inflammation, cartilage degradation, bone erosion, and irreversible joint deformity. Unlike osteoarthritis, which primarily results from mechanical wear and tear, RA is an immune-mediated disorder involving complex interactions among genetic susceptibility, environmental triggers, and immune dysregulation. The disease predominantly affects small synovial joints of the hands and feet but may also involve larger joints and extra-articular organs, including the lungs, cardiovascular system, skin, and eyes. If left untreated, RA leads to chronic pain, reduced physical function, disability, and diminished quality of life, imposing a substantial socioeconomic burden on healthcare systems worldwide[1-2].

Over the past two decades, advances in disease-modifying antirheumatic drugs (DMARDs), biological agents, and Janus kinase (JAK) inhibitors have significantly improved disease management. However, conventional therapies remain limited by poor tissue specificity, frequent dosing, systemic toxicity, inadequate drug accumulation at inflamed joints, and variable therapeutic responses among patients. Consequently, there is growing interest in developing targeted drug delivery systems capable of enhancing therapeutic efficacy while minimizing adverse effects[3-4].

Nanomedicine has emerged as a promising interdisciplinary field that integrates nanotechnology with pharmaceutical sciences to improve drug delivery

and disease management. Nanocarrier-based systems can selectively accumulate within inflamed synovial tissues, protect therapeutic agents from premature degradation, prolong systemic circulation, and provide controlled or stimuli-responsive drug release. Recent advances in nanoparticle engineering have enabled the development of multifunctional nanoplatforms capable of delivering anti-inflammatory drugs, biologics, nucleic acids, and immunomodulatory agents with improved precision. These innovations offer considerable potential for overcoming the limitations of conventional RA therapies and advancing personalized treatment strategies[5].

### 1.1 Global Burden and Epidemiology of Rheumatoid Arthritis

Rheumatoid arthritis affects approximately **0.5–1% of the global population**, making it one of the most prevalent autoimmune diseases worldwide. The disease affects individuals of all ethnicities and geographical regions, although prevalence varies depending on genetic background, environmental exposure, and socioeconomic factors. Women are disproportionately affected, with a female-to-male ratio of approximately **3:1**, primarily due to hormonal and immunological differences. RA most commonly develops between **30 and 60 years of age**, although juvenile and elderly-onset forms have also been recognized[6-7].

The global burden of RA continues to increase because of population aging, improved diagnostic capabilities, and prolonged patient survival resulting from better therapeutic interventions. According to recent estimates from the Global Burden of Disease (GBD) Study, millions of individuals worldwide live with RA, contributing substantially to years lived with disability (YLDs). Persistent inflammation and progressive joint destruction significantly impair physical mobility, occupational productivity, and psychosocial well-being. Moreover, RA is associated with numerous comorbidities, including cardiovascular disease, osteoporosis, pulmonary complications, metabolic syndrome, depression, and increased susceptibility to infections, all of which contribute to increased healthcare expenditure and mortality[8]. Consequently, improving therapeutic efficacy while reducing long-term complications remains a major priority in rheumatology research.

### 1.2 Pathophysiology and Immunological Mechanisms

Rheumatoid arthritis develops through a multifactorial process involving genetic predisposition, environmental triggers, immune dysregulation, and chronic inflammation. The disease is characterized by abnormal activation of innate and adaptive immune responses, leading to persistent synovitis and progressive destruction of cartilage and bone. Multiple immune cells—including macrophages, dendritic cells, T lymphocytes, B lymphocytes, neutrophils, and fibroblast-like synoviocytes (FLS)—participate in maintaining chronic inflammation within the synovial membrane. These cells produce numerous inflammatory mediators that amplify immune responses and promote irreversible joint damage[9-10].

#### Synovial Inflammation

Synovial inflammation is the hallmark pathological feature of rheumatoid arthritis. Under normal physiological conditions, the synovial membrane consists of a thin layer of synoviocytes responsible for producing synovial fluid that lubricates and nourishes articular cartilage. During RA, infiltration of inflammatory immune cells causes synovial hyperplasia, angiogenesis, edema, and formation of pannus tissue. The proliferative pannus aggressively invades adjacent cartilage and bone, releasing proteolytic enzymes and inflammatory mediators that accelerate tissue destruction[11-12].

#### Autoimmune Responses

RA is fundamentally an autoimmune disease in which immune tolerance to self-antigens is disrupted. Activated antigen-presenting cells stimulate autoreactive $CD4^+$ T cells and B cells, resulting in the production of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs). These autoantibodies form immune complexes that activate the complement cascade and recruit inflammatory cells into synovial tissues. Persistent activation of adaptive immunity sustains chronic inflammation and contributes to disease progression.

#### Cytokine Network (TNF-α, IL-1β, IL-6)

The inflammatory microenvironment in RA is regulated by a complex cytokine network. Tumor necrosis factor-alpha (TNF-α) is considered the master inflammatory cytokine because it stimulates production of IL-1β, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), and matrix metalloproteinases (MMPs). IL-1β promotes cartilage degradation and osteoclast activation, whereas IL-6 regulates B-cell differentiation, T-cell activation, acute-phase protein synthesis, and systemic inflammatory responses. Together, these cytokines maintain chronic inflammation, promote angiogenesis, stimulate osteoclastogenesis, and accelerate joint destruction, making them major therapeutic targets in RA[13-14].

#### Oxidative Stress

Oxidative stress plays a crucial role in amplifying inflammation and tissue damage in RA. Activated neutrophils and macrophages generate excessive reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to lipid peroxidation, DNA damage, mitochondrial dysfunction, and protein oxidation. Oxidative stress also activates redox-sensitive signaling pathways, including nuclear factor-kappa B (NF-κB), thereby enhancing inflammatory cytokine production and perpetuating chronic synovial inflammation. Persistent oxidative injury contributes to cartilage degeneration and disease progression[15].

#### Joint Destruction

Progressive joint destruction results from the combined effects of chronic inflammation, enzymatic degradation

of cartilage, and increased osteoclast-mediated bone resorption. Fibroblast-like synoviocytes secrete matrix metalloproteinases that degrade extracellular matrix components, while receptor activator of nuclear factor-kappa B ligand (RANKL) stimulates osteoclast differentiation and bone erosion. Without effective intervention, irreversible structural damage leads to joint deformity, impaired mobility, chronic pain, and permanent disability[15-16].

### 1.3 Limitations of Conventional RA Therapy

Conventional pharmacological therapies have significantly improved RA management; however, several limitations continue to compromise long-term treatment outcomes. Most therapeutic agents require repeated administration and exhibit nonspecific systemic distribution, increasing the risk of adverse effects while reducing drug concentration at inflamed joints.

**NSAIDs:** Nonsteroidal anti-inflammatory drugs (NSAIDs) effectively alleviate pain and inflammation by inhibiting cyclooxygenase enzymes and prostaglandin synthesis. However, they do not alter disease progression and are associated with gastrointestinal ulceration, renal dysfunction, cardiovascular complications, and hepatotoxicity following prolonged use.

**Corticosteroids:** Glucocorticoids rapidly suppress inflammation and are commonly prescribed during disease flares. Nevertheless, chronic corticosteroid therapy may result in osteoporosis, hypertension, hyperglycemia, weight gain, cataracts, adrenal suppression, and increased susceptibility to infections, limiting their long-term clinical use.

**Conventional DMARDs:** Conventional disease-modifying antirheumatic drugs (csDMARDs), including methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide, remain first-line treatments for RA. Although effective in slowing disease progression, these agents exhibit delayed onset of action, variable patient responsiveness, hepatotoxicity, bone marrow suppression, gastrointestinal intolerance, and pulmonary toxicity.

**Biological DMARDs:** Biological DMARDs specifically inhibit inflammatory cytokines or immune cells, including TNF-α inhibitors, IL-6 receptor antagonists, CTLA-4 inhibitors, and B-cell-depleting antibodies. Despite remarkable therapeutic efficacy, biologics require parenteral administration, are expensive, may induce immunogenicity, and increase the risk of opportunistic infections and malignancies.

**JAK Inhibitors:** Janus kinase inhibitors provide effective oral treatment by blocking intracellular cytokine signaling pathways. However, concerns remain regarding thromboembolic events, cardiovascular complications, herpes zoster infection, lipid abnormalities, and long-term safety, particularly in elderly patients and individuals with pre-existing cardiovascular disease.

**Systemic Adverse Effects:** Because most conventional therapies distribute throughout the body rather than selectively targeting inflamed joints, systemic toxicity remains a major clinical concern. Frequent dosing, poor patient compliance, drug resistance, and insufficient drug accumulation within synovial tissues further limit therapeutic effectiveness. These shortcomings emphasize the need for targeted drug delivery systems capable of improving efficacy while minimizing off-target toxicity[17-19].

