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Revolutionizing rheumatoid arthritis therapy: the potential of lipid nanocarriers

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Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by synovitis, systemic inflammation and autoantibodies, leading to joint damage and disability. RA pathogenesis is characterized by a dysregulated interaction between immune cells, particularly B cells and T cells, which release inflammatory cytokines. This review explores the pivotal role of these immune cells in sustaining the inflammatory response and contributing to tissue injury. We provide a comprehensive overview of current RA therapies, highlighting the limitations of conventional treatments and the pressing need for targeted drug delivery systems such as lipid nanocarrier-based therapies, including nano-emulsions, solid lipid nanoparticles (SLNs), niosomes, liposomes, transferosomes, and ethosomes. Emphasizing niosomes, we discuss their capacity to encapsulate multiple drugs, significantly enhancing bioavailability and therapeutic efficacy. By directing drug-loaded niosomes to inflamed synovial sites, this innovative approach minimizes systemic side effects while maximizing localized drug concentrations, thereby optimizing treatment outcomes for RA patients. This review underscores the importance of targeted (nano)drug delivery in improving patient's life quality and represents a significant step toward more effective, personalized RA therapies by deepening our understanding of the underlying mechanisms.

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Introduction

Arthritis is one of the most prevalent chronic illnesses that affects millions of people worldwide. According to the Global RA Network, in 2021, more than 350 million people suffered from arthritis globally.[1] When an intra-articular inflammation affects one or more joints, including knees, knuckles, wrists, or ankles, which can occur from various etiological reasons, it is referred to as arthritis.[1] In the first stage, arthritis can develop into pain, edema, or stiffness. If untreated, it will result in degenerative joint disease, which is destructive.[2] From a pathological point of view, the synovium, articular cartilage, and supporting subcomponent structures are the primary cause of the wide range of ailments that make up arthritis. Arthritis end-stage is frequently accompanied by excruciating pain and impairment. Patients with arthritis often experience discomfort in the affected joint, a declined motion, and an increased risk of malformation and instability. Nonoperative therapy is typically the cornerstone of care in clinics, where patients are treated with anti-inflammatory drugs.[2]

Arthritis can be generally divided into two main groups: inflammatory arthritis and non-inflammatory arthritis. The patient must be correctly diagnosed to be treated accordingly.[3] Non-inflammatory arthritis typically occurs due to deterioration or harm inflicted upon various joint components, such as cartilage. Even though the causes of this arthritis type remain uncertain, several significant risk factors come into play, including genetic predisposition, body weight, and joint stress. Non-inflammatory arthritis tends to remain localized within the affected joints and does not extend throughout the body. A predominant form of non-inflammatory arthritis is the osteoarthritis.[3,4] Furthermore, this autoimmune condition presents an atypical immune response that explicitly targets synovial cells, cartilage, and bone, causing joint impairment and lasting disability.[5] This disease is closely associated with irregularities in the immune system, wherein the body erroneously assaults its tissues; in this case, increased inflammation centred on the joints leads to swelling and discomfort. In contrast, inflammatory arthritis is a systemic immune response that can spread throughout the body, affecting other joints and organs if not properly managed. Examples of inflammatory arthritis are rheumatoid arthritis (RA), juvenile idiopathic arthritis, and seronegative spondylarthritis.[5–8]

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This review will focus on RA, a systemic condition that typically presents a symmetrical inflammatory polyarthritis, most commonly affecting hands and feet, although it can affect any synovial joint.[8] The synovial membrane thickens and becomes inflamed, leading to a deterioration of cartilage and joints. This prolonged inflammation in the synovium can trigger inflammation throughout the body over time. The main symptoms include persistent pain, stiffness, joint swelling, fatigue, and, frequently, anaemia. Approximately 1% of the population between the ages of 20 and 50 suffer from RA, with a clear predominance in women and a woman-to-man ratio of 3 : 1.[9]

Although the exact cause of RA remains unknown, it is suggested to be linked to the human leukocyte antigen variant (HLA-DRβ1), even though this connection is not fully understood.[9,10]

RA is a complicated autoimmune condition shaped by a combination of genetic predisposition and environmental factors. The immune system begins to recognize self-antigens as foreign, especially citrullinated proteins, causing the production of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs).[11,12] These autoantibodies form immune complexes that deposit in the synovial joints, triggering activation of the complement cascade and resident immune cells, which initiates local inflammation.[13] As the disease progresses, $CD4^+$ T cells (especially the Th1 and Th17 subsets) and B cells infiltrate the synovium, where they activate macrophages and fibroblast-like synoviocytes (FLS). These cells produce high levels of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-17, perpetuating a state of chronic synovial inflammation.[14–16] This sustained immune activation promotes synovial hyperplasia (pannus formation), cartilage degradation, and bone erosion, primarily through osteoclast activation, ultimately resulting in irreversible joint destruction.[17,18] The pathogenesis of RA can be broken down as shown in Table 1. The combination of all these factors contributes to the persistence and impairment nature of RA, resulting in symptoms such as joint pain, swelling, stiffness, and joint deterioration (Fig. 1). RA can be controlled thanks to the administration of disease-modifying antirheumatic drugs (DMARDs) and anti-inflammatory drugs to target specific cytokines (*e.g.*, TNF-α, IL-1β, IL-6) to control inflammation effectively, slow the progression of the disease, and alleviate symptoms.[28,29] Additionally, non-steroidal anti-inflammatory drugs (NSAIDs) and corticoids are commonly employed as a RA treatment to modulate cytokine activity, reducing inflammation and preventing joint damage. However, these drugs come with associated drawbacks. For example, NSAIDs may cause stomach irritation and bleeding,[30] leading to kidney dysfunction and an elevated risk of suffering a heart attack or a thromboembolic event.[31] Common side effects of DMARDs involve skin rashes, diarrhoea, alopecia, interstitial lung disease, deficiency in folic acid, and liver cirrhosis.[32,33] Corticosteroids, while valuable in controlling the inflammation and immune response, can be associated with a range of adverse effects.[34] Prolonged or high-dosage may lead to systemic side effects such as weight gain, fluid retention,[35] hypertension,[36] and diabetes.[37] They can cause osteoporosis and increase the risk of infections due to immune system suppression.[38] Skin problems like thinning and bruising, mood swings, insomnia, and gastrointestinal issues may occur.[39] Additionally, long-term use can have an impact on the adrenal gland function, requiring a gradual dose reduction when discontinuing treatment.[40] Therefore, corticosteroids should be used carefully under medical supervision due to the potential adverse effects.

