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A NOVEL APPROACH FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder characterized by persistent inflammation that primarily affects the joints but can also involve extra-articular organs such as the heart, lungs, and kidneys. Current treatment modalities, which include nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs), provide symptom relief but are often hindered by off-target effects, short therapeutic half-lives, and systemic toxicity. Nanotechnology has emerged as a promising solution to address these limitations. This review explores various nanoparticle (NP)-based strategies for RA treatment, including lipid-based systems like liposomes, ethosomes, and solid lipid nanoparticles; polymeric nanoparticles; and metallic nanoparticles such as gold, silver, and iron oxide. Thesesystemsenhancedrugdeliverybyimproving stability, facilitating controlled release, and enabling both active and passive targeting of inflamed tissues. The advantages of NP-based therapies include reduced dosing frequency, minimized side effects, and potential theranostic applications, paving the way for more effective and patient-centered management of RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disorder associated with a chronic inflammatory process that can cause damage to both joints and extra-articular organs, including the heart, kidneys, lungs, digestive system, eyes, skin, and nervous system.[1] This chronic systemic autoimmune disease occurs more frequently in females than in males and is predominantly observed in older adults.[2] According to a prevalence rate reported in 2002, RA affects between 0.5% and 1% of the population, with variations noted across different regions.[3] In individuals with RA, the immune system erroneously targets the synovium, the lining of the membranes surrounding the joints, resulting in inflammation, cartilage damage, pain, swelling, and, ultimately, joint deterioration.[4] Various types of arthritis have been studied and classified, which includes differentiating between non-inflammatory arthritis (such as osteoarthritis) and inflammatory arthritis resulting from crystal deposition (including pseudogout and gout), bacterial and viral infections (like those caused by Staphylococcus aureus, Neisseria gonorrhoeae, and certain complications from Lyme disease, as well as viruses such as Parvovirus and Enterovirus), or autoimmune processes.[5]

Pathophysiology

The inflammation associated with rheumatoid arthritis (RA) begins in the synovium. While various mechanisms, including lymphocyte activation, cytokine networks, and the production of pro-inflammatory molecules, trigger the inflammatory response in RA, the exact pathway leading to this response remains unidentified.[6] In reaction to RA inflammation, thesynovialtissueexhibits hyperplasia of the synovial lining due to the accumulation of fibroblast-like synoviocytes (FLS) and macrophage-like synoviocytes (MLS). Notably, the synovial intimal lining in RA can be up to five times deeper than

normal, typically consisting of only one or two cell layers.[7] These macrophages- and fibroblast-like cells contribute to inflammation by producing chemical mediators, including pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), chemokines like interleukin-8 (IL-8), and proteinases, including matrix metalloproteinases (MMPs). As a result, additional macrophages, lymphocytes, and fibroblasts become activated, perpetuating the RA inflammatory process. [8]