### 1.4 Emergence of Nanomedicine in Rheumatoid Arthritis

Nanomedicine has emerged as an innovative therapeutic strategy for overcoming many limitations associated with conventional RA treatment. Nanocarriers with dimensions typically ranging from 1 to 200 nm can encapsulate therapeutic agents, protect them from premature degradation, improve aqueous solubility, prolong circulation time, and enhance accumulation within inflamed synovial tissues through passive and active targeting mechanisms. Passive targeting exploits the enhanced permeability of inflamed synovial vasculature, whereas active targeting employs ligands such as antibodies, peptides, folic acid, hyaluronic acid, or aptamers that specifically recognize receptors overexpressed on activated macrophages, fibroblast-like synoviocytes, or endothelial cells[20].

Modern nanomedicine platforms—including liposomes, polymeric nanoparticles, dendrimers, polymeric micelles, solid lipid nanoparticles, nanostructured lipid carriers, metallic nanoparticles, mesoporous silica nanoparticles, hydrogels, and extracellular vesicles—have demonstrated significant potential for delivering anti-inflammatory drugs, biologics, nucleic acids, and antioxidant agents directly to diseased joints. Furthermore, stimuli-responsive nanocarriers capable of releasing drugs in response to pH changes, oxidative stress, enzymes, or external stimuli provide improved therapeutic precision and sustained drug release. Recent advances in multifunctional and biomimetic nanoplatforms are expected to facilitate personalized treatment strategies with enhanced efficacy, reduced systemic toxicity, and improved patient outcomes[21].

This review aims to provide a comprehensive overview of recent advances in nanomedicine-based approaches for the treatment of rheumatoid arthritis, with a particular focus on targeted drug delivery and controlled drug release systems. It discusses the pathophysiological basis of rheumatoid arthritis that supports the application of nanotherapeutics, examines the design principles and therapeutic potential of various nanocarrier platforms, and highlights passive and active targeting strategies for selective drug delivery to inflamed synovial tissues. The review further evaluates stimuli-responsive and controlled drug release systems, summarizes recent preclinical and clinical developments, and critically addresses the current challenges associated with biosafety, large-scale manufacturing, regulatory approval, and clinical translation. Finally, it explores emerging trends, including biomimetic nanocarriers, precision

nanomedicine, and multifunctional therapeutic platforms, that may improve the efficacy, safety, and long-term management of rheumatoid arthritis.

## 2. FUNDAMENTALS OF NANOMEDICINE FOR RHEUMATOID ARTHRITIS

### 2.1 Principles of Nanomedicine

Nanomedicine is an interdisciplinary field that applies nanotechnology to the diagnosis, prevention, and treatment of diseases through the use of nanoscale materials ranging from approximately 1 to 1000 nm. In rheumatoid arthritis (RA), nanomedicine aims to improve therapeutic efficacy by enhancing drug solubility, protecting drugs from premature degradation, prolonging systemic circulation, and enabling targeted delivery to inflamed joints. Compared with conventional formulations, nanocarriers facilitate higher drug accumulation at diseased tissues while minimizing systemic exposure and associated adverse effects.

The therapeutic effectiveness of nanomedicine relies on the unique physicochemical properties of nanoparticles, including their high surface-area-to-volume ratio, tunable surface chemistry, and capacity for functionalization with targeting ligands. Nanocarriers can encapsulate both hydrophilic and hydrophobic drugs, biological molecules, and nucleic acids, allowing controlled and sustained drug release. Furthermore, multifunctional nanoplatforms can integrate therapeutic and diagnostic functions, supporting precision medicine approaches for rheumatoid arthritis[22-23].

### 2.2 Classification of Nanocarriers

Nanocarriers employed in rheumatoid arthritis therapy are broadly classified into lipid-based, polymer-based, inorganic, and biologically derived systems. Common lipid-based nanocarriers include liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and polymeric micelles, which improve drug solubility and bioavailability while reducing systemic toxicity. Polymeric nanoparticles and dendrimers offer excellent drug-loading capacity and controlled release characteristics (**Table 1**).

Inorganic nanocarriers such as metallic nanoparticles and mesoporous silica nanoparticles possess unique optical, magnetic, and structural properties that enable targeted drug delivery and imaging applications. Hydrogels provide localized and sustained drug release within inflamed joints, whereas exosomes, naturally derived extracellular vesicles, have gained considerable attention due to their excellent biocompatibility, low immunogenicity, and inherent targeting capabilities. The selection of an appropriate nanocarrier depends on the physicochemical properties of the therapeutic agent, disease severity, and desired release profile[24].

### 2.3 Physicochemical Properties Influencing Drug Delivery

The therapeutic performance of nanocarriers is strongly influenced by their physicochemical characteristics, which determine circulation time, cellular uptake, biodistribution, and drug release behavior.

#### Size

Nanoparticle size is a critical determinant of therapeutic efficacy. Particles ranging between **50 and 200 nm** exhibit prolonged circulation and enhanced accumulation within inflamed synovial tissues due to increased vascular permeability. Extremely small nanoparticles may undergo rapid renal clearance, whereas larger particles are more susceptible to uptake by the reticuloendothelial system.

#### Shape

Nanoparticle shape significantly influences blood circulation, cellular internalization, and tissue penetration. While spherical nanoparticles are most commonly used because of their ease of synthesis and stability, rod-shaped, disc-shaped, and elongated nanoparticles may exhibit prolonged circulation and improved interactions with inflamed endothelial cells, thereby enhancing targeted drug delivery.

#### Surface Charge

Surface charge governs nanoparticle stability and interactions with biological membranes. Positively charged nanoparticles generally exhibit enhanced cellular uptake because of electrostatic interactions with negatively charged cell membranes. However, excessive positive charge may increase cytotoxicity and nonspecific protein adsorption. Neutral or slightly negative nanoparticles often demonstrate improved circulation and reduced immune recognition.

#### Hydrophobicity

The hydrophobic or hydrophilic nature of nanocarriers influences drug loading and biological interactions. Hydrophobic nanoparticles are particularly suitable for encapsulating poorly water-soluble drugs, whereas hydrophilic surface modifications, such as polyethylene glycol (PEG) coating, reduce protein adsorption, improve circulation time, and enhance biocompatibility.

#### Drug Encapsulation

Efficient drug encapsulation ensures adequate therapeutic payloads while protecting drugs from enzymatic degradation and premature release. High encapsulation efficiency enables sustained drug delivery, reduces dosing frequency, and improves treatment efficacy by maintaining therapeutic drug concentrations at inflamed joints.

#### Stability

Nanocarrier stability is essential for maintaining structural integrity during storage and systemic circulation. Stable nanoparticles resist aggregation, premature drug leakage, and physicochemical degradation, ensuring consistent therapeutic performance. Surface modifications and optimized formulation techniques further improve colloidal stability and extend shelf life.

### 2.4 Passive and Active Targeting in Inflamed Synovium

Targeted drug delivery is one of the major advantages of nanomedicine in rheumatoid arthritis. Passive targeting utilizes the enhanced vascular permeability of inflamed synovial tissues, allowing nanoparticles to preferentially accumulate within arthritic joints. This phenomenon, known as the ELVIS (Extravasation through Leaky Vasculature and Inflammatory Cell-mediated Sequestration) effect, improves local drug concentration while reducing systemic exposure (**Fig. 1**).

Active targeting further enhances delivery specificity by modifying nanoparticle surfaces with ligands such as antibodies, peptides, folic acid, hyaluronic acid, aptamers, or transferrin. These ligands recognize receptors overexpressed on activated macrophages, fibroblast-like synoviocytes, endothelial cells, and other inflammatory cells, facilitating receptor-mediated endocytosis and improved intracellular drug delivery. Active targeting enhances therapeutic efficacy while minimizing off-target toxicity and improving patient outcomes.

### 2.5 Stimuli-Responsive Drug Release Mechanisms

Stimuli-responsive nanocarriers are engineered to release therapeutic agents selectively in response to the pathological conditions present within inflamed joints. These intelligent delivery systems improve treatment precision while minimizing systemic drug exposure.

#### pH-Responsive Drug Release

Inflamed synovial tissues exhibit a mildly acidic microenvironment compared with healthy tissues. pH-responsive nanocarriers exploit this difference by remaining stable during circulation and releasing encapsulated drugs only under acidic conditions. This selective release enhances local drug concentration while reducing adverse systemic effects.

#### ROS-Responsive Drug Release

Reactive oxygen species (ROS) are significantly elevated in rheumatoid arthritis due to chronic inflammation. ROS-responsive nanoparticles contain oxidation-sensitive chemical linkers that degrade in the presence of excessive ROS, enabling localized drug release specifically within inflamed joints. This strategy effectively suppresses oxidative stress and inflammatory signaling.

#### Enzyme-Responsive Drug Release

Inflamed joints contain increased levels of enzymes such as matrix metalloproteinases (MMPs), phospholipases, and hyaluronidases. Enzyme-responsive nanocarriers are designed with biodegradable linkers that are selectively cleaved by these enzymes, resulting in controlled drug release at disease sites while minimizing drug leakage in healthy tissues.