Nanocarriers, characterized as colloidal nanoparticles (NPs) ranging in size from 1 to 100 nanometres (nm), are essential in drug delivery. Due to the high surface area-to-volume ratio exhibited by nanocarriers, they can potentially encapsulate and protect therapeutic drugs by improving their bioactivity. They can be used for the systemic administration of RA drugs, through the spatial and temporal control of the drug release they offer.[41] Thus, nanocarriers serve as tiny transporters that can be tailored in charge and shape to convey therapeutic substances to specific targeted tissues efficiently.

However, given that microcapillaries in the human body have a diameter of approximately 200 nm, it is crucial for drug-delivery nanocarriers to be smaller than this threshold.[42] There are several types of nanoparticulate carriers, including polymeric, lipid and protein, as for the type of material; and dendrimers or nanocapsules, as for the type of structure; amongst others.[43] Changes in their physicochemical properties, such as surface functionalization, composition, and shape, have been demonstrated to improve their selectivity towards targeting organs, tissues, or cell types while simultaneously minimizing undesirable side effects in off-targeting organs.[44]

Consequently, in the frame of lack of effective RA treatments, to address the limitations associated with RA drugs, nanocarriers offer a promising solution to improve the oral delivery of these drugs for future treatments. Specifically, those composed of lipids offer great advantages. This is because lipid-based nanocarriers offer several advantages, including enhanced bioavailability of drugs, protection, and stabilization of sensitive compounds like proteins by reducing adverse effects and facilitating precise targeting when needed.[45]

Issues of rheumatoid arthritis (RA) current treatments

NSAIDs such as celecoxib and nabumetone are widely used to control symptoms due to their potent anti-inflammatory and pain-relieving effects. They inhibit the production of prostaglandins at the cyclooxygenase enzyme level. Prostaglandins, derived from arachidonic acid, promote inflammation, vasodilation, and increased pain sensitivity. NSAIDs effectively reduce prostaglandin levels by hindering cyclooxygenase, alleviating associated inflammation and pain.[46] However, the most common adverse reaction to NSAIDs involves the upper gastrointestinal tract, leading to discomfort, ulcer formation, and bleeding. The formation of ulcers and bleeding is dose-dependent; with higher doses, it increases the risk, causing thousands of hospitalizations and fatalities annually, particularly among rheumatoid arthritis patients.[47] Glucocorticoids

Table 1 Rheumatoid arthritis (RA) pathogenesis

Pathogenesis	Explanation	Ref.
Environmental triggers	Environmental factors, such as infections, microbiota or smoking, may trigger the onset of RA in genetically susceptible individuals	19 and 20
Genetic predisposition	The most prominent risk factor for RA is genetic. First-degree relatives of patients with rheumatoid arthritis have a risk of disease increased by a factor of 2 to 5	19 and 20
Autoimmune component	The exact cause of RA remains unclear, but it is believed to involve expression of human major histocompatibility protein HLA-DRβ1, where the immune system mistakenly targets the own body tissues	21 and 22
Activation of immune cells	RA is characterized by the inappropriate activation of various immune cells, including B cells, T cells, plasma cells, neutrophils, dendritic cells, and macrophages	23
Release of inflammatory cytokines	These activated immune cells release pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which play a central role in promoting inflammation and driving the disease process	24 and 25
Synovial changes	RA involves immune cell infiltration into the synovium and the formation of lymphoid aggregates contributing to the ongoing inflammation	19 and 20
Formation of pannus	Pannus formation refers to the abnormal growth of inflamed tissue in the synovium. It consists of immune cells infiltration as a hallmark of RA, contributing to joint inflammation, cartilage erosion, and joint deformities	26
Systemic inflammation	TNF-α, IL-1β, and IL-6 can also enter the bloodstream, leading to systemic inflammation. This systemic inflammation can affect various organs and systems, causing systemic complications often observed in RA patients	27

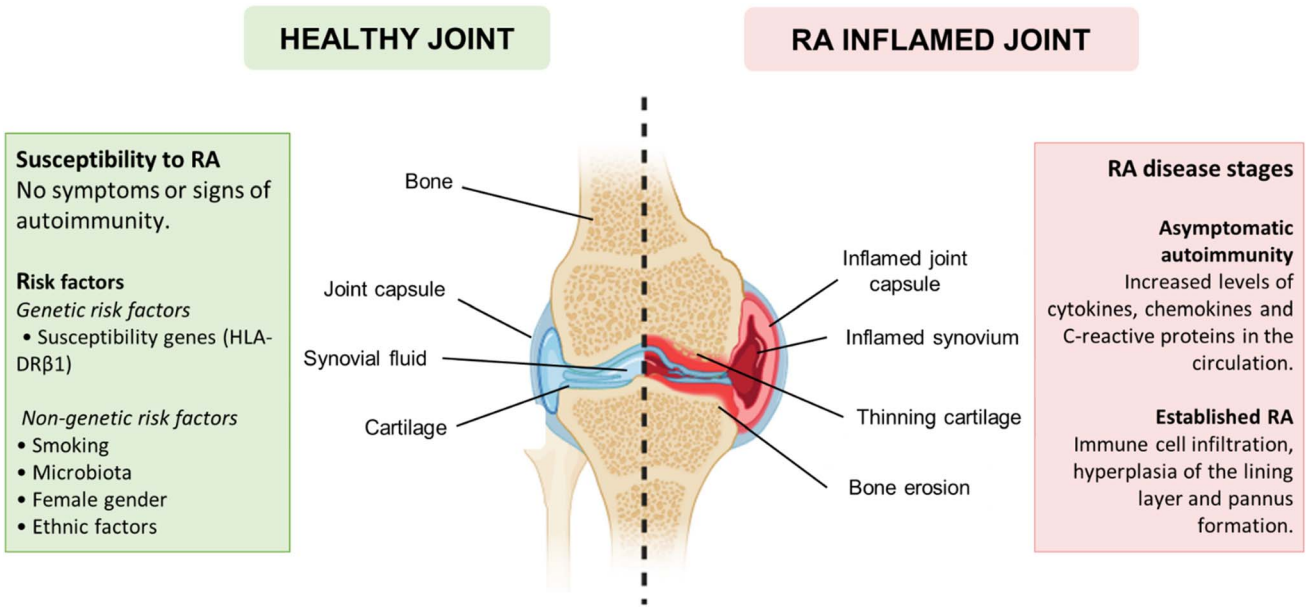


Fig. 1 Structure of healthy and rheumatoid arthritis (RA) inflamed joint.

