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Review Article

Nanocarrier-Mediated Drug Delivery in Rheumatoid Arthritis: Overcoming Therapeutic Limitations through Targeted Approaches

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder characterized by persistent joint inflammation and progressive cartilage and bone destruction. Current treatments, including disease-modifying antirheumatic drugs (DMARDs) and biologics, have limitations such as incomplete responses, loss of efficacy, and adverse effects.

Purpose: This review explores the potential of nanotechnology in overcoming the limitations of current RA treatments, focusing on nanocarrier-based drug delivery systems.

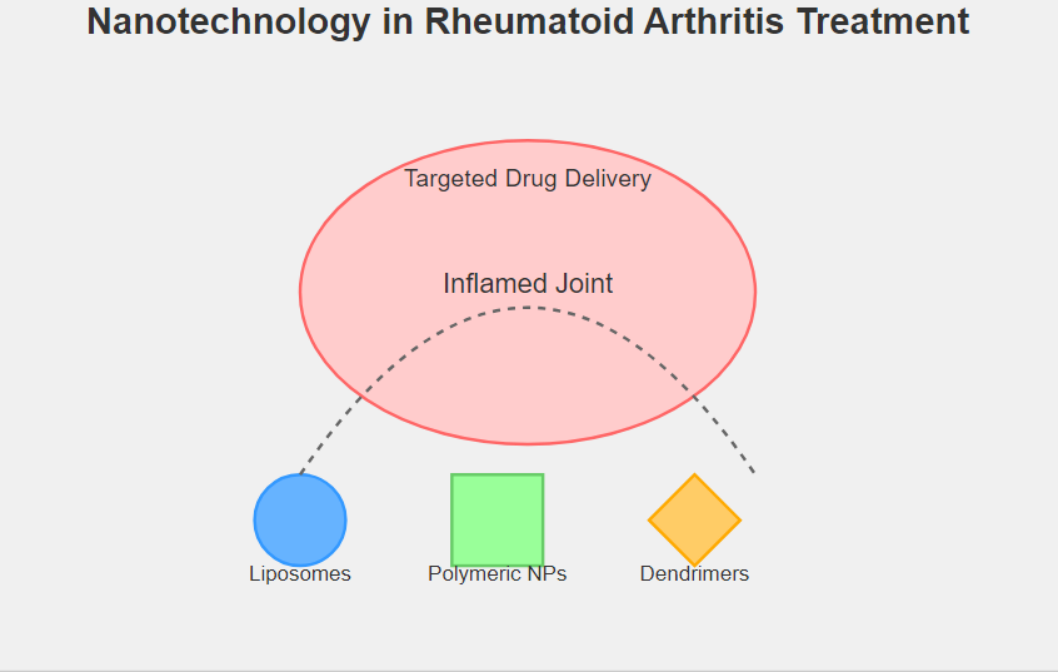
Main Body: Nanocarriers, including liposomes, polymeric nanoparticles, dendrimers, and inorganic nanoparticles, offer promising solutions for RA treatment. These systems can improve drug delivery by enhancing bioavailability, reducing off-target effects, and enabling controlled release. Passive targeting exploits the enhanced permeability and retention (EPR) effect in inflamed joints, while active targeting strategies utilize receptor-mediated and antibody-mediated approaches to enhance specificity. Nanocarrier-based systems have been developed to deliver anti-inflammatory drugs, DMARDs, and biologics with improved efficacy and reduced toxicity. Additionally, multifunctional nanoplatforms combining therapeutic and diagnostic capabilities pave the way for personalized medicine approaches in RA.

Conclusion: Nanotechnology-based drug delivery systems show significant potential in addressing the limitations of current RA treatments, offering enhanced targeting, improved efficacy, and reduced side effects. Further research and clinical trials are needed to translate these promising approaches into clinical practice.