#### Temperature-Responsive Drug Release

Inflammatory processes often produce localized increases in tissue temperature. Temperature-responsive nanocarriers undergo structural changes when exposed to elevated temperatures, triggering controlled drug release within inflamed joints. External heating methods such as ultrasound or near-infrared irradiation can further enhance site-specific drug delivery and therapeutic efficacy[25-30].

**Table 1.** Classification of nanocarriers employed in rheumatoid arthritis therapy, highlighting representative examples, major advantages, and therapeutic applications.[31-33]

| Nanocarrier Class | Representative Examples | Major Advantages | Therapeutic Applications in Rheumatoid Arthritis |
|---|---|---|---|
| Liposomes | PEGylated liposomes, Methotrexate (MTX)-loaded liposomes, Prednisolone liposomes | High biocompatibility, improved drug solubility, prolonged circulation, reduced systemic toxicity | Targeted delivery of DMARDs and corticosteroids, suppression of synovial inflammation |
| Polymeric Nanoparticles | PLGA nanoparticles, Chitosan nanoparticles, PEG-PLA nanoparticles | Controlled and sustained drug release, high drug-loading capacity, biodegradable | Delivery of methotrexate, dexamethasone, siRNA, and anti-inflammatory agents |
| Solid Lipid Nanoparticles (SLNs) | Curcumin-loaded SLNs, Diclofenac SLNs, MTX-SLNs | Enhanced drug stability, improved bioavailability, protection of labile drugs | Sustained anti-inflammatory drug delivery and reduction of joint inflammation |
| Nanostructured Lipid Carriers (NLCs) | Celecoxib NLCs, Piroxicam NLCs, Curcumin NLCs | Higher drug loading than SLNs, controlled release, excellent stability | Long-term management of chronic inflammation and improved drug bioavailability |
| Polymeric Micelles | PEG-PCL micelles, PEG-PLA micelles, Dexamethasone micelles | Solubilization of hydrophobic drugs, prolonged circulation, passive targeting | Delivery of poorly soluble anti-inflammatory drugs and corticosteroids |

| | | | |
|---|---|---|---|
| Dendrimers | PAMAM dendrimers, PPI dendrimers | Highly branched architecture, multivalent surface functionalization, high drug encapsulation | Targeted delivery of anti-inflammatory drugs, genes, and biological therapeutics |
| Metallic Nanoparticles | Gold nanoparticles (AuNPs), Silver nanoparticles (AgNPs), Iron oxide nanoparticles (IONPs) | Intrinsic anti-inflammatory activity, imaging capability, surface modification flexibility | Drug delivery, oxidative stress reduction, imaging-guided therapy, macrophage targeting |
| Mesoporous Silica Nanoparticles (MSNs) | SBA-15, MCM-41, Drug-loaded MSNs | Large pore volume, high drug-loading efficiency, tunable release kinetics | Controlled drug release, delivery of DMARDs, proteins, and nucleic acids |
| Hydrogels | Chitosan hydrogel, Hyaluronic acid hydrogel, Thermosensitive hydrogels | Injectable, localized sustained release, excellent biocompatibility | Intra-articular drug delivery, prolonged retention within synovial joints |
| Exosomes | Mesenchymal stem cell-derived exosomes, Macrophage-derived exosomes | Natural carrier system, low immunogenicity, high biocompatibility, intrinsic targeting ability | Delivery of miRNA, siRNA, proteins, immunomodulators, and regenerative therapy |

**Abbreviations:** PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic acid); PLA, polylactic acid; PCL, polycaprolactone; PAMAM, poly(amidoamine); PPI, polypropyleneimine; MTX, methotrexate; DMARDs, disease-modifying antirheumatic drugs; siRNA, small interfering RNA; AuNPs, gold nanoparticles; AgNPs, silver nanoparticles; IONPs, iron oxide nanoparticles; MSNs, mesoporous silica nanoparticles.

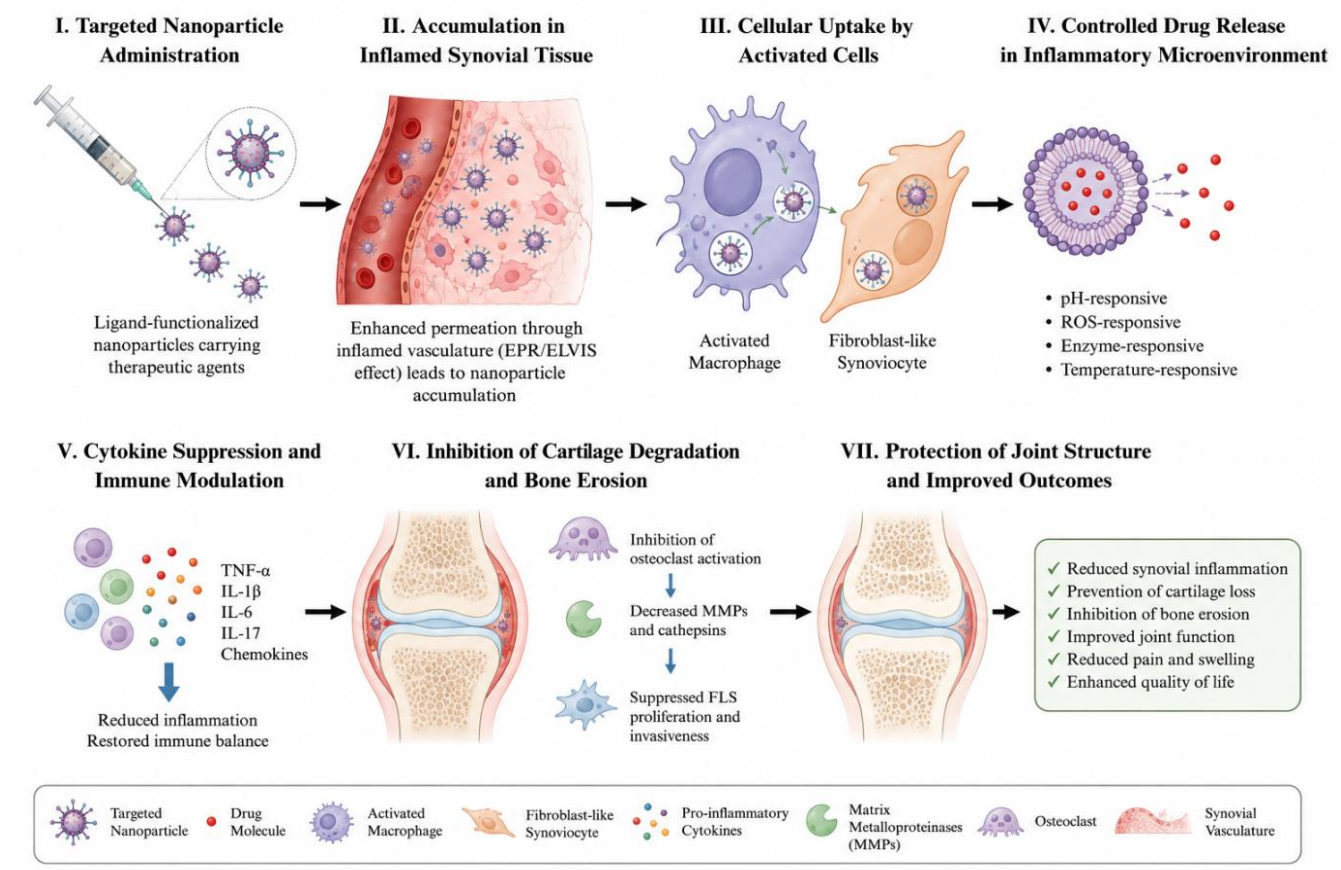


**Figure 1.** Schematic representation of targeted nanomedicine delivery in rheumatoid arthritis showing nanoparticle accumulation within inflamed synovial tissue, cellular uptake by activated macrophages and synoviocytes, controlled drug release, cytokine suppression, and inhibition of cartilage and bone destruction.

## 3. TARGETED NANOMEDICINE STRATEGIES FOR RHEUMATOID ARTHRITIS

Targeted nanomedicine has emerged as a promising strategy for improving the therapeutic efficacy of rheumatoid arthritis (RA) treatment by delivering drugs selectively to inflamed synovial tissues while minimizing systemic exposure and adverse effects. Unlike conventional drug delivery systems, nanocarriers can exploit the pathological characteristics of arthritic joints, including enhanced vascular permeability, overexpression of inflammatory receptors, and the presence of activated immune cells. Surface-functionalized nanoparticles further enhance targeting specificity by recognizing molecular biomarkers expressed on macrophages, fibroblast-like synoviocytes (FLS), endothelial cells, and other inflammatory cells. These targeted approaches increase local drug accumulation, improve cellular uptake, prolong drug retention, and reduce dosing frequency, thereby offering significant advantages over traditional RA therapies[34-35].

