

Development And Formulation Of Nanotechnology-Based Lipid Nanoliposomes For The Treatment Of Arthritis: A Comprehensive Review

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ABSTRACT

Arthritis is a chronic inflammatory disorder affecting millions worldwide, characterized by joint pain, swelling, and progressive cartilage degradation. Conventional therapies, including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs), are often associated with systemic side effects and limited targeting efficiency. Nanotechnology-based drug delivery systems, particularly lipid nanoliposomes, have emerged as promising carriers for improving therapeutic outcomes in arthritis treatment. Liposomes are biocompatible and biodegradable vesicular systems capable of encapsulating both hydrophilic and lipophilic drugs, thereby enhancing drug solubility, stability, and bioavailability. Recent advancements in formulation strategies, including PEGylation, surface modification, and ligand-mediated targeting, have enabled site-specific drug delivery to inflamed joints. This review highlights the development, formulation techniques, characterization methods, and therapeutic applications of lipid nanoliposomes in arthritis management. Furthermore, recent research (2020–2025), challenges, and future perspectives are discussed to provide insights into their clinical translation.

Keywords: Arthritis; Liposomes; Nanotechnology; Drug delivery; Rheumatoid arthritis; Lipid nanocarriers; Targeted therapy; Formulation.

INTRODUCTION

Arthritis is a broad term encompassing a range of inflammatory and degenerative joint disorders, with Rheumatoid Arthritis (RA) and Osteoarthritis (OA) being the most prevalent forms. RA is an autoimmune disease characterized by chronic synovial inflammation, leading to joint destruction, whereas OA is primarily a degenerative disorder involving cartilage breakdown and joint remodeling. Both conditions result in pain, stiffness, swelling, and reduced mobility, significantly impairing the quality of life of affected individuals. The global burden of arthritis is steadily increasing due to aging populations, sedentary lifestyles, and rising obesity rates, making it a major public health concern worldwide [1,2].

Conventional pharmacological treatments for arthritis include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs). While these

therapies provide symptomatic relief and slow disease progression, they are often associated with significant limitations such as poor bioavailability, frequent dosing requirements, systemic toxicity, and lack of site-specific targeting. Long-term use of these drugs can lead to adverse effects including gastrointestinal complications, cardiovascular risks, and immunosuppression, highlighting the need for safer and more effective therapeutic strategies [3,4].

In recent years, nanotechnology-based drug delivery systems have emerged as promising alternatives to overcome these challenges. These advanced systems enable targeted drug delivery, controlled release, and improved pharmacokinetic profiles, thereby enhancing therapeutic efficacy while minimizing side effects. Among various nanocarriers, lipid-based nanoliposomes have gained considerable attention due to their unique structural and functional properties. Liposomes are spherical vesicles composed of one or more phospholipid bilayers surrounding an aqueous core, closely resembling

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biological membranes. This structural similarity imparts excellent biocompatibility, biodegradability, and low immunogenicity [5].

Furthermore, lipid nanoliposomes are capable of encapsulating both hydrophilic and lipophilic drugs, protecting them from degradation and enhancing their stability. Their surface can be modified with polymers such as polyethylene glycol (PEG) or targeting ligands to achieve prolonged circulation time and site-specific delivery to inflamed joints. These advantages make liposomes highly suitable for the treatment of arthritis, where targeted and sustained drug delivery is crucial for improving therapeutic outcomes [6].

OVERVIEW OF LIPID NANOLIPOSOMES

1. Definition and Structure

Lipid nanoliposomes are nanoscale vesicular drug delivery systems composed of one or more phospholipid bilayers enclosing an aqueous core. These bilayers are primarily formed from natural or synthetic phospholipids such as phosphatidylcholine, often stabilized with cholesterol to enhance membrane rigidity and stability. Due to their amphiphilic nature, liposomes are capable of encapsulating both hydrophilic and lipophilic therapeutic agents, making them highly versatile carriers in drug delivery systems.