Keywords: rheumatoid arthritis; nanocarriers; targeted drug delivery; liposomes; polymeric nanoparticles

Article Highlights:

- Nanocarriers enhance drug delivery in RA, improving efficacy and reducing side effects
- Active targeting strategies increase specificity of nanocarrier-based systems for inflamed joints
- Multifunctional nanoplatforms offer potential for personalized medicine approaches in RA treatment



Graphical Abstract

I. Introduction

A. Overview of Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder primarily affecting synovial joints. It is characterized by persistent joint inflammation, synovial hyperplasia, and progressive cartilage and bone destruction, leading to severe disability if untreated. The pathogenesis of RA involves a complex interplay between genetic predisposition and environmental factors, which triggers an aberrant immune response [1-2]. This immune dysregulation promotes the activation of T-cells, B-cells, macrophages, and synoviocytes, which secrete pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). These cytokines drive the inflammatory cascade, perpetuating joint damage and systemic manifestations [3-4].

B. Limitations of Current Treatments

Despite significant advancements in RA management, current treatments remain suboptimal. Conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, and biologic agents targeting TNF-α, IL-1, IL-6, and other cytokines, have shown efficacy in controlling disease activity. However, these therapies have notable limitations, such as incomplete responses, loss of efficacy over time, and adverse effects, including increased susceptibility to infections and malignancies. Furthermore, the need for frequent administration, systemic off-target effects, and high costs limit patient adherence and accessibility. Therefore, there is an urgent need for more precise and effective therapeutic strategies to improve outcomes for RA patients [5-6].

C. Potential of Nanotechnology in RA Treatment

Nanotechnology offers a promising solution to overcome the limitations of current RA treatments. Nanocarriers, including liposomes, polymeric nanoparticles, dendrimers, and inorganic nanoparticles, can improve drug delivery by enhancing bioavailability, reducing off-target effects, and enabling controlled release. These systems can be engineered to target inflamed joints specifically, maximizing therapeutic efficacy while minimizing systemic toxicity. Furthermore, nanotechnology enables the development of multifunctional nanoplatforms that combine therapeutic and diagnostic capabilities, paving the way for personalized medicine approaches in RA [7-12].

II. Nanocarriers for RA Drug Delivery

A. Liposomes

Liposomes are spherical vesicles composed of phospholipid bilayers that can encapsulate both hydrophilic and hydrophobic drugs as presented in **Table 1**. Their biocompatibility and ability to fuse with cell membranes make them attractive candidates for RA drug delivery. Liposomes can be modified with polyethylene glycol (PEG) to prolong circulation time and with targeting ligands to enhance accumulation in inflamed joints. In RA, liposomes have been used to deliver anti-inflammatory drugs, DMARDs, and biologics, improving their therapeutic index by reducing systemic exposure and enabling sustained drug release [13-14].

Nanocarrier Type	Composition	Advantages	Limitations	Examples of RA Applications
Liposomes	Phospholipid bilayers	- Biocompatible- Can encapsulate hydrophilic and hydrophobic drugs- Fusogenic with cell membranes	- Limited stability- Potential for rapid clearance	- Delivery of corticosteroids- Encapsulation of DMARDs

Nanocarrier Type	Composition	Advantages	Limitations	Examples of RA Applications
Polymeric Nanoparticles	Biodegradable polymers (e.g., PLGA, PCL)	- Controlled release- Tunable size and surface properties- High drug loading capacity	- Potential toxicity of some polymers- Challenges in large-scale production	- Delivery of methotrexate- Encapsulation of siRNA
Dendrimers	Highly branched macromolecules	- Well-defined structure- Multifunctional capabilities- High drug payload	- Complex synthesis- Potential cytotoxicity at higher generations	- Delivery of indomethacin- Conjugation with folate for targeting
Inorganic Nanoparticles	Gold, silica, or magnetic materials	- Unique physicochemical properties- Potential for theranostic applications	- Concerns about long-term biocompatibility- Challenges in biodegradation	- Gold nanoparticles for photothermal therapy- Magnetic nanoparticles for targeted delivery

Table 1: Comparison of Nanocarrier Types for Rheumatoid Arthritis Drug Delivery

B. Polymeric Nanoparticles

Polymeric nanoparticles are composed of biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA) or polycaprolactone (PCL). These nanoparticles can encapsulate a wide variety of drugs and provide controlled, sustained release. Their tunable size, surface charge, and composition allow for precise control over drug pharmacokinetics and biodistribution. In RA, polymeric nanoparticles have been investigated for the delivery of corticosteroids, DMARDs, and nucleic acids, offering enhanced therapeutic efficacy and reduced toxicity compared to conventional formulations [15-20].