### 3.1 Passive Targeting through Inflamed Synovial Vasculature

Passive targeting is one of the most widely utilized approaches in nanomedicine for rheumatoid arthritis. Inflamed synovial tissues exhibit increased vascular permeability due to chronic inflammation and angiogenesis, allowing nanoparticles to preferentially extravasate into diseased joints through the **Extravasation through Leaky Vasculature and Inflammatory Cell-mediated Sequestration (ELVIS)** effect. This phenomenon enables nanocarriers of appropriate size to accumulate selectively within inflamed synovial tissues without requiring specific targeting ligands. Following extravasation, nanoparticles are retained within the inflammatory microenvironment because of impaired lymphatic drainage and increased infiltration of immune cells. Passive targeting significantly enhances local drug concentration while reducing systemic toxicity associated with conventional therapies. Liposomes, polymeric nanoparticles, and lipid-based nanocarriers have demonstrated effective passive targeting of inflamed joints, resulting in sustained drug release, reduced inflammation, and improved therapeutic outcomes in experimental models of rheumatoid arthritis[36-37].

### 3.2 Active Targeting

Active targeting further enhances the specificity of nanomedicine by modifying nanoparticle surfaces with ligands that recognize receptors overexpressed on inflammatory and synovial cells. Ligand-receptor interactions facilitate receptor-mediated endocytosis, increasing intracellular drug delivery while minimizing off-target effects.

#### Folate Receptor

Activated macrophages within rheumatoid synovium overexpress the folate receptor-β (FR-β), making it an attractive target for selective drug delivery. Nanocarriers conjugated with folic acid specifically bind to FR-β-expressing macrophages, promoting efficient cellular internalization and localized drug release. Folate-targeted nanoparticles have demonstrated enhanced delivery of methotrexate, dexamethasone, and other anti-inflammatory agents, leading to reduced cytokine production and attenuation of synovial inflammation.

#### CD44

CD44 is a transmembrane glycoprotein highly expressed on activated fibroblast-like synoviocytes, macrophages, and endothelial cells in rheumatoid arthritis. Hyaluronic acid (HA), the natural ligand of CD44, is frequently used to functionalize nanoparticles for selective targeting. HA-coated nanocarriers exhibit enhanced accumulation within inflamed joints, improved cellular uptake, and prolonged retention, making them highly effective for delivering anti-inflammatory drugs and nucleic acid therapeutics.

#### Integrins

Integrins play essential roles in leukocyte adhesion, migration, angiogenesis, and inflammatory signaling during rheumatoid arthritis progression. Nanocarriers functionalized with peptides such as arginine-glycine-aspartic acid (RGD) selectively bind integrins overexpressed on activated endothelial cells and inflammatory leukocytes. This targeting strategy improves nanoparticle localization within inflamed synovial tissues and enhances therapeutic efficacy.

#### ICAM-1

Intercellular adhesion molecule-1 (ICAM-1) is significantly upregulated on synovial endothelial cells and inflammatory cells during active rheumatoid arthritis. ICAM-1-targeted nanoparticles improve selective drug delivery by facilitating receptor-mediated internalization into inflamed endothelial cells. Targeting ICAM-1 reduces leukocyte recruitment, suppresses inflammatory responses, and improves the anti-inflammatory effects of encapsulated therapeutics.

#### VCAM-1

Vascular cell adhesion molecule-1 (VCAM-1) is another important adhesion molecule overexpressed in inflamed synovial vasculature. VCAM-1-targeted nanocarriers selectively accumulate in inflamed joints and inhibit leukocyte adhesion and transmigration. This strategy enhances localized drug delivery while reducing systemic toxicity and chronic synovial inflammation[38-39].

### 3.3 Macrophage-Targeted Nanotherapy

Macrophages are among the principal effector cells responsible for initiating and sustaining chronic inflammation in rheumatoid arthritis. Activated M1 macrophages secrete high levels of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and reactive oxygen species (ROS), contributing to synovial hyperplasia, cartilage degradation, and bone erosion. Consequently, macrophages represent one of the most attractive cellular targets for nanomedicine-based interventions.

Nanocarriers decorated with folic acid, mannose, dextran, or specific antibodies selectively target macrophage surface receptors, facilitating efficient intracellular drug delivery. These nanoparticles have been employed to deliver corticosteroids, methotrexate, small interfering RNA (siRNA), antioxidants, and immunomodulatory agents directly to activated macrophages. Macrophage-targeted nanotherapy suppresses inflammatory cytokine production, promotes polarization from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype, and effectively reduces joint inflammation and tissue destruction[40].

### 3.4 Fibroblast-Like Synoviocyte Targeting

Fibroblast-like synoviocytes (FLS) are specialized stromal cells that become highly activated in rheumatoid arthritis and play a central role in disease progression. Activated FLS exhibit aggressive proliferation, invade adjacent cartilage and bone, produce matrix metalloproteinases (MMPs), and secrete inflammatory cytokines and chemokines that sustain chronic synovitis. Their resistance to apoptosis further contributes to persistent inflammation.

Nanomedicine strategies targeting FLS involve surface modification of nanoparticles with ligands recognizing CD44, cadherin-11, fibroblast activation protein (FAP), or other disease-specific biomarkers. These targeted nanocarriers efficiently deliver disease-modifying drugs, gene-silencing molecules, and anti-inflammatory therapeutics directly to pathogenic synoviocytes. Suppression of FLS proliferation and inflammatory mediator production significantly reduces pannus formation, cartilage destruction, and disease progression.

### 3.5 Immune Cell Modulation and Cytokine Targeting

Immune dysregulation is the hallmark of rheumatoid arthritis, involving excessive activation of T lymphocytes, B lymphocytes, dendritic cells, macrophages, and neutrophils. These immune cells generate an extensive cytokine network that maintains chronic inflammation and progressive joint destruction. Targeting immune cells and inflammatory cytokines has therefore become a major focus of nanomedicine research. Advanced nanocarriers have been developed to selectively deliver cytokine inhibitors, monoclonal antibodies, nucleic acids, and immunomodulatory agents that suppress key inflammatory mediators such as TNF-α, IL-1β, IL-6, IL-17, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Nanoparticle-mediated delivery of siRNA and microRNA further enables selective silencing of genes involved in inflammatory signaling pathways, including NF-κB, JAK/STAT, and MAPK pathways. These targeted immunotherapeutic approaches restore immune homeostasis, reduce synovial inflammation, inhibit osteoclast activation, and preserve joint integrity while minimizing systemic immunosuppression[41-42].

Targeted nanomedicine represents a transformative approach for rheumatoid arthritis management by enabling selective drug delivery to inflamed synovial tissues and pathogenic immune cells. Passive targeting exploits the pathological characteristics of inflamed joints, whereas active targeting enhances specificity through receptor-mediated interactions with macrophages, fibroblast-like synoviocytes, endothelial cells, and adhesion molecules. These strategies significantly improve therapeutic efficacy, reduce systemic toxicity, and support controlled drug release. Continued advances in ligand engineering, biomimetic nanocarriers, and multifunctional delivery systems are expected to further optimize targeted therapies and facilitate the clinical translation of nanomedicine for rheumatoid arthritis[43].

## 4. CONTROLLED DRUG RELEASE SYSTEMS IN RHEUMATOID ARTHRITIS

Controlled drug release systems have emerged as a cornerstone of nanomedicine for the management of rheumatoid arthritis (RA), offering significant advantages over conventional drug delivery approaches. Traditional anti-rheumatic therapies often require repeated administration and produce fluctuating drug concentrations, leading to reduced therapeutic efficacy and increased systemic toxicity. In contrast, nanocarrier-based controlled release systems are designed to deliver therapeutic agents at a predetermined rate or in response to disease-specific stimuli, ensuring sustained drug concentrations within inflamed joints. These intelligent delivery platforms improve drug bioavailability, prolong therapeutic effects, reduce dosing frequency, and minimize off-target adverse effects (**Table 2**). Recent advances in stimuli-responsive nanotechnology have further enabled selective drug release in response to pathological conditions such as acidic pH, oxidative stress, enzymatic activity, and temperature changes, thereby enhancing treatment precision and patient outcomes[44-45].

### 4.1 Controlled Release Principles

Controlled drug release refers to the regulated and sustained delivery of therapeutic agents over an extended period while maintaining drug concentrations within the therapeutic window. In rheumatoid arthritis, controlled release systems are designed to protect drugs from premature degradation during systemic circulation and release them selectively at inflamed synovial tissues. This approach improves pharmacokinetic behavior, increases drug retention at disease sites, and reduces the frequency of drug administration.