- **Hydrophilic drugs** are encapsulated within the aqueous core
- **Lipophilic drugs** are incorporated within the phospholipid bilayer

The structural resemblance of liposomes to biological membranes contributes to their excellent biocompatibility, biodegradability, and reduced immunogenicity. Additionally, their size (typically 50–500 nm) allows them to accumulate preferentially in inflamed tissues through enhanced permeability and retention (EPR) effects, which is particularly beneficial in arthritis treatment [7,8].

2. Types of Liposomes

Lipid nanoliposomes can be classified based on size, lamellarity, and surface modification:

- **Small Unilamellar Vesicles (SUVs):** These consist of a single phospholipid bilayer with a size range of 20–100 nm. They exhibit high stability and are suitable for systemic drug delivery [9].
- **Large Unilamellar Vesicles (LUVs):** Larger vesicles (100–1000 nm) with a single bilayer, offering higher drug encapsulation efficiency, particularly for hydrophilic drugs [10].
- **Multilamellar Vesicles (MLVs):** Composed of multiple concentric bilayers, these vesicles provide sustained drug release but may have lower uniformity in size [9].
- **PEGylated (Stealth) Liposomes:** Modified with polyethylene glycol (PEG), these liposomes evade rapid clearance by the reticuloendothelial system (RES), resulting in prolonged circulation time and enhanced therapeutic efficacy [11].
- **Targeted Liposomes:** Surface-functionalized with ligands such as antibodies, peptides, or sugars to achieve site-specific drug delivery to inflamed joints or specific cells [12].

ADVANTAGES OF LIPID NANOLIPOSOMES IN ARTHRITIS TREATMENT

Lipid nanoliposomes offer several advantages over conventional drug delivery systems, particularly in the management of inflammatory diseases like arthritis:

- **Enhanced Drug Bioavailability:** Liposomes improve solubility and absorption of poorly water-soluble drugs, increasing their therapeutic effectiveness [13].
- **Targeted Delivery to Inflamed Joints:** Liposomes can accumulate at inflamed sites via passive targeting (EPR effect) or active targeting using ligands, ensuring localized drug action [14].
- **Reduced Systemic Toxicity:** Encapsulation of drugs within liposomes minimizes exposure to healthy tissues, thereby reducing adverse effects commonly associated with conventional therapies [15].

- **Controlled and Sustained Drug Release:** Liposomal formulations allow gradual drug release, maintaining therapeutic concentrations over an extended period and reducing dosing frequency [16].
- **Protection of Drug from Degradation:** Liposomes protect encapsulated drugs from enzymatic degradation and chemical instability, enhancing drug stability [17].
- **Improved Patient Compliance:** Reduced dosing frequency and minimized side effects contribute to better patient adherence to treatment regimens [18].

FORMULATION STRATEGIES OF LIPID NANOLIPOSOMES

1. Thin Film Hydration Method

- Most widely used technique
- Lipid film formed and hydrated to produce vesicles

The thin film hydration method, also known as the Bangham method, is the most commonly employed technique for liposome preparation. In this method, phospholipids and cholesterol are dissolved in an organic solvent such as chloroform or methanol. The solvent is then evaporated under reduced pressure using a rotary evaporator to form a thin lipid film on the inner wall of a round-bottom flask. This film is subsequently hydrated with an aqueous phase containing the drug, resulting in the formation of multilamellar vesicles. Further size reduction can be achieved through sonication or extrusion. This method is simple, reproducible, and suitable for a wide range of drugs [19,20].

2. Ethanol Injection Method

- Rapid and simple method
- Produces small-sized liposomes

In the ethanol injection method, lipids are dissolved in ethanol and rapidly injected into an aqueous phase under continuous stirring. The rapid diffusion of ethanol into the aqueous medium leads to spontaneous formation of liposomes. This method is advantageous due to its simplicity, scalability, and ability to produce

small unilamellar vesicles. However, residual solvent removal and lower encapsulation efficiency for hydrophilic drugs may be limitations [21].

3. Reverse Phase Evaporation Method

- Suitable for high drug encapsulation
- Produces large unilamellar vesicles

This method involves the formation of a water-in-oil emulsion by mixing an aqueous drug solution with lipids dissolved in an organic solvent. Upon removal of the organic solvent under reduced pressure, the emulsion collapses, forming large unilamellar vesicles with high encapsulation efficiency. This technique is particularly useful for incorporating hydrophilic drugs into liposomes [22].