C. Dendrimers

Dendrimers are highly branched, tree-like macromolecules with a well-defined structure and numerous surface functional groups. Their unique architecture allows for the conjugation of multiple therapeutic agents and targeting moieties, making them ideal for multifunctional drug delivery systems. Dendrimers can encapsulate drugs within their core or conjugate them to their surface, enabling both passive and active targeting of inflamed tissues. In RA, dendrimer-based systems have shown promise in delivering anti-inflammatory drugs and biologics with improved efficacy and reduced side effects [21-22].

D. Inorganic Nanoparticles

Inorganic nanoparticles, such as gold nanoparticles, silica nanoparticles, and magnetic nanoparticles, offer unique physicochemical properties that make them attractive for RA treatment. Gold nanoparticles, for example, have been explored for their anti-inflammatory properties and ability to deliver drugs or genes to inflamed joints. Magnetic nanoparticles can be guided to specific tissues using external magnetic fields, allowing for targeted drug delivery. Additionally, inorganic nanoparticles can serve as platforms for theranostic applications, combining therapeutic and imaging capabilities into a single system [23-24].

III. Targeting Strategies

A. Passive Targeting

Passive targeting exploits the enhanced permeability and retention (EPR) effect, a phenomenon where nanoparticles accumulate in inflamed tissues due to their leaky vasculature and impaired lymphatic drainage as presented in **Table 2**. In RA, the inflamed synovium exhibits increased vascular permeability, allowing nanocarriers to preferentially accumulate in the joint space. This approach enhances drug concentration at the site of inflammation while minimizing systemic exposure, thereby reducing side effects. However, passive targeting alone may not be sufficient for achieving optimal therapeutic efficacy, as it relies solely on the physicochemical properties of the nanocarriers [25].

Targeting Strategy	Mechanism	Advantages	Limitations	Examples in RA
Passive Targeting	Exploitation of EPR effect in inflamed joints	- Simple implementation- Reduced systemic exposure	- Limited specificity- Variability in EPR effect among patients	- PEGylated liposomes accumulating in synovium
Active Targeting: Receptor-Mediated	Conjugation of ligands to nanocarriers for specific receptor binding	- Enhanced cellular uptake- Improved specificity	- Potential immunogenicity of targeting ligands- Heterogeneity of receptor expression	- Folate-conjugated nanoparticles targeting activated macrophages
Active Targeting: Antibody-Mediated	Use of monoclonal antibodies or their fragments for targeting	- High specificity- Potential for blocking pathological pathways	- High production costs- Potential for immunogenicity	- Anti-CD20 antibody-conjugated nanoparticles targeting B cells
Stimuli-Responsive Targeting	Nanocarriers responsive to pH, temperature, or enzymes in RA joints	- Controlled drug release at target site- Reduced off-target effects	- Complex design and synthesis- Potential for premature drug release	- pH-sensitive polymeric nanoparticles releasing drug in acidic synovial fluid

Table 2: Targeting Strategies for Nanocarrier-based Drug Delivery in Rheumatoid Arthritis

B. Active Targeting

1. Receptor-Mediated Targeting

Active targeting involves the functionalization of nanocarriers with ligands that recognize and bind to specific receptors overexpressed on target cells. In RA, several cell surface receptors, such as folate receptors, integrins, and CD44, are overexpressed on synoviocytes, macrophages, and endothelial cells in inflamed joints. By conjugating ligands such as peptides, antibodies, or small molecules to the surface of nanocarriers, receptor-mediated targeting allows for selective delivery of therapeutic agents to these cells, enhancing drug efficacy and reducing off-target effects [26-30].

2. Antibody-Mediated Targeting

Antibody-mediated targeting involves the use of monoclonal antibodies (mAbs) or antibody fragments that bind specifically to antigens expressed on inflamed tissues or immune cells. In RA, antibodies targeting pro-

inflammatory cytokines (e.g., anti-TNF-α, anti-IL-6) or immune cell markers (e.g., CD20 on B-cells) have been successfully used as therapeutics. Nanocarriers can be functionalized with these antibodies to enhance their specificity for inflamed joints, enabling targeted delivery of anti-inflammatory agents or immunomodulatory drugs. This strategy holds great potential for improving the efficacy of current biologic therapies [31-36].