Nanocarriers such as liposomes, polymeric nanoparticles, hydrogels, dendrimers, and lipid nanoparticles encapsulate therapeutic agents and gradually release them through diffusion, polymer degradation, swelling, or environmental stimuli. Controlled release minimizes fluctuations in plasma drug concentrations, enhances patient compliance, and reduces systemic toxicity associated with repeated high-dose administration. Consequently, these systems provide prolonged anti-inflammatory activity and

improved disease management in chronic rheumatoid arthritis[46-47].

### 4.2 pH-Responsive Nanocarriers

The inflammatory microenvironment of rheumatoid arthritis is characterized by a mildly acidic pH resulting from increased glycolysis, hypoxia, and immune cell metabolism within inflamed synovial tissues. pH-responsive nanocarriers exploit this pathological feature by remaining stable under physiological conditions (pH ~7.4) while undergoing structural changes and releasing therapeutic agents selectively in acidic environments (pH 6.5–6.8). These nanocarriers are commonly fabricated using acid-sensitive polymers, hydrazone bonds, Schiff-base linkages, or pH-sensitive lipids that degrade or swell in response to reduced pH. This selective release enhances local drug accumulation while minimizing premature leakage during systemic circulation. pH-responsive systems have been successfully employed for the delivery of methotrexate, dexamethasone, curcumin, and biologic agents, demonstrating improved anti-inflammatory efficacy and reduced systemic adverse effects in experimental models of rheumatoid arthritis[48-49].

### 4.3 ROS-Responsive Drug Delivery

Reactive oxygen species (ROS), including superoxide radicals, hydrogen peroxide, and hydroxyl radicals, are excessively produced within inflamed joints during rheumatoid arthritis. Elevated ROS levels contribute to oxidative stress, activation of inflammatory signaling pathways, cartilage degradation, and bone erosion. ROS-responsive nanocarriers utilize oxidation-sensitive chemical linkers that remain stable under normal physiological conditions but degrade rapidly in the presence of elevated ROS concentrations. Upon exposure to oxidative stress, these nanocarriers release encapsulated anti-inflammatory drugs, antioxidants, or nucleic acid therapeutics directly within inflamed tissues. This targeted release suppresses oxidative damage, inhibits inflammatory cytokine production, and restores redox homeostasis. ROS-responsive nanoparticles have shown considerable promise in delivering methotrexate, curcumin, and antioxidant compounds, resulting in improved therapeutic efficacy while minimizing systemic toxicity[50-51].

### 4.4 Enzyme-Responsive Nanoplatforms

Inflamed synovial tissues exhibit significantly increased expression of enzymes such as matrix metalloproteinases (MMPs), phospholipases, hyaluronidases, and cathepsins. These enzymes contribute to extracellular matrix degradation, cartilage destruction, and disease progression. Enzyme-responsive nanoplatforms are specifically engineered with biodegradable peptide sequences or enzyme-cleavable chemical linkers that respond selectively to these disease-associated enzymes. Following accumulation within inflamed joints, the overexpressed enzymes cleave the responsive linkers, triggering localized drug release. This mechanism enables precise delivery of anti-inflammatory drugs, biologics, and gene therapeutics while minimizing drug exposure in healthy tissues. Enzyme-responsive nanocarriers therefore provide improved targeting efficiency, prolonged therapeutic action, and reduced systemic adverse effects compared with conventional formulations[52-53].

### 4.5 Thermo-Responsive and External Stimuli Systems

Thermo-responsive nanocarriers are designed to release therapeutic agents in response to changes in temperature associated with inflamed tissues or externally applied thermal stimuli. During active rheumatoid arthritis, local joint temperature may increase due to enhanced metabolic activity and inflammation. Temperature-sensitive polymers undergo reversible structural transitions when exposed to elevated temperatures, resulting in controlled drug release at inflamed sites. In addition to endogenous temperature changes, external stimuli such as ultrasound, near-infrared (NIR) light, magnetic fields, and electrical stimulation have been investigated to precisely control drug release. These externally triggered systems allow clinicians to regulate the timing and location of therapeutic delivery, improving treatment precision and minimizing systemic toxicity. Such smart nanoplatforms have demonstrated significant potential for personalized and on-demand drug delivery in rheumatoid arthritis management[54-55].

### 4.6 Sustained Drug Release for Chronic RA Management

Rheumatoid arthritis is a lifelong chronic disease requiring continuous suppression of inflammation to prevent irreversible joint damage. Sustained drug release systems are therefore particularly valuable because they maintain therapeutic drug concentrations over prolonged periods while reducing the need for frequent dosing. Nanocarriers such as polymeric nanoparticles, hydrogels, liposomes, and lipid-based carriers gradually release encapsulated drugs through controlled diffusion and biodegradation, ensuring long-lasting therapeutic effects. Sustained release formulations improve patient adherence, reduce fluctuations in drug concentration, minimize systemic side effects, and decrease cumulative drug exposure. Furthermore, prolonged local drug retention within inflamed joints enables continuous suppression of inflammatory mediators, reducing disease progression and improving joint function. Recent advances in multifunctional sustained-release nanoplatforms capable of combining targeted delivery with stimuli-responsive drug release represent a promising strategy for the long-term management of rheumatoid arthritis.

Controlled drug release systems have significantly enhanced the therapeutic potential of nanomedicine for rheumatoid arthritis by providing sustained, site-specific, and stimuli-responsive delivery of anti-rheumatic agents. Strategies based on pH, reactive oxygen species, enzymatic activity, temperature, and externally applied stimuli enable precise drug release within inflamed synovial tissues while minimizing systemic toxicity. Together with sustained-release formulations, these advanced nanoplatforms improve

therapeutic efficacy, prolong drug action, enhance patient compliance, and support personalized treatment approaches. Continued research focusing on multifunctional and clinically translatable controlled release systems is expected to further advance the management of rheumatoid arthritis and improve long-term clinical outcomes[56-67].

**Table 2.** Representative nanomedicine-based therapeutic formulations for rheumatoid arthritis, summarizing encapsulated drugs, nanocarrier platforms, therapeutic targets, clinical benefits, and stages of development.[58-59]

| Encapsulated Drug/Therapeutic Agent | Nanocarrier Platform | Therapeutic Target | Clinical/Therapeutic Benefits | Stage of Development |
|---|---|---|---|---|
| Methotrexate (MTX) | Liposomes | Inflamed synovium, activated macrophages | Improved joint accumulation, reduced systemic toxicity, prolonged circulation | Preclinical/Clinical |
| Methotrexate (MTX) | PLGA Polymeric Nanoparticles | Synovial macrophages and fibroblast-like synoviocytes (FLS) | Sustained drug release, enhanced anti-inflammatory activity, reduced dosing frequency | Preclinical |
| Dexamethasone | Polymeric Micelles | Inflamed synovial tissue | Improved solubility, prolonged circulation, enhanced anti-inflammatory efficacy | Preclinical |
| Prednisolone | PEGylated Liposomes | Activated macrophages | Targeted glucocorticoid delivery, reduced adverse effects, prolonged therapeutic action | Clinical |
| Celecoxib | Nanostructured Lipid Carriers (NLCs) | Inflamed joints | Enhanced oral bioavailability, sustained release, improved pain and inflammation control | Preclinical |
| Curcumin | Solid Lipid Nanoparticles (SLNs) | Oxidative stress and inflammatory cytokines | Antioxidant activity, ROS suppression, improved bioavailability | Preclinical |
| Diclofenac | Solid Lipid Nanoparticles | Synovial inflammation | Controlled release, prolonged analgesic effect, reduced gastrointestinal toxicity | Preclinical |
| TNF-α siRNA | Lipid Nanoparticles | TNF-α-producing macrophages | Gene silencing, inhibition of inflammatory cytokine production | Preclinical |
| IL-1β siRNA | Polymeric Nanoparticles | Activated immune cells | Reduced inflammatory signaling and cartilage destruction | Preclinical |
| Anti-TNF-α Antibody | Polymeric Nanoparticles | TNF-α pathway | Enhanced stability, prolonged circulation, reduced inflammation | Preclinical |
| Tocilizumab (Anti-IL-6 Receptor) | Liposomes | IL-6 receptor | Improved targeting and reduced systemic immunosuppression | Experimental/Preclinical |
| Tacrolimus | Polymeric Nanoparticles | Activated T lymphocytes | Immunosuppression with reduced systemic exposure | Preclinical |
| Hydroxychloroquine | Liposomes | Synovial macrophages | Improved intracellular drug delivery and reduced inflammatory activity | Preclinical |
| Small Interfering RNA (siRNA) | Dendrimers | NF-κB and inflammatory signaling pathways | Selective gene silencing and immune modulation | Preclinical |

| | | | | |
|---|---|---|---|---|
| MicroRNA (miRNA) | Exosomes | Immune cells and fibroblast-like synoviocytes | Regulation of inflammatory gene expression and tissue repair | Experimental |
| Resveratrol | Polymeric Nanoparticles | Oxidative stress and macrophages | Anti-inflammatory and antioxidant effects with sustained release | Preclinical |
| Curcumin + Methotrexate | Polymeric Nanoparticles | Multiple inflammatory pathways | Synergistic anti-inflammatory activity and reduced drug toxicity | Preclinical |
| Mesenchymal Stem Cell-Derived Exosomes | Exosome-Based Delivery | Immune cells and damaged cartilage | Immunomodulation, cartilage regeneration, reduced synovial inflammation | Preclinical |
| Gold Nanoparticles (Drug-Conjugated) | Metallic Nanoparticles | Activated macrophages and ROS | Anti-inflammatory activity, imaging capability, targeted delivery | Preclinical |

**Abbreviations:** MTX, methotrexate; PLGA, poly(lactic-co-glycolic acid); PEG, polyethylene glycol; SLNs, solid lipid nanoparticles; NLCs, nanostructured lipid carriers; siRNA, small interfering RNA; miRNA, microRNA; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; IL-6, interleukin-6; ROS, reactive oxygen species; NF-κB, nuclear factor-kappa B.