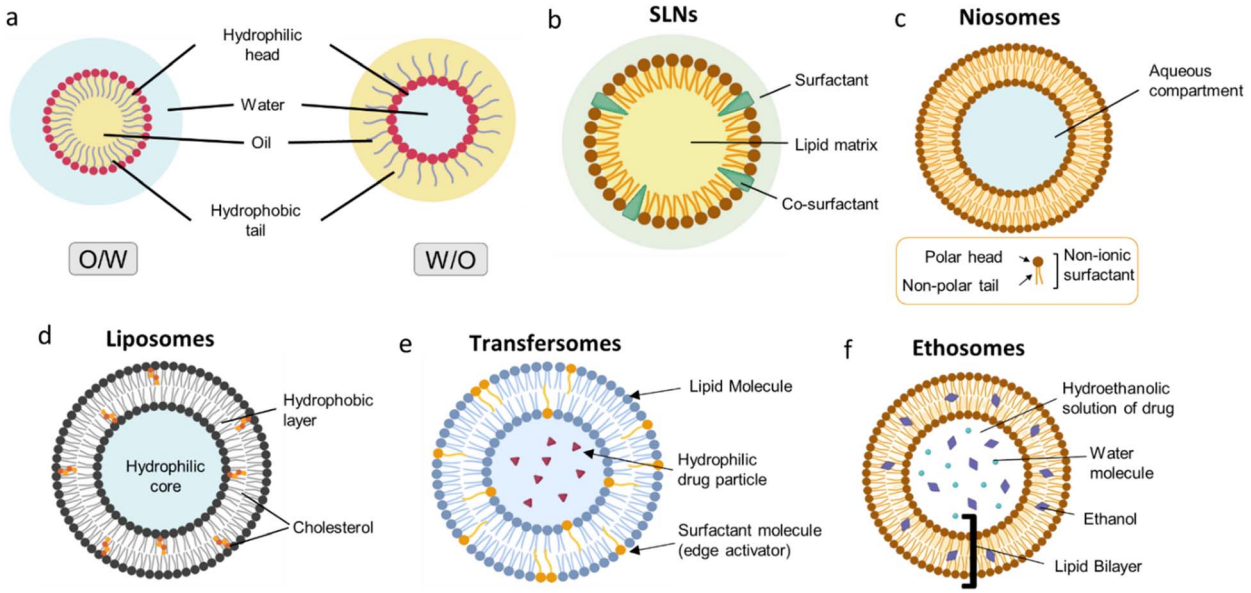


Fig. 2 Structure of the different mentioned lipid nanostructures. (a) Nano-emulsions, (b) solid lipid nanoparticles (SLNs), (c) niosomes, (d) liposomes, (e) transferosomes, and (f) ethosomes.

(GCs), like prednisone and dexamethasone, exert a broad influence on immune cells, hindering their movement and disrupting their physiological functions while also dampening the production of humoral factors through cGCR-mediated classical genomic effects.[48] Meanwhile, corticosteroids produce mood and behaviour alterations, such as restlessness, anxiety, irritability, and difficulty concentrating.[49]

DMARDs, which are commonly prescribed for RA, with methotrexate (MTX) being the most used one, are known for their ability to reduce joint inflammation, relieve pain and stiffness, and potentially slow disease progression in RA patients.[50] However, MTX treatment can lead to haematological toxicity, including leukopenia, thrombocytopenia, megaloblastic anaemia, and pancytopenia, with an estimated prevalence of 3%.[51] Furthermore, respiratory issues such as coughing, wheezing, and breathlessness are reported in over 25% of individuals undergoing MTX therapy.[52] MTX toxicity can lead to bone marrow suppression, gastrointestinal ulcers, and the development of cutaneous ulcers in individuals with underlying psoriasis vulgaris.[53,54]

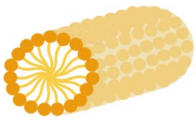
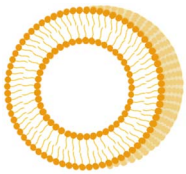
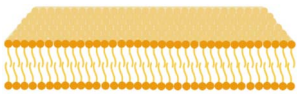
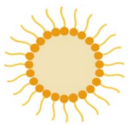
Types of lipid-based nanoparticles (NPs) and their advantages

Lipid-based NPs represent a cutting-edge approach within the pharmaceutical industry, harnessing the unique properties of lipids to revolutionize drug delivery systems.[55] These NPs, comprised of lipids such as phospholipids, cholesterol, and triglycerides, offer numerous advantages for pharmaceutical applications. One of the main advantages is their biocompatibility and ability to mimic biological membranes, reducing the risk of immune reactions and enhancing drug uptake by cells. Lipid-based NPs also provide a versatile platform for encapsulating both hydrophilic and hydrophobic drugs, ensuring optimal solubility and stability. Furthermore, their tuneable properties allow for controlled drug release kinetics, enabling sustained or triggered release profiles tailored to specific therapeutic needs. With their potential to improve drug bioavailability, target-specific delivery, and minimize systemic toxicity,[56] lipid-based NPs are poised to significantly advance drug delivery technology and enhance patient outcomes in the pharmaceutical landscape.