IV. Nanocarrier-Based Drug Delivery Systems for RA

A. Anti-Inflammatory Drugs

Nanocarriers have been designed to deliver conventional anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to inflamed joints. These systems enhance drug solubility, prolong circulation time, and enable controlled release, thereby reducing the frequency of administration and minimizing systemic side effects. For example, liposomal formulations of corticosteroids have been shown to improve joint targeting and reduce the risk of adrenal suppression and other systemic toxicities [37-38].

B. Disease-Modifying Antirheumatic Drugs (DMARDs)

DMARDs, including methotrexate, leflunomide, and sulfasalazine, are the cornerstone of RA treatment. However, their use is often limited by poor bioavailability and off-target effects. Nanocarrier-based delivery systems can improve the pharmacokinetics and biodistribution of DMARDs, enhancing their therapeutic efficacy while reducing toxicity. Polymeric nanoparticles and liposomes have been explored for the delivery of methotrexate, showing improved drug accumulation in inflamed joints and reduced systemic exposure [39-44].

C. Biologics

Biologic agents, such as TNF-α inhibitors, IL-6 receptor blockers, and B-cell depleting agents, have revolutionized RA treatment. However, their high molecular weight and immunogenicity pose challenges for efficient delivery. Nanocarriers can protect biologics from degradation, extend their half-life, and enhance their targeting to inflamed tissues. Dendrimer-based systems and polymeric nanoparticles have been investigated for the delivery of biologics, showing promise in improving drug stability and therapeutic outcomes [45-46].

D. Gene Therapy Approaches

Gene therapy holds great potential for treating RA by targeting the underlying molecular mechanisms driving inflammation and joint destruction. Nanocarriers can deliver therapeutic genes, such as those encoding anti-inflammatory cytokines (e.g., IL-10) or gene-silencing agents (e.g., siRNA targeting pro-inflammatory cytokines), to inflamed joints. Polymeric nanoparticles, liposomes, and dendrimers have been explored for gene delivery in RA, offering the potential for long-lasting therapeutic effects with minimal off-target toxicity [47-52].

V. Recent Advancements in Nanotechnology for RA Treatment

A. Stimuli-Responsive Nanocarriers

Stimuli-responsive nanocarriers are designed to release their payload in response to specific physiological or pathological stimuli, such as pH changes, enzymatic activity, or reactive oxygen species (ROS) levels. In RA, the inflamed synovium exhibits an acidic microenvironment and elevated ROS levels, providing opportunities for the development of pH-sensitive and ROS-responsive nanocarriers. These systems can achieve site-specific drug release, minimizing systemic exposure and enhancing therapeutic efficacy [53-54].

B. Combination Therapy Approaches

Combination therapy, which involves the simultaneous delivery of multiple therapeutic agents, is an emerging strategy for improving RA treatment. Nanocarriers can be engineered to co-deliver anti-inflammatory drugs, DMARDs, or biologics, allowing for synergistic effects and improved therapeutic outcomes. For example, liposomes or polymeric nanoparticles can encapsulate both methotrexate and a corticosteroid, providing enhanced anti-inflammatory and immunomodulatory effects in RA [55-59].

C. Theranostic Nanoparticles

Theranostic nanoparticles combine therapeutic and diagnostic capabilities into a single platform, enabling real-time monitoring of disease progression and treatment response. In RA, theranostic systems can deliver anti-inflammatory drugs while simultaneously providing imaging contrast for techniques such as magnetic resonance imaging (MRI) or positron emission tomography (PET). This approach allows for personalized treatment regimens based on individual patient responses, improving clinical outcomes and minimizing adverse effects [60-63].

VI. Challenges and Future Perspectives

A. Toxicity and Biocompatibility Concerns

One of the major challenges in the clinical translation of nanocarrier-based therapies is ensuring their safety and biocompatibility. Nanomaterials can induce immunogenicity, oxidative stress, or cytotoxicity, particularly when used for long-term treatment. Extensive preclinical testing and optimization of nanoparticle composition, size, and surface properties are required to minimize toxicity and ensure safe use in RA patients [64-65].