## 5. RECENT ADVANCES AND CLINICAL TRANSLATION

The rapid advancement of nanotechnology has significantly accelerated the development of innovative therapeutic platforms for rheumatoid arthritis (RA). Recent progress in nanomedicine has focused on improving drug targeting, enhancing bioavailability, prolonging circulation time, and minimizing systemic toxicity through the rational design of multifunctional nanocarriers. Modern nanoplatforms not only deliver conventional anti-rheumatic drugs but also facilitate the delivery of biologics, nucleic acids, peptides, antioxidants, and regenerative therapeutics. In addition, biomimetic nanoparticles, extracellular vesicles, and theranostic systems have emerged as next-generation technologies capable of combining targeted therapy with real-time disease monitoring. Although many nanomedicine platforms remain in the preclinical stage, several formulations have progressed to clinical evaluation, demonstrating encouraging safety profiles and therapeutic efficacy[60]. This section summarizes the recent advances in nanomedicine for rheumatoid arthritis and discusses their translational potential toward clinical application.

### 5.1 Lipid-Based Nanomedicines

Lipid-based nanomedicines represent one of the most extensively studied drug delivery platforms for rheumatoid arthritis because of their excellent biocompatibility, biodegradability, and capacity to encapsulate both hydrophilic and hydrophobic therapeutic agents. Common lipid-based systems include liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid nanoparticles (LNPs). These nanocarriers improve drug solubility, prolong circulation time, protect encapsulated drugs from degradation, and facilitate preferential accumulation within inflamed synovial tissues. Recent investigations have demonstrated that lipid-based nanoparticles effectively deliver methotrexate, dexamethasone, prednisolone, curcumin, celecoxib, and biological therapeutics with enhanced anti-inflammatory efficacy and reduced systemic toxicity. Surface modification with polyethylene glycol (PEG), folic acid, or hyaluronic acid further improves targeting specificity toward activated macrophages and fibroblast-like synoviocytes[61-62]. The success of lipid nanoparticles in nucleic acid delivery has also expanded their application for transporting siRNA, microRNA, and mRNA, highlighting their potential as next-generation therapeutic platforms for rheumatoid arthritis.

### 5.2 Polymeric Nanoparticles

Polymeric nanoparticles have attracted considerable attention because of their excellent structural versatility, biodegradability, and controlled drug release capabilities. Biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), polyethylene glycol (PEG), polycaprolactone (PCL), and chitosan are widely employed to fabricate nanoparticles capable of sustained therapeutic delivery[63].

Recent advances include multifunctional polymeric nanoparticles designed to co-deliver anti-inflammatory drugs, antioxidants, nucleic acids, and immunomodulatory agents. Surface-functionalized polymeric nanoparticles improve receptor-mediated targeting of activated immune cells while reducing premature drug release. Stimuli-responsive polymeric nanocarriers capable of responding to acidic pH, reactive oxygen species, and inflammatory enzymes have demonstrated superior therapeutic outcomes in experimental rheumatoid arthritis models[64-65]. These advances position polymeric nanoparticles among the

most promising candidates for long-term disease management.

### 5.3 Biomimetic Nanocarriers

Biomimetic nanocarriers have emerged as an innovative strategy that combines synthetic nanotechnology with naturally occurring biological membranes to improve targeting efficiency and immune compatibility. These nanocarriers are typically coated with cell membranes derived from macrophages, neutrophils, erythrocytes, platelets, or stem cells, enabling them to evade immune recognition while selectively accumulating at inflammatory sites.

Macrophage membrane-coated nanoparticles have demonstrated enhanced targeting of inflamed synovial tissues due to their intrinsic affinity for inflammatory chemokines and cytokines. Similarly, neutrophil membrane-coated nanoparticles effectively migrate toward inflamed joints and deliver anti-inflammatory therapeutics with improved precision. Biomimetic systems also reduce rapid clearance by the mononuclear phagocyte system, prolong circulation time, and enhance therapeutic efficacy. Owing to their excellent biocompatibility and low immunogenicity, biomimetic nanocarriers are considered one of the most promising next-generation drug delivery platforms for rheumatoid arthritis[66-67].

### 5.4 Exosome-Based Drug Delivery

Exosomes are naturally occurring extracellular vesicles secreted by various cell types that mediate intercellular communication through the transfer of proteins, lipids, messenger RNA, microRNA, and other bioactive molecules. Their nanoscale size, intrinsic biocompatibility, low immunogenicity, and natural targeting capabilities make them attractive drug delivery vehicles for rheumatoid arthritis therapy. Recent studies have demonstrated that mesenchymal stem cell-derived exosomes possess intrinsic anti-inflammatory and immunomodulatory properties capable of suppressing synovial inflammation, regulating macrophage polarization, and promoting cartilage repair. Furthermore, engineered exosomes have been successfully employed to deliver anti-inflammatory drugs, siRNA, microRNA, and therapeutic proteins directly to inflamed joints. Although challenges related to large-scale production, purification, and storage remain, exosome-based therapeutics represent a promising frontier in regenerative and precision medicine for rheumatoid arthritis[68].

### 5.5 Nanotheranostics

Nanotheranostics integrate diagnostic imaging and therapeutic delivery into a single multifunctional nanoparticle platform, enabling simultaneous disease detection, targeted treatment, and therapeutic monitoring (**Fig. 2**). These systems incorporate imaging agents such as magnetic nanoparticles, gold nanoparticles, quantum dots, or fluorescent probes together with therapeutic payloads, facilitating real-time visualization of nanoparticle biodistribution and treatment response.

In rheumatoid arthritis, nanotheranostic platforms improve early diagnosis of synovial inflammation, monitor disease progression, and evaluate therapeutic efficacy using imaging modalities including magnetic resonance imaging (MRI), computed tomography (CT), fluorescence imaging, and photoacoustic imaging. Simultaneously, these nanoparticles release anti-inflammatory drugs at inflamed sites, reducing disease activity while allowing clinicians to assess treatment outcomes non-invasively. Nanotheranostics therefore represent an important step toward precision medicine and individualized rheumatoid arthritis management[69].

### 5.6 Clinical Trials and Approved Nanomedicines

Although numerous nanomedicine platforms have demonstrated encouraging preclinical results, relatively few have progressed to clinical evaluation for rheumatoid arthritis. Liposomal corticosteroid formulations and hyaluronic acid-based intra-articular delivery systems have shown improved therapeutic efficacy, prolonged drug retention, and reduced systemic toxicity in clinical studies. Lipid-based nanoparticles have also gained considerable attention due to their successful application in nucleic acid delivery technologies, providing a strong foundation for future RNA-based therapies in autoimmune diseases.

Several ongoing clinical investigations are evaluating nanoparticle-mediated delivery of methotrexate, glucocorticoids, biologics, and gene therapeutics to improve treatment specificity and reduce adverse effects. However, widespread clinical translation remains limited by manufacturing complexity, regulatory challenges, large-scale production, long-term biosafety evaluation, and cost-effectiveness. Continued optimization of nanocarrier design, standardized quality-control procedures, and well-designed clinical trials will be essential to facilitate regulatory approval and routine clinical implementation of nanomedicine-based therapies for rheumatoid arthritis.

Recent advances in nanomedicine have substantially expanded therapeutic opportunities for rheumatoid arthritis through the development of lipid-based nanomedicines, polymeric nanoparticles, biomimetic nanocarriers, exosome-based delivery systems, and multifunctional nanotheranostic platforms. These technologies have demonstrated improved targeting efficiency, controlled drug release, enhanced therapeutic efficacy, and reduced systemic toxicity compared with conventional therapies. Despite significant progress, challenges related to clinical translation, large-scale manufacturing, regulatory approval, and long-term safety remain. Future integration of advanced nanotechnology with precision medicine, biomarker-guided therapy, and regenerative approaches is expected to accelerate the successful clinical application of nanomedicine and improve long-term outcomes for patients with rheumatoid arthritis[70].