4. Microfluidization Technique

- High reproducibility
- Uniform particle size distribution

Microfluidization is an advanced technique that utilizes high-pressure homogenization to produce liposomes with uniform size distribution. Lipid and aqueous phases are forced through microchannels at high velocity, resulting in the formation of small, homogeneous vesicles. This method offers excellent reproducibility, scalability, and control over particle size, making it suitable for industrial production [23].

5. Surface Modification Techniques

- PEGylation (for prolonged circulation)
- Ligand attachment (for targeting inflamed tissues)

Surface modification of liposomes enhances their therapeutic performance. PEGylation involves the attachment of polyethylene glycol (PEG) chains to the liposome surface, which reduces recognition by the reticuloendothelial system (RES) and prolongs circulation time. Ligand-based targeting involves conjugation of antibodies, peptides, or other molecules that specifically bind to receptors on inflamed tissues, enabling site-specific drug delivery and improved therapeutic efficacy [24,25].

CHARACTERIZATION OF LIPOSOMES

Proper characterization of liposomal formulations is essential to ensure their stability, efficacy, and reproducibility.

- **Particle Size and Distribution (Dynamic Light Scattering):**
Determines vesicle size and polydispersity index (PDI), which influence drug release and biodistribution [26].
- **Zeta Potential (Stability Indicator):**
Measures surface charge of liposomes, indicating physical stability; higher absolute values suggest better stability due to electrostatic repulsion [27].
- **Entrapment Efficiency:**
Represents the percentage of drug encapsulated within liposomes, which is critical for therapeutic effectiveness [28].
- **Morphology (TEM, SEM):**
Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) provide information on shape, size, and structural integrity of liposomes [29].
- **In vitro Drug Release Studies:**
Evaluate the release profile of the drug from liposomes under controlled conditions, helping to predict in vivo performance [30].
- **Stability Studies:**
Assess physical and chemical stability under different storage conditions, including temperature and pH, to determine shelf life [31].

APPLICATION OF LIPOSOMES IN ARTHRITIS TREATMENT

1. Rheumatoid Arthritis (RA)

- Targeted delivery of methotrexate, diclofenac
- Reduction of joint inflammation
- Improved therapeutic efficacy

In Rheumatoid Arthritis (RA), liposomal drug delivery systems have shown significant potential in improving therapeutic outcomes. Liposomes encapsulating drugs such as Methotrexate and Diclofenac enable targeted delivery to inflamed synovial tissues, thereby enhancing drug

concentration at the site of action while minimizing systemic toxicity. Liposomal formulations have been reported to reduce synovial inflammation, inhibit cytokine production, and improve overall disease management. Additionally, sustained drug release from liposomes reduces dosing frequency and enhances patient compliance [32,33].

2. Osteoarthritis (OA)

- Delivery of anti-inflammatory and cartilage-protective agents
- Reduction of cartilage degradation

In Osteoarthritis (OA), liposomes are used to deliver anti-inflammatory drugs as well as chondroprotective agents directly to affected joints. These formulations help reduce cartilage degradation and improve joint function. Liposomal encapsulation of bioactive molecules such as corticosteroids and natural compounds has demonstrated enhanced therapeutic efficacy and prolonged retention in joint tissues, contributing to better disease control [34].

3. Targeted Drug Delivery

- Passive targeting via enhanced permeability and retention (EPR) effect
- Active targeting using ligands (antibodies, peptides)

Liposomal drug delivery systems facilitate both passive and active targeting mechanisms. Passive targeting occurs through the enhanced permeability and retention (EPR) effect, where liposomes accumulate in inflamed tissues due to leaky vasculature. Active targeting involves surface modification of liposomes with ligands such as antibodies, peptides, or receptors that specifically bind to inflamed cells or tissues. This targeted approach enhances therapeutic efficacy and reduces off-target effects [35].