Nano-emulsions, defined as colloidal dispersions of nanometric droplets immiscible to the continuous phase, with kinetic but not thermodynamic stability, are characterized by stable liquid-in-liquid mixtures with droplets below 200 nm in size, presenting several advantages due to their exceptional properties.[55–57] Their nanometric size imparts a high surface area relative to volume, ensuring efficient encapsulation and delivery of active compounds. The robust stability of nano-emulsions, attributed to small droplet size and the use of suitable surfactants,[56] enhances their applicability across diverse industries. The visually clear appearance and fine-tuned flow properties make nano-emulsions versatile for pharmaceutical applications.[57] The composition flexibility allows tailoring to target needs, generating oil-in-water (O/W) or water-in-oil (W/O) emulsions based on surfactant solubility (Fig. 2A).[56,57] Also, if required, a double emulsion, typically composed of W/O/W, can be prepared to encapsulate hydrophilic and hydrophobic drugs simultaneously. Emulsifying agents, including surfactants, hydrophilic colloids, and solids, contribute to stability by preventing droplet coalescence and forming protective films.[58] Nano-emulsions with an absolute zeta potential above 30 mV exhibit enhanced stability due to electrostatic repulsion forces between droplets.[59]

Achieving high encapsulation efficiency ensures effective retention and delivery of active compounds.[60] Storage stability, assessed through physical stability parameters, is critical.[61] The

Table 2 Relationship between the shape of surfactant monomer, critical packing parameter (CPP) and preferred aggregate morphology

Shape	CPP value	Aggregate morphology
 Cone	0 < CPP < 1/3	 Spherical micelles
 Truncated Cone	1/3 < CPP < 1/2	 Cylindrical micelles
 Truncated Cone	1/2 < CPP < 1	 Vesicles
 Cylinder	CPP ~ 1	 Planar bilayers
 Inverted Truncated Cone or Wedge	CPP > 1	 Inverted micelles, inverted hexagonal

emulsification methods, both high-energy and low-energy, offer flexibility and control, with high-energy methods providing better dispersion control and working with low surfactant concentrations and low-energy methods being cost-effective and efficient, producing uniform droplet sizes.[62,63]

In the 19th century, Müller and Gascon explored the concept of using lipid NPs for drug delivery.[64] Solid-lipid nanoparticles (SLNs) are characterized by their solid lipid-based core, ranging from 50 to 1000 nm, offering numerous advantages for pharmaceutical applications (Fig. 2B).[65] These biocompatible and biodegradable lipid NPs are non-toxic, ensuring safe drug delivery, and their production does not require organic solvents, addressing environmental and safety concerns. SLNs exhibit excellent physical stability, prolonging the shelf life of pharmaceutical products, enabling controlled drug release and targeted delivery, improving therapeutic selectivity.[66–68] Moreover, SLNs protect active substances; both lipophilic and hydrophilic drugs, from degradation when encapsulated. They are amenable to large-scale manufacturing solidifying their use in drug delivery systems.[66–68] Several synthetic methods have been reported for SLNs, offering diverse approaches to tailor their properties for specific drug delivery applications.[69,70] High Pressure Homogenization (HPH) has emerged as a highly effective method for producing SLNs, forming uniform and stable spherical NPs by applying pressure gradients and mechanical forces.[71] HPH allows to optimize SLN production for specific drug loading and delivery needs, enabling the production of smaller NPs with increased surface area to increase drug loading efficiency and bioavailability.[72] However, SLNs also present some disadvantages, because prolonged storage can lead to alterations in drug release patterns due an increase in NPs size. In addition, polymorphic transitions within SLNs and gelation are also potential drawbacks. Despite these challenges, the stability provided by SLNs within biological systems, protecting the cargo against biochemical and physicochemical damage, underscores their significance in pharmaceutical research and development.[73]

Another approach in lipid-based systems are niosomes, arising from the self-organization of nonionic surfactants, present specialized delivery systems exploited in pharmaceutical and cosmetic industries (Fig. 2C).[74] Unlike ionic surfactants, nonionic surfactants lack a net electrical charge, facilitating their arrangement into stable bilayer structures and allowing niosomes to encapsulate both hydrophilic and hydrophobic substances within their vesicular structures.[75] This versatility makes niosomes valuable tools in drug delivery and for exploitation in topical formulations, particularly for active molecules with poor water solubility. Niosomes allow to modify their size, surface properties, and lipid composition to optimize drug loading and release.[74] The physicochemical attributes of niosomes or vesicles are influenced by factors such as the surfactant selection, surfactant type, alkyl chain length, and the Critical Packing Parameter (CPP) of surfactant, which determines the preferred aggregate morphology as shown in Table 2.[76–78] Additionally, the physical state of niosome bilayers, whether liquid or gel, is influenced by temperature, lipid/surfactant type, and the presence of components like cholesterol, providing further control over niosome formulations for drug delivery applications.[79,80] To form niosomes it is needed to hydrate a combination of surfactants and lipids, followed by ether injection, manual shaking, sonication, or microfluidization, which offers flexibility and adaptability in the preparative methods.[81] A notable strength of niosomes is their superior chemical stability when compared to liposomes, exhibiting a higher resistance to chemical degradation and oxidation, leading to significantly extended storage periods.[82] The surfactants used in niosome formulations offer biodegradability, biocompatibility, and non-immunogenicity, making them suitable for a wide range of applications.[79–83] The ease of handling and storing these surfactants, along with the ability to precisely control niosome composition, size, lamellarity, stability, and surface charge, further enhances the interest to use them as drug delivery systems.[84]

Some challenges include aggregation, fusion of vesicles, drug leakage, and hydrolysis of encapsulated drugs over time.[85] To effectively decontaminate niosomes, gamma sterilization is emerging as a viable solution that offers rapid clean up and