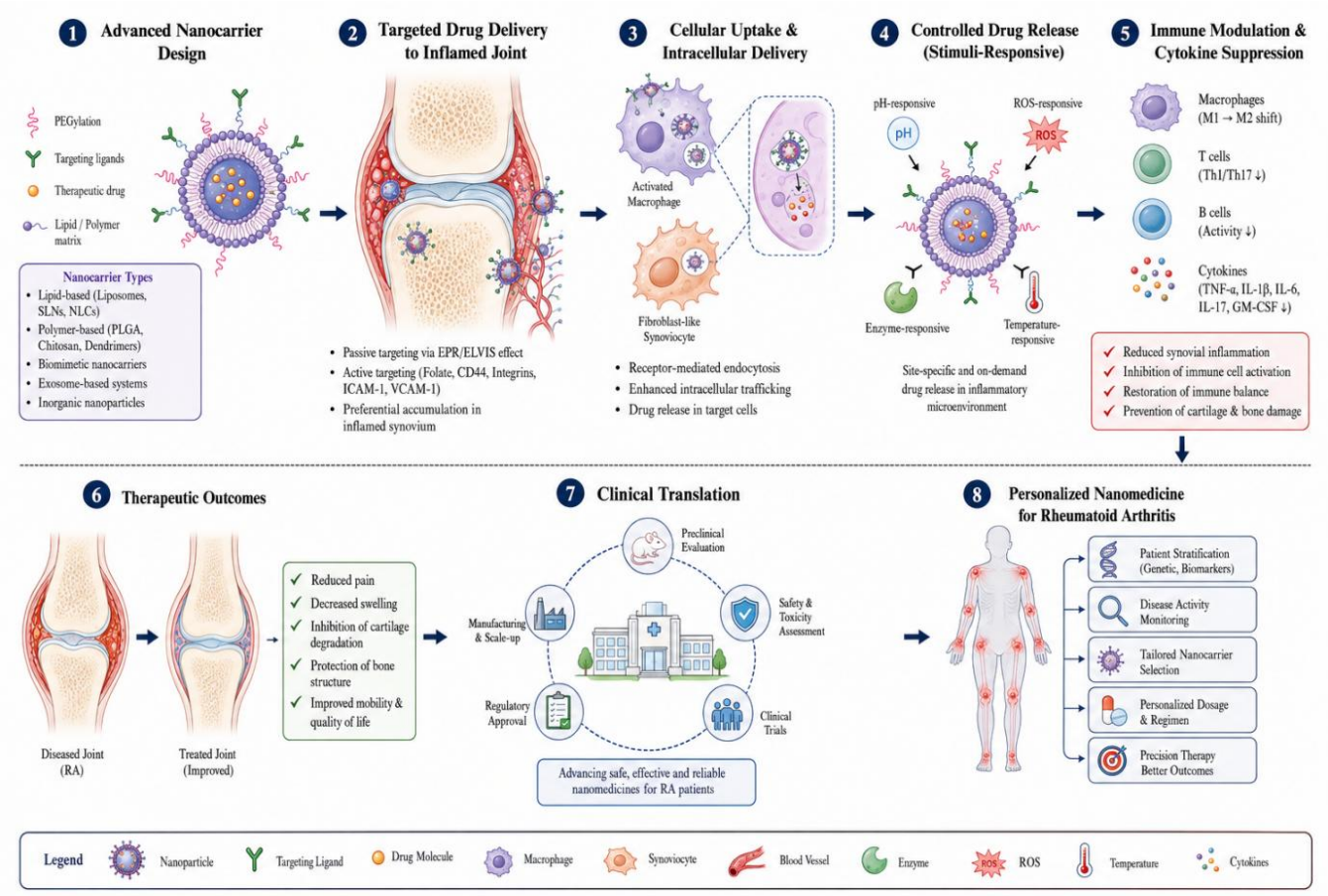


**Figure 2.** Overview of current and emerging nanomedicine strategies for rheumatoid arthritis, illustrating the progression from advanced nanocarrier design and targeted drug delivery to controlled release, immune modulation, clinical translation, and personalized therapeutic approaches.

## 6. CURRENT CHALLENGES, LIMITATIONS, AND FUTURE PERSPECTIVES

Despite remarkable progress in nanomedicine-based drug delivery for rheumatoid arthritis (RA), several scientific, technological, and regulatory challenges continue to impede its successful clinical translation. Although nanocarriers have demonstrated significant improvements in targeted drug delivery, controlled release, and therapeutic efficacy in preclinical studies, their widespread clinical application remains limited by biological barriers, manufacturing complexities, long-term safety concerns, and regulatory uncertainties. Furthermore, the heterogeneous nature of rheumatoid arthritis and inter-patient variability present additional obstacles to achieving consistent therapeutic outcomes. Addressing these limitations through multidisciplinary research, standardized manufacturing processes, and innovative technologies will be essential for advancing nanomedicine toward routine clinical practice[71-72]. This section discusses the major challenges associated with nanomedicine for rheumatoid arthritis and highlights emerging strategies that may shape the future of personalized RA treatment.

### 6.1 Biological and Therapeutic Challenges

The biological complexity of rheumatoid arthritis presents several challenges that limit the effectiveness of nanomedicine-based therapies. The inflammatory microenvironment, variable disease progression, and immune interactions significantly influence nanoparticle biodistribution, cellular uptake, and therapeutic efficacy.

#### Synovial Penetration

Efficient penetration of nanocarriers into inflamed synovial tissues remains a major challenge. Although increased vascular permeability facilitates nanoparticle accumulation through the ELVIS effect, dense extracellular matrix components, synovial hyperplasia, and elevated interstitial fluid pressure often restrict deep tissue penetration. Consequently, many nanoparticles remain localized near blood vessels, reducing their ability to reach fibroblast-like synoviocytes, macrophages, and other pathogenic cells distributed throughout the inflamed Synovium.[73]

#### Disease Heterogeneity

Rheumatoid arthritis is a highly heterogeneous disease with considerable variability in disease severity, inflammatory pathways, genetic background, and therapeutic response among patients. Differences in cytokine expression, immune cell populations, receptor availability, and vascular permeability can substantially influence nanoparticle targeting efficiency and drug release behavior. This heterogeneity complicates the

development of universal nanomedicine formulations capable of providing consistent therapeutic outcomes across diverse patient populations.

**Immune Clearance**

Nanoparticles administered systemically are frequently recognized and eliminated by the mononuclear phagocyte system (MPS), particularly macrophages located in the liver and spleen. Opsonization by plasma proteins further accelerates immune clearance, reducing circulation time and limiting nanoparticle accumulation within inflamed joints. Although surface modifications such as polyethylene glycol (PEG) coating and biomimetic membrane camouflage improve immune evasion, complete avoidance of immune recognition remains challenging.

**Target Specificity**

Achieving highly selective drug delivery remains one of the primary goals of nanomedicine. Many molecular targets, including CD44, folate receptors, ICAM-1, and VCAM-1, are not exclusively expressed within inflamed joints but may also be present in healthy tissues or other inflammatory conditions. Consequently, nonspecific nanoparticle uptake may reduce targeting efficiency and increase the risk of off-target effects. Developing highly selective ligands and multifunctional targeting strategies remains an important area of ongoing research.

### 6.2 Manufacturing, Biosafety, and Regulatory Challenges

In addition to biological limitations, successful clinical translation requires overcoming numerous pharmaceutical, engineering, and regulatory challenges associated with nanoparticle production and evaluation.

**Long-Term Toxicity**

Although many nanocarriers are considered biocompatible, their long-term safety remains insufficiently understood. Repeated administration may result in nanoparticle accumulation within organs such as the liver, spleen, kidneys, or lungs, potentially causing chronic toxicity or inflammatory responses. Comprehensive long-term toxicological studies are therefore essential before widespread clinical application[73-74].

**Biocompatibility**

Nanocarriers must exhibit excellent compatibility with biological systems while avoiding excessive immune activation, complement activation, thrombogenicity, or cellular toxicity. Surface chemistry, particle composition, degradation products, and nanoparticle size all influence biocompatibility. Optimizing these properties is essential for ensuring safe therapeutic use in patients with chronic autoimmune diseases.

**Batch Reproducibility**

Consistent nanoparticle production remains one of the greatest manufacturing challenges. Variations in particle size, morphology, drug-loading efficiency, surface charge, and release kinetics between production batches may significantly influence therapeutic performance. Standardized manufacturing protocols and rigorous quality control procedures are therefore required to ensure product consistency and reproducibility[75-76].

**Scale-Up**

Most nanomedicine formulations have been developed using laboratory-scale manufacturing techniques that are difficult to translate into industrial production. Scaling up nanoparticle synthesis while maintaining uniform physicochemical characteristics, sterility, and cost-effectiveness represents a major obstacle to commercialization. Advanced manufacturing technologies and continuous production systems may facilitate large-scale production in the future.