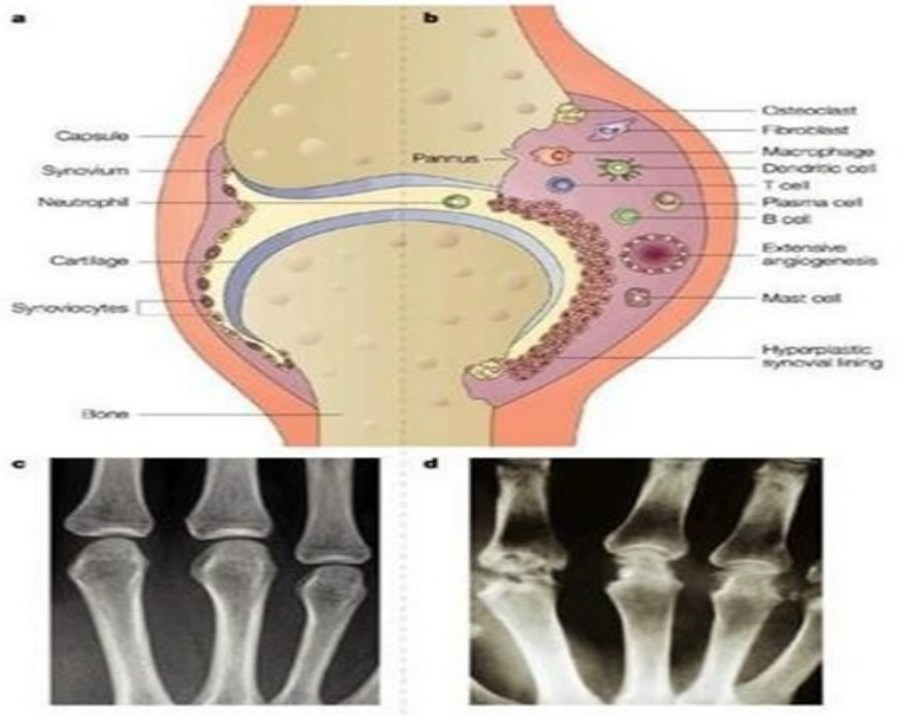

Figure 1 :-

(a) Schematic diagram of a healthy synovial joint;
(b) Schematic diagram of a synovial joint affected by rheumatoid arthritis (RA);
(c) Radiograph of healthy metacarpophalangeal joints;
(d) Radiograph of metacarpophalangeal joints affected by RA.

Challenges in Diagnosis and treatment of Rheumatoid Arthritis

Currently, there is no cure for rheumatoid arthritis (RA). The most frequently utilized conventional treatments for managing this condition include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), and disease-modifying antirheumatic drugs (DMARDs).[9] DMARDs comprise a range of medications, such as antimalarials (chloroquine and hydroxychloroquine), sulfasalazine, gold compounds (auranofin and sodium aurothiomalate), penicillamine, and immunosuppressants (including methotrexate, adalimumab, anakinra, azathioprine, cyclosporin, cyclophosphamide, etanercept, infliximab, and leflunomide)[10]. Advances in molecular and cell biology have identified numerous promising molecules and pathways that can be targeted for interventions in immunologic and inflammatory diseases. Consequently, several biological DMARDs have been developed. There is a growing emphasis on the early diagnosis and treatment of RA with DMARDs, which, when used in combination with other medications, have demonstrated effectiveness in controlling disease progression in many patients.[11].

It is believed that most DMARDs work by inhibiting the release or activity of cytokines that play a key role in sustaining the inflammatory process, although additional mechanisms may also be involved. The systemic administration of these agents often leads to indiscriminate distribution and a lack of specificity for the affected organs or tissues in rheumatoid arthritis (RA), which can result in

extraarticular adverse effects. Furthermore, due to their short half-life and inadequate concentrations at the site of action, these agents typically require high and frequent dosing, which can lead to severe side effects and significant costs. To address these challenges, the development of new agents and therapeutic strategies has been suggested. A notable example of such strategies includes the use of innovative drug delivery systems like nanoparticles (NPs).[12]

Nanotechnology and nanoparticles (NPs)are important in biology, offering new ways to image, sense, deliver drugs,and study biological processes.[13] The main benefits of NPs include their capacity to protect drugs, deliver them to specific areas, control how they are released,and be produced in large amounts. Drug targeting with NPs can happen through passive or active methods. Passive targeting uses the properties of the particles and how macrophages in inflamed joints take them up,a process known as the enhanced permeability and retention (EPR) effect.

[14] However, when drugs are given systemically, they often face problems like being quickly removed by macrophages in the reticuloendothelial system (RES).[15] To deal with these challenges, scientists are working on surface modifications and active targeting strategies that use ligands such as peptides and antibodies. In this review, I will cover different new methods being used to treat rheumatoid arthritis.[16]

TYPES OF NPs USED IN TREATMENT OF RA :-

{A} LIPID BASED NPs

a. Liposomes

Over the years, liposomes have garnered considerable attention as a carrier system for therapeutic compounds due to their distinctive properties.[17] These properties include the ability to encapsulate both hydrophilic and hydrophobic drugs, exceptional biocompatibility, low toxicity, minimal immune system activation, and the capacity to deliver bioactive compounds directly to their target sites.[18] A liposome is defined as a microscopic vesicle featuring an aqueous core encased by one or more natural phospholipid bilayers.[19] This structural composition renders liposomes versatile delivery systems, capable of accommodating a wide range of compounds while ensuring high biocompatibility. [20]

The biphasic nature of liposomes enables them to transport both hydrophilic (water-soluble) and lipophilic (fat- soluble) drugs. The positioning of drug molecules within the liposome is determined by their solubility and partitioning characteristics, which significantly influence their entrapment and release behavior. Lipophilic drugs are typically integrated within the lipid bilayers, where their limited water solubility helps to minimize drug loss during storage. In contrast, hydrophilic drugs can be encapsulated within the aqueous core or remain in the surrounding water phase. This adaptability makes liposomes an exceptionally effective drug delivery system.[21]