RECENT ADVANCES (2020–2025)

- Development of PEGylated liposomes for prolonged circulation
- Stimuli-responsive liposomes (pH-sensitive, temperature-sensitive)

- Dual drug-loaded liposomes for combination therapy
- Integration with nanotheranostics (diagnosis + therapy)
- Use of natural compounds such as Curcumin and Resveratrol in liposomal form
- Personalized nanomedicine
- Improved targeting strategies
- Clinical trials and commercialization
- Hybrid nanocarriers (liposome + polymer systems)

Recent advancements in liposomal technology have significantly improved their application in arthritis treatment. PEGylated (stealth) liposomes exhibit prolonged circulation time and enhanced accumulation at inflamed sites. Stimuli-responsive liposomes release drugs in response to environmental triggers such as pH or temperature changes, ensuring site-specific delivery. Dual drug-loaded liposomes enable combination therapy, improving treatment efficacy by targeting multiple pathways simultaneously. Additionally, nanotheranostic approaches integrate diagnostic and therapeutic functions into a single system. Encapsulation of natural anti-inflammatory compounds like curcumin and resveratrol has also gained attention due to their enhanced stability and bioavailability in liposomal formulations [36–38].

CHALLENGES AND LIMITATIONS

- Stability issues (leakage, fusion)
- High production cost
- Scale-up difficulties
- Regulatory challenges
- Limited clinical translation

Despite promising results, several challenges hinder the widespread application of liposomal drug delivery systems. Stability issues such as drug leakage and vesicle fusion can affect efficacy. High production costs and difficulties in large-scale manufacturing limit commercial feasibility. Additionally, stringent regulatory requirements and limited clinical studies pose barriers to clinical translation. Addressing these challenges is crucial for successful commercialization [39].

FUTURE PERSPECTIVES

- AI-based formulation design

Future research in liposomal drug delivery is expected to focus on the integration of artificial intelligence (AI) for optimizing formulation parameters and predicting drug behavior. Personalized nanomedicine approaches will enable tailored treatments based on individual patient profiles. Advances in targeting strategies, including ligand engineering and stimuli-responsive systems, will further enhance therapeutic efficacy. Hybrid nanocarriers combining liposomes with polymers or other nanomaterials are also being explored to overcome current limitations. Continued research and clinical evaluation will pave the way for the successful translation of liposomal therapies into clinical practice [40,41].

CONCLUSION

Lipid nanoliposomes have emerged as a highly promising nanotechnology-based platform for the effective management of arthritic disorders, particularly Rheumatoid Arthritis and Osteoarthritis. Their unique structural characteristics, including a phospholipid bilayer and aqueous core, enable the encapsulation of a wide range of therapeutic agents, thereby improving drug solubility, stability, and bioavailability. One of the most significant advantages of liposomal systems is their ability to deliver drugs selectively to inflamed joint tissues through passive and active targeting mechanisms, which enhances therapeutic efficacy while minimizing systemic toxicity and adverse effects commonly associated with conventional therapies.

Recent advancements in formulation strategies, such as PEGylation, ligand-mediated targeting, and stimuli-responsive systems, have further optimized the performance of lipid nanoliposomes. These innovations have enabled prolonged circulation time, controlled and sustained drug release, and improved interaction with specific cellular targets involved in inflammatory pathways. Additionally, the integration of nanotechnology with modern tools such as

computational modeling and nanotheranostics has accelerated the development of multifunctional liposomal systems capable of both diagnosis and therapy.

Despite these promising developments, several challenges remain to be addressed. Issues related to physical and chemical stability, large-scale manufacturing, high production costs, and stringent regulatory requirements continue to limit widespread clinical application. Furthermore, the lack of extensive clinical trials and long-term safety data presents a barrier to their successful translation from laboratory research to clinical practice.

In conclusion, lipid nanoliposomes represent a versatile and effective drug delivery system with significant potential to revolutionize arthritis treatment. Continued interdisciplinary research combining pharmaceutical sciences, nanotechnology, and clinical studies is essential to overcome existing limitations. With further advancements, liposomal formulations are expected to play a crucial role in the development of safer, targeted, and more efficient therapeutic strategies for arthritis management.

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