**Regulatory Approval**

The regulatory evaluation of nanomedicines remains more complex than that of conventional pharmaceuticals because nanoparticle behavior depends on multiple physicochemical characteristics rather than solely on chemical composition. Regulatory agencies require comprehensive characterization of nanoparticle size, morphology, stability, pharmacokinetics, biodistribution, toxicity, and manufacturing consistency. The absence of universally harmonized regulatory guidelines further delays clinical translation and market approval.

### 6.3 Emerging Trends and Future Perspectives

Rapid advances in nanotechnology, biotechnology, artificial intelligence, and precision medicine are driving the development of next-generation nanomedicine platforms capable of overcoming many current limitations.

**AI-Assisted Nanomedicine**

Artificial intelligence (AI) and machine learning are increasingly being used to accelerate nanomedicine development by predicting nanoparticle behavior, optimizing formulation parameters, identifying optimal drug combinations, and analyzing large biological datasets. AI-assisted design can significantly reduce formulation development time while improving targeting efficiency and therapeutic performance[77].

**Precision Medicine**

Precision medicine aims to customize therapeutic strategies according to individual patient characteristics, including genetic profile, disease phenotype, biomarker expression, and immune status. Integrating nanomedicine with molecular diagnostics may enable patient-specific drug selection, optimized dosing, and improved therapeutic outcomes while minimizing adverse effects.

**Biomimetic Nanoparticles**

Biomimetic nanoparticles coated with natural cell membranes derived from macrophages, neutrophils, platelets, erythrocytes, or stem cells exhibit enhanced immune evasion and improved targeting of inflamed tissues. These biologically inspired delivery systems

closely mimic natural cellular interactions and are expected to play an increasingly important role in future rheumatoid arthritis therapy.

### Exosome Delivery

Exosomes represent one of the most promising naturally derived nanocarriers because of their intrinsic biocompatibility, low immunogenicity, and efficient intercellular communication. Engineered exosomes capable of delivering anti-inflammatory drugs, proteins, messenger RNA, microRNA, or small interfering RNA have demonstrated significant therapeutic potential for immune modulation and cartilage regeneration. Advances in large-scale exosome production and purification are expected to facilitate future clinical applications[76].

### CRISPR-Based Nanomedicine

The integration of CRISPR/Cas gene-editing technology with nanocarrier systems offers new opportunities for precise genetic modulation of inflammatory pathways involved in rheumatoid arthritis. Nanoparticle-mediated CRISPR delivery may enable selective editing of genes associated with cytokine production, immune activation, and tissue destruction while minimizing off-target effects associated with viral vectors.

### Multifunctional Nanotheranostics

Multifunctional nanotheranostic platforms combine targeted drug delivery with diagnostic imaging, allowing simultaneous disease detection, treatment, and therapeutic monitoring. These integrated systems facilitate real-time visualization of nanoparticle biodistribution, assessment of treatment response, and individualized therapeutic adjustment, thereby supporting precision medicine approaches for rheumatoid arthritis.

### Personalized RA Therapy

Future rheumatoid arthritis management is expected to shift toward personalized nanomedicine, in which therapeutic strategies are tailored according to each patient's clinical presentation, molecular biomarkers, genetic background, and disease progression. Personalized nanocarrier systems capable of combining targeted delivery, controlled drug release, and biomarker-guided therapy may significantly improve treatment efficacy while reducing systemic toxicity and unnecessary drug exposure[78].

Although nanomedicine has demonstrated considerable promise for improving the treatment of rheumatoid arthritis through targeted drug delivery and controlled drug release, several biological, technological, manufacturing, and regulatory challenges continue to limit its widespread clinical implementation. Overcoming barriers such as inadequate synovial penetration, disease heterogeneity, immune clearance, large-scale manufacturing, long-term biosafety, and regulatory standardization will be essential for successful clinical translation. Emerging innovations, including AI-assisted nanomedicine, biomimetic nanoparticles, exosome-based delivery systems, CRISPR-enabled gene editing, multifunctional nanotheranostics, and precision medicine approaches, are expected to address many of these limitations. Continued collaboration among pharmaceutical scientists, rheumatologists, biomedical engineers, materials scientists, and regulatory agencies will accelerate the development of safe, effective, and personalized nanomedicine platforms, ultimately improving long-term disease management and quality of life for patients with rheumatoid arthritis[79-80].

## CONCLUSION

Nanomedicine has emerged as a transformative approach for the treatment of rheumatoid arthritis (RA), offering innovative solutions to many of the limitations associated with conventional therapeutic strategies. The integration of nanoscale drug delivery systems with targeted therapy and controlled drug release has significantly improved the precision, efficacy, and safety of anti-rheumatic treatments. Various nanocarrier platforms, including liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, polymeric micelles, hydrogels, metallic nanoparticles, mesoporous silica nanoparticles, and exosome-based systems, have demonstrated remarkable potential to enhance drug bioavailability, prolong circulation time, improve pharmacokinetic profiles, and facilitate selective accumulation within inflamed synovial tissues. By exploiting passive and active targeting mechanisms, these advanced delivery systems effectively reduce systemic toxicity while maximizing therapeutic concentrations at disease sites. Despite these promising developments, several challenges continue to hinder the successful clinical translation of nanomedicine. Biological barriers, including limited synovial penetration, immune clearance, disease heterogeneity, and variable receptor expression, reduce targeting efficiency and therapeutic consistency. Furthermore, issues related to long-term biosafety, nanoparticle biodegradation, large-scale manufacturing, batch-to-batch reproducibility, regulatory standardization, and cost-effective commercialization remain significant obstacles to widespread clinical implementation. Addressing these challenges requires comprehensive preclinical evaluation, well-designed clinical trials, standardized manufacturing protocols, and internationally harmonized regulatory frameworks. Future research should focus on the development of intelligent and multifunctional nanocarriers capable of integrating targeted drug delivery, controlled release, molecular imaging, and immune regulation into a single therapeutic platform. Nanomedicine represents a highly promising frontier in rheumatoid arthritis management, with the potential to revolutionize disease treatment by enabling safer, more effective, and patient-specific therapeutic interventions. Continued interdisciplinary collaboration among researchers, clinicians, pharmaceutical industries, and regulatory agencies will be crucial for translating these innovative nanotherapeutic strategies into routine clinical practice and ultimately improving the long-term health and

quality of life of patients living with rheumatoid arthritis.

## LIST OF ABBREVIATIONS

ACPAs, anti-citrullinated protein antibodies; AgNPs, silver nanoparticles; AI, artificial intelligence; AuNPs, gold nanoparticles; CD44, cluster of differentiation 44; CRISPR, clustered regularly interspaced short palindromic repeats; CT, computed tomography; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DMARDs, disease-modifying antirheumatic drugs; ELVIS, Extravasation through Leaky Vasculature and Inflammatory Cell-mediated Sequestration; FAP, fibroblast activation protein; FLS, fibroblast-like synoviocytes; FR-β, folate receptor-beta; GBD, Global Burden of Disease; GM-CSF, granulocyte-macrophage colony-stimulating factor; HA, hyaluronic acid; ICAM-1, intercellular adhesion molecule-1; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-17, interleukin-17; IONPs, iron oxide nanoparticles; JAK, Janus kinase; LNPs, lipid nanoparticles; MAPK, mitogen-activated protein kinase; miRNA, microRNA; MMPs, matrix metalloproteinases; MPS, mononuclear phagocyte system; MRI, magnetic resonance imaging; MSNs, mesoporous silica nanoparticles; MTX, methotrexate; NF-κB, nuclear factor-kappa B; NIR, near-infrared; NLCs, nanostructured lipid carriers; PAMAM, poly(amidoamine); PCL, polycaprolactone; PEG, polyethylene glycol; PLA, polylactic acid; PLGA, poly(lactic-co-glycolic acid); PPI, polypropyleneimine; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor-kappa B ligand; RF, rheumatoid factor; RGD, arginine-glycine-aspartic acid; RNS, reactive nitrogen species; ROS, reactive oxygen species; siRNA, small interfering RNA; SLNs, solid lipid nanoparticles; TNF-α, tumor necrosis factor-alpha; VCAM-1, vascular cell adhesion molecule-1; YLDs, years lived with disability.

## ETHICAL APPROVAL

Not applicable.

## CONSENT FOR PUBLICATION

Not applicable.

## HUMAN AND ANIMAL ETHICAL RIGHT

Not applicable.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, and no funding was required to conduct these review data.

## ACKNOWLEDGMENTS

The corresponding authors would like to thank, all involved members and faculty staff for their collaboration.

## AVAILABILITY OF DATA AND MATERIALS

The data supporting this study's findings will be available in the cited references.

## FUNDING

The research received no external funding.

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