Table 3 Application of lipid-based NPs for RA

Lipid nanocarriers	Lipid composition	Drugs	Benefits	Route of administration	Preclinical/clinical	Ref.
Nano-emulsions (LNE)	Egg phosphatidylcholine, triolein, cholesteryloleate, and cholesterol	Methotrexate	LNE-MTX significantly decreased leukocyte influx, leading to a reduction in mononuclear cell counts and polymorphonuclear cell counts. LNE-MTX offers several advantages, including its non-immunogenic and non-toxic nature. Additionally, it is cost-effective and easy to produce on a large scale, making it a favourable choice	Intravenous	Preclinical	121
Solid lipid nanoparticles (SLN)	Cetyl palmitate and stearic acid	Methotrexate	These formulations offer an enhanced delivery method as theranostic agents, being safe and cost-effective, which can be scaled up and customized to fulfil specific purposes, including targeted delivery	Intravenous	Preclinical	122
	Polysorbate 80 and soy lecithin	Curcumin	Antioxidant, anti-inflammatory, and immune-modulatory effects within the joint synovium, potentially improving arthritis. In contrast, curcumin in its free form, even in equivalent doses, can only mitigate induced oxidative stress and TNF-α levels. It cannot alleviate acute phase reactants and auto-antibodies to citrullinated proteins	Intramuscular	Preclinical	123
	GMS, cholesterol and DDAB	Prednisolone	SLNs loaded with prednisolone and coated with hyaluronic acid (HA) exhibited prolonged circulation and enabled selective release thanks to the ability of HA to bind to the CD44 receptor overexpressed in targeted cells	Intravenous	Preclinical	127
	Tristearin, soy lecithin an stearylamine	Methotrexate aceclofenac	SLN conjugated with chondroitin sulphate for targeted drug delivery into the joint reduced drug dosage and side effects	Intravenous	Preclinical	128
Niosomes	Tween 80 and cholesterol	Piroxicam	Increased solubility of drugs	Transdermal patches	Preclinical	130
	Span20, Span60, Span80 and cholesterol	Ibuprofen	Drug extended duration, higher effectiveness	Topical gel	Preclinical	131
	Span60 and cholesterol	Thiocolchicoside	Drug extended duration on skin, effectively managing RA pain and side effects with fewer doses	Topical gel	Preclinical	132
Liposomes	DPPC, cholesterol and ethanol	Prednisone	Nanocarriers persisted in the bloodstream for 50 hours after administration, and a single dose of this preparation completely resolved paw inflammation within 2 days of injection, maintaining its effect for 2 weeks	Systemic	Preclinical	133

Table 3 (*Contd.*)

Lipid nanocarriers	Lipid composition	Drugs	Benefits	Route of administration	Preclinical/clinical	Ref.
	PEG	Prednisolone	Enhanced permeability and retention	Intravenous injection	Clinical	134
	DPPC, DPPG and cholesterol	Dexamethasone	Prolonged half-life, enhanced targeting effect. All liposomal versions of dexamethasone exhibited superior therapeutic effects compared to free dexamethasone. Significantly reduce joint swelling and inflammation, even when administered in lower doses within the liposomal formulation	Intravenous injection	Preclinical	136–138
	Phospholipids	Tofacitinib citrate	Increased distribution at inflamed sites	Intravenous	Preclinical	139
	DSPC, cholesterol and PEG	Berberine	Reduced inflammatory reaction	Intravenous	Clinical	140
	Soybean lecithin, cholesterol, stearylamine and dicetyl phosphate (DCP)	Indomethacin	Enhanced effectiveness compared to free drug	Intravenous	Preclinical	141
	DPPC, DSPE and cholesterol	Prednisolone phosphate	Prevented bone erosion and a single dose with liposomal PLP inhibited erosion in the tibial epiphysis trabecular bone and demonstrated anti-inflammatory effects	Intravenous	Preclinical	142
	DMPE	Methotrexate	Prolonged circulation after intravenous administration, strong anti-inflammatory effects in rat arthritis. These anti-inflammatory properties might be attributed to the suppression of IL-1β	Intravenous	Preclinical	143
	DSPC, stearylamine and cholesterol	Prednisolone methotrexate	Development of a system based on double liposomes loaded with both PRD, an anti-inflammatory, and MTX, a DMARD. The synergistic action of the double liposome system conjugated with folate enhances the targeting capability, stability, and loading capacity of the system	Intravenous	Preclinical	144
Transfersomes	Lecithin, Tween80 and span 80/Span 20	Imatinib	Increased imatinib flux through rat skin, demonstrating enhanced drug permeability and an improved therapeutic response in RA animals in comparison to conventional drug-incorporated gel systems.	Transdermal	Preclinical	145
	Carbopol934	Curcumin	*In vivo* greater cutaneous penetration compared to curcumin alone, and it exhibited good therapeutic efficacy in rats	Transdermal	Preclinical	146
	Phosphatidylcholine, ethanol and tween 80	Capsaicin	Superior inhibitory activity in reducing arthritis and enhanced cutaneous tolerance, reducing inflammation and	Transdermal	Preclinical	147

Table 3 (*Contd.*)

Lipid nanocarriers	Lipid composition	Drugs	Benefits	Route of administration	Preclinical/clinical	Ref.
			burning sensation compared to the marketed thermagel formulation			
Ethosomes	SPC, cholesterol and deoxycholic acid	Indomethacin	Delivering indomethacin through the skin achieved a higher efficiency with this formulation, ensuring faster delivery	Transdermal	Preclinical	148
	PC90G and alcohol	Mometasone furoate	Exhibited higher skin penetration compared to the drug alone.	Transdermal	Preclinical	149
	Phospholipon 90 G	Capsaicin	Improved penetration and minimized irritation led to notable reduction of inflammation and pain, enhancing the drug's effectiveness and promoting better patient compliance	Transdermal	Preclinical	150
	PC, propylene glycol and ethanol	Tetrandrine	Enhancement of tetrandrine topical delivery increased transdermal flux and drug deposition in rat skin compared to liposomes	Transdermal	Preclinical	151

excellent penetration capabilities while generating minimal heat during the process.[86,87]