B. Scalability and Manufacturing Issues

The large-scale production of nanocarriers with consistent quality and reproducibility remains a significant hurdle. Variability in nanoparticle size, drug loading efficiency, and surface functionalization can affect therapeutic efficacy and safety. Developing robust, scalable manufacturing processes that meet regulatory standards is essential for the successful clinical translation of nanocarrier-based therapies [66].

C. Regulatory Hurdles

Regulatory approval for nanocarrier-based therapies presents unique challenges due to the complexity of these systems. Regulatory agencies require comprehensive data on the safety, efficacy, and pharmacokinetics of nanomedicines. Standardizing guidelines for the evaluation of nanoparticle-based therapies is critical to facilitating their approval and clinical use in RA [67-69].

D. Emerging Trends and Future Research Directions

The field of nanotechnology for RA treatment is rapidly evolving, with several promising trends on the horizon. Advances in biomaterials, such as the development of biodegradable and stimuli-responsive polymers, are enabling the design of more sophisticated nanocarriers. The integration of artificial intelligence (AI) and machine learning (ML) into nanomedicine is also expected to accelerate the discovery and optimization of nanoparticle-based therapies. Furthermore, ongoing research into the use of nanocarriers for gene editing technologies, such as CRISPR-Cas9, holds the potential to revolutionize RA treatment by directly targeting disease-causing genes [70-72].

Conclusions:

Nanotechnology-based drug delivery systems demonstrate significant potential in addressing the limitations of current rheumatoid arthritis (RA) treatments. The use of nanocarriers, including liposomes, polymeric nanoparticles, dendrimers, and inorganic nanoparticles, offers enhanced drug targeting, improved efficacy, and reduced side effects. Passive targeting via the EPR effect and active targeting strategies utilizing receptor-mediated and antibody-mediated approaches have shown promise in increasing the specificity of drug delivery to inflamed joints. The development of multifunctional nanoplatforms combining therapeutic and diagnostic capabilities paves the way for personalized medicine approaches in RA management. However, challenges remain in translating these promising

approaches from bench to bedside, including optimizing nanocarrier design for improved stability and biocompatibility, addressing potential long-term toxicity concerns, and overcoming regulatory hurdles. Despite these challenges, the field of nanomedicine in RA treatment continues to evolve rapidly, offering hope for more effective and tailored therapies in the future.

Recommendations:

Future research should focus on optimizing nanocarrier design to enhance stability, biocompatibility, and targeting efficiency in the complex physiological environment of RA. Long-term safety studies are crucial to address potential toxicity concerns associated with repeated administration of nanoparticles. Clinical trials should be designed to evaluate the efficacy and safety of nanocarrier-based therapies in comparison to current standard treatments, with a focus on patient-reported outcomes and quality of life measures. Efforts should be made to develop standardized protocols for nanoparticle characterization and manufacturing to facilitate regulatory approval and clinical translation. Collaborative research between nanotechnologists, rheumatologists, and immunologists should be encouraged to drive innovation in targeted drug delivery and personalized medicine approaches for RA. Additionally, economic analyses should be conducted to assess the cost-effectiveness of nanocarrier-based therapies compared to conventional treatments, considering both direct and indirect costs associated with RA management.

List of abbreviations:

1. RA - Rheumatoid Arthritis
2. DMARDs - Disease-Modifying Antirheumatic Drugs
3. TNF-α - Tumor Necrosis Factor-alpha
4. IL-1 - Interleukin-1
5. IL-6 - Interleukin-6
6. PEG - Polyethylene Glycol
7. PLGA - Poly(lactic-co-glycolic acid)
8. PCL - Polycaprolactone
9. EPR - Enhanced Permeability and Retention
10. CD44 - Cluster of Differentiation 44
11. ASCP - American Society for Clinical Pathology

Declarations:

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Clinical trial number: not applicable.

Consent for publication: Not Applicable

Availability of data and materials: all data are available and sharing is available as well as publication.

Competing interests: The author hereby that they have no competing interests.

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