Liposomes, with diameters typically ranging from 50 to 500 nm, represent a prominent class of nanocarriers extensively investigated for targeted drug delivery systems. These spherical lipid vesicles, formed by emulsifying natural or synthetic lipids in an aqueous environment, have shown significant potential in delivering drugs to specific targets within the body (Fig. 2D).[88,89] Categorized into structural types such as small unilamellar vesicles (SUV), large unilamellar vesicles (LUV), multilamellar vesicles (MLV), and multivesicular vesicles (MVV), liposomes offer versatility for various drug delivery applications based on their size and the number of bilayers they possess.[90] Larger liposomes with fewer bilayers exhibit increased encapsulation efficiency for hydrophilic compounds, influencing drug loading and release profiles in liposomal drug delivery systems.[91] Lipid and phospholipid composition in liposome formulations involves the self-assembly of diacyl-chain phospholipids, creating a lipid bilayer structure in aqueous solutions.[92] Predominantly composed of glycerophospholipids and sphingomyelins, lipids in liposomes feature hydrophilic heads and hydrophobic tails, forming an amphiphilic structure crucial for stability through electrostatic repulsion.[93,94] Sphingomyelin, a type of phospholipid, replaces glycerol in its structure and is used in formulations such as Marqibo (vincristine sulfate liposome injection) to enhance liposome stability within an acidic environment, leading to improved pharmacokinetic characteristics and drug delivery to target tissues.[95,96] Cholesterol is commonly employed to enhance membrane flexibility, bolster bilayer stability, and reduce the passage of water-soluble substances through the lipid bilayer.[97] Various techniques, including thin-film hydration, ethanol injection, and double emulsion methods, are employed for liposome creation. These manufacturing processes involve steps such as the production of Multilamellar Vesicles (MLVs) or Unilamellar Vesicles (ULVs), reduction of liposome size, if necessary, preparation of drug solutions and loading, buffer exchange and concentration, ensuring sterility, and lyophilization if deemed necessary.[98] Liposomes offer advantages in gene delivery by effectively binding with charged genetic molecules, providing protection against enzymatic degradation, and allowing the transport of large genetic fragments. Additionally, modifications enabling targeted delivery, such as attaching ligands or antibodies to the liposome surface, make liposomes a versatile tool for gene delivery with promising capabilities.[99] Despite these advantages, liposomes have limitations, including high production costs, susceptibility to leakage and fusion, potential chemical changes in their components over time, short half-life in the bloodstream, and reduced stability over extended periods. Ongoing research aims to address these challenges and enhance the performance of liposomes for drug delivery applications.[100]

A breakthrough in drug delivery systems is transfersomes, the innovative and highly flexible drug carriers introduced recently that exhibit the capability to transport large molecules through intact mammalian skin.[100,101] These deformable vesicular structures, sharing a lipid-based morphology with

liposomes, distinguish themselves through remarkable deformability, enabling them to navigate through pores significantly smaller than their size.[102] Composed of phospholipids, edge activators (typically surfactants), and water, transfersomes possess a bilayer structure that accommodates both hydrophilic and hydrophobic drugs (Fig. 2E).[103] Hydrophilic drugs are enclosed within or adsorbed to the aqueous core, while hydrophobic drugs are encapsulated within the space between the phospholipid-lipid bilayers. Key components, such as phosphatidylcholine C18, known for its skin-friendly and non-toxic properties, and surfactants like sodium cholate, sodium deoxycholate, Polysorbate 80, Span 80, and dipotassium glycyrrhizinate, contribute to the stability and functionality of transfersomes.[104] Studies indicate that transfersomes incorporating Tween 80 exhibit vesicles ranging in size from 140 to 270 nm; this size reduction is linked to increased solubility and the ability of Polysorbate 80 to form hydrogen bonds during swelling.[105] This drug delivery system is characterized by biocompatibility and biodegradability, ensuring its safety in the body and the environment. Transfersomes demonstrate an impressive entrapment capacity of around 90%, effectively encapsulating lipophilic drugs with varying molecular weights, including high and low molecular weight compounds. Moreover, their unique ability to undergo shape change enhances tissue infiltration for optimized drug delivery.[106,107] Despite these advantages, certain drawbacks exist such as the potential impurities that atural phospholipids may contain. Additionally, formulation of transfersomes can be relatively expensive, and challenges may arise when attempting to encapsulate hydrophobic drugs. However, their utility in controlled and sustainable drug delivery makes transfersomes a promising advancement in the field.[105,106]

Ethosomes, a class of lipid-based nanocarriers introduced by Touitou in 1997, emerged as an innovative drug delivery system, due to their ability to enhance transdermal or skin delivery of a diverse range of drugs and therapeutic compounds.[107] Comprising ethanol, phospholipids, and water, ethosomes uniquely incorporate ethanol into their composition (Fig. 2F), enabling them to effectively penetrate the skin's barrier and facilitate the efficient transport of drugs into deeper skin layers or the bloodstream. This distinctive feature makes them particularly valuable for topical and transdermal drug delivery applications, addressing challenges from conventional formulations.[107,108] The adaptability of ethosomes in terms of size, ranging from nm to microns, offers precise control over the transport of therapeutic drugs, making them versatile for enhancing the effectiveness of transdermal and topical applications.[109] Ethosomes are classified into three categories: Classical Ethosomes, derived from traditional liposomes; Binary Ethosomes, which incorporate an additional alcohol component to fine-tune properties; and Transethosomes, considered the next generation with presumed enhanced characteristics.[109–111]

Despite the complex, time-consuming synthesis and limited stability due to sensitivity to temperature and humidity, ethosomes offer significant advantages. They can deliver a wide range of molecules, including peptides and macromolecules, effectively through the skin.[112] Their ability to fuse with the skin's lipid bilayers facilitates transcutaneous drug delivery. Ethosomes can be tailored into different formulations, enhancing patient compliance and offering new possibilities for therapeutic outcomes and skincare products.[112] However, ethosomes have some limitations, such as the complex preparation process, which reduces production efficiency, limited stability, and potential skin irritation or incompatibility with certain drugs.[113–117]

Addressing these limitations through optimization of composition and preparation methods and suitable formulations is crucial. Further, *in vivo* studies are needed to comprehensively understand the potential benefits and limitations of ethosomes as a drug delivery system.[118,119]

Examples of nanotherapeutic approaches in RA treatment

RA autoimmune activation involves the overactivation of T cells, autoantibody-producing B cells, and the continuous production of inflammatory cytokines (*e.g.*, TNF-α, IL-1, IL-6). The effectiveness of anti-inflammatory therapeutics is often hindered by their toxicity to both inflamed and healthy cells, limiting their use in clinics. To overcome this challenge, lipid-based nanocarriers have gained attention recently. Lipid-based nanoformulations alleviate this autoimmunity by enhancing drug delivery, modulating immune responses, and reducing systemic toxicity. These nanocarriers, made from physiological-like lipids, are well tolerated, generally non-toxic, and are broken down into harmless residues. In the past decade, many researchers have focused on exploiting innovative lipid-based nanocarriers, such as liposomes, niosomes, ethosomes, transfersomes, SLNs and lipid nano-emulsions. These nanocarriers provide a safe way to deliver anti-inflammatory drugs in a time and location-controlled way selectively. Table 3 provides an extensive revision of lipid-based NPs' application in RA treatment.[120] For instance, liposomal formulations of dexamethasone (DPPC, DPPG, and cholesterol) have shown prolonged half-life and enhanced targeting effects, significantly reducing joint swelling and inflammation compared to free drug, even at lower dose.[121–123] Similarly, PEGylated liposomes loaded with prednisolone have progressed to clinical trials, showcasing enhanced permeability and retention at inflamed site.[123] Liposomes, thanks to the presence of cholesterol, enhances membrane stability, ensuring sustained drug release in biological fluids like synovial fluids (Fig. 3). When functionalized with ligands or antigens, liposomes can induce tolerance in autoreactive T and B cells. For example, liposomes displaying the joint-homing peptide ART-2, loaded with Dex, preferentially accumulated in arthritic joints and reduced joint swelling and inflammation in both adjuvant induced arthritis (AA) in rats and collagen antibody-induced arthritis (CAIA) in mice models compared to free Dex.[124] Also, liposomes around 100 nm containing steroids such as prednisolone phosphate (PLP) and methylprednisolone hemisuccinate, as well as methotrexate (MTX), enhanced drug stability and encapsulation efficiency *via* passive EPR effect, achieving complete inflammation remission in the joint.[125] Orally administered liposomal bovine lactoferrin

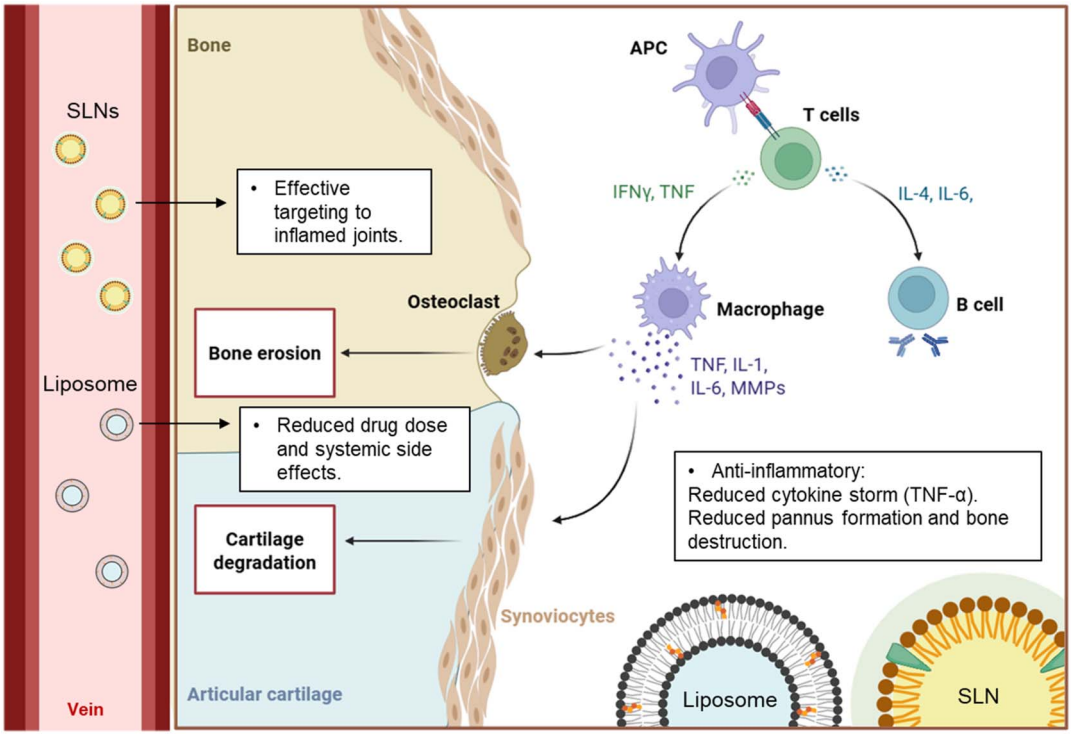


Fig. 3 Mechanism of how liposomes and SLNs can suppress the RA disease. The autoantibodies form immune complexes that deposit in the synovial joints, triggering activation of the complement cascade and resident immune cells. The activation of antigen presenting cells (APCs) can activate $CD4^+$ T cells (especially the Th1 and Th17 subsets) and B cells to infiltrate the synovium. As the disease progresses, macrophages and fibroblast-like synoviocytes (FLS) get activated and produce high levels of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-17, perpetuating a state of chronic synovial inflammation. NPs once administered systemically they can target inflamed joints, with a lower drug dose they can reduce the inflammation of the joints by reducing TNF-α, pannus formation and bone destruction.

(LbLF) in a murine arthritis model suppressed inflammatory progression, reduced TNF-α expression, restored Th17/Treg balance, and prevented pannus formation and bone destruction.[126] Solid lipid nanoparticles (SLNs) have also shown promise. SLNs loaded with prednisolone and coated with hyaluronic acid (HA) exploit CD44 receptor targeting for selective delivery, extending circulation time and increasing therapeutic precision.[127] Another SLN system, conjugated with chondroitin sulfate and co-loaded with methotrexate and aceclofenac, achieved effective targeting of inflamed joints while reducing drug dose and systemic side effects.[128] SLNs can protect drugs from degradation, providing controlled release of immunosuppressive agents such as MTX or dexamethasone, and reducing the need for high doses to target synovial macrophages and T-cells, mitigating cytokine storms. Oral administration of curcumin-SLNs (10–30 mg kg^{-1}) significantly alleviated arthritis symptoms compared to free curcumin, reducing TNF-α expression, C-reactive protein, citrullinated peptide antibodies, and oxidative/nitrosative stress markers.[129] Topical delivery has been optimized using niosomes, ethosomes and transfersomes, offering non-invasive alternatives for localized treatment. Niosomal ibuprofen and thiocolchicoside formulations enhanced skin retention and prolonged therapeutic effect, reducing dosing frequency and improving pain management.[130–132] Additionally, transfersomes and ethosomes encapsulating curcumin or imatinib demonstrated superior skin penetration and bioavailability, increasing drug efficacy while minimizing systemic exposure.[133,134] The development of diclofenac- and methotrexate-loaded niosomal gels significantly improved skin permeation *versus* standard gels, with greater anti-inflammatory and analgesic effect in mice formalin and edema models.[135] Engineered for transdermal penetration, they can deliver anti-inflammatory drugs in a non-invasive way to the inflamed joints, helping reduce immune activation by concentrating the therapy in the joint (Fig. 4). Collectively, these findings underscore the versatility and clinical potential of lipid-based nanocarriers for the controlled and targeted treatment of RA, offering improved drug efficacy, reduced toxicity, and enhanced patient compliance.

Limitations of lipid-based nanocarriers in RA

Nanomedicine offers promising opportunities for the treatment of RA in clinics, however, there are some limitations that need to be overcome to fully reach RA patients. While NPs can be functionalized to reach specific organs, tissues or cells, achieve selective targeting to the RA environment remains a challenge due to the limited access to joints, as the tissue in that area is very thick and there is not enough blood flow for systemic administration. Furthermore, NPs in circulation suffer from opsonization which can cause the activation of the immune system such as the mononuclear phagocyte system (MPS) that can detect and remove

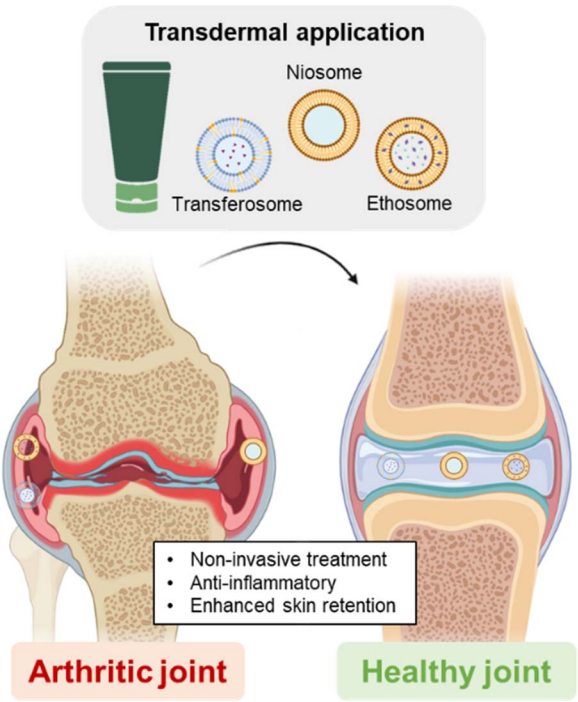


Fig. 4 Mechanism of how transfersome, noisome and ethosome can suppress RA. Once topically administered, the NPs enhance skin retention and reduces the inflammation in the joint.

the nanomaterials from the bloodstream towards organs from the reticuloendothelial system (RES) such as spleen, liver (specifically Kupffer cells), bone marrow, lymph nodes, and lungs (alveolar macrophages). The extended impact of nanomaterials on the human body is still not fully understood, as there are concerns regarding their potential toxicity and effect over time after the accumulation in organs. It is important to prove that the NPs can break down, be degraded after a stimuli or safely removed from the organism to avoid chronic diseases.

Finally, meeting clinical requirements presents a significant challenge *per se*, NPs manufacturing should be scalable, and the process should be reproducible in size, shape and properties. To reach the clinical burden, it is important to conduct clinical trials to evaluate the efficacy and safety of nanomedicines in RA patients, but also, considering that the regulatory pathways are always evolving.

Future perspectives and conclusion

Significant advancements have been made in the treatment of rheumatoid arthritis (RA), yet conventional therapies still face notable limitations, including the necessity for prolonged dosing regimens that can lead to adverse effects. In this context, lipid nanocarriers have emerged as a promising strategy to enhance treatment outcomes. They facilitate the targeted transport of therapeutic agents to inflamed sites, extending drug half-life and improving accumulation in specific tissues while minimizing systemic toxicity.

Among various lipid-based NPs, niosomes stand out as an optimal choice for intra-articular drug delivery.[152,153] These nanocarriers not only offer enhanced stability and controlled release[153] but also surpass conventional liposomes in terms of stability, shelf life, and cost-effectiveness.[154] Their versatility in encapsulating both hydrophilic and hydrophobic drugs underscore their adaptability for delivering a diverse range of therapeutic agents. Furthermore, the amphiphilic bilayer structure of niosomes enables precise drug targeting and efficient delivery mechanisms.[154] While other nanocarrier systems have been investigated for RA treatment, niosomes present a particularly promising alternative due to their superior drug encapsulation capabilities and optimized therapeutic outcomes.[155–157] Administered through intra-articular injection, niosomes provide a targeted approach that minimizes systemic side effects while maximizing therapeutic impact at the site of inflammation.[152] In fact, the inherent biocompatibility, controlled release properties, and ability of niosomes to enhance drug bioavailability within the joint space position them as a leading strategy for the effective and targeted treatment of joint-related disorders such as RA.[153]

Despite the progress made in developing various nanocarrier systems for RA therapy, only a limited number have advanced to clinical trials. Key challenges remain, including instability in circulation, premature drug release prior to reaching inflamed sites, and insufficient targeting capabilities, often resulting in sequestration by the reticuloendothelial system. Other alternatives such as stimuli-responsive hydrogels represent a promising emerging strategy for RA therapy, offering a site-specific sustained drug release in response to the inflamed joint microenvironment, thereby minimizing systemic side effects.[158] Current research efforts are focused on addressing these challenges by developing safer and more efficient nanocarrier systems, with the ultimate goal of revolutionizing RA therapy.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Author contributions

Conceptualization, N. A. and C. F.; writing – original draft preparation, N. R. K. and N. A.; visualization, N. R. K., C. P. and J. F. A.; project administration, N. A. and C. F.; writing – review & editing, N. A., N. S. M. Y., J. M., J. F. A., J. R. M., M. G. R., S. B. and C. F.; The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

The authors declare no competing financial interest.

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