The liposome system is increasingly utilized to enhance the efficacy of rheumatoid arthritis treatments.[22] When administered intravenously, liposomes accumulate in the synovial tissue of patients with rheumatoid arthritis.[23] Studies have shown that liposomes containing cholesterol and phosphatidylcholine encapsulated with clodronate, when given to arthritic rats, lead to a reduction in bone resorption due to their anti-inflammatory properties.[24] These liposomes demonstrate a decrease in joint inflammation and reduced toxicity.[25] One notable example is the stealth liposome, which enhances the therapeutic efficacy of glucocorticoids commonly administered intravenously, while minimizing non-specific organ toxicity. [25]

b. Ethosome

Ethanol influences the intercellular regions of the stratum corneum and serves as a permeation enhancer. When incorporated in relatively high concentrations alongside phospholipids and water, it forms a soft vesicular structure known as an Ethosome. [26] These carriers significantly improve drug delivery

through the skin. The vesicle formation, characterized by soft and malleable structures, is attributed to the fluidizing effect of ethanol on the phospholipid bilayer. Ethanol concentrations typically range from 20% to 50%. By disrupting the bilayer of the stratum corneum and increasing its fluidity, ethanol facilitates the penetration of ethosomes. This, in turn, promotes the fusion of the ethosomes with the cell membrane in the deeper layers of the skin, triggering drug release.[27]

c. Transferosomes

A specialized type of liposome, known for its highly flexible, elastic, and ultradeformable structure, is composed of phospholipids, such as phosphatidylcholine, combined with edge activators including sodium cholate, deoxycholate, Span 80, and Tween 80.[28] Transferosomes are ultra-flexible lipid vesicles made of phospholipids and edge activators. Their deformability allows them to squeeze through the skin's stratum corneum and deliver drugs into deeper layers. They can carry both hydrophilic and lipophilic drugs, and surface modification enables targeted and controlled release. In RA therapy, transferosomes improve drug penetration, provide sustained release, and reduce systemic side effects.[29] Studies have shown that indomethacin-, celecoxib-, and capsaicin-loaded transfer osomal gels offer better skin penetration, stronger anti-inflammatory action, and superior anti-arthritic activity compared to conventional or marketed gels.[30]

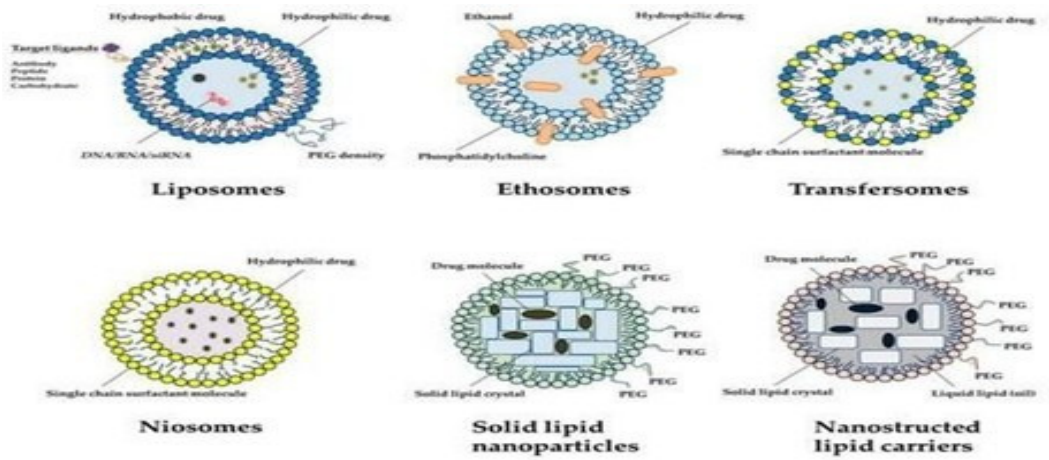

Figure 2. This is an overview of various lipid nanocarrier systems utilized in the treatment of arthritic diseases, summarized

In summary

liposomes are generally made up of natural phospholipids, which are a fundamental component of most biological membranes. Ethosomes consist of lipid vesicles that include phospholipids and a significant amount of ethanol. Transfersomes are specialized liposomes with deformable characteristics that allow them to penetrate the stratum corneum and deeply infiltrate the skin. Solid lipid nanoparticles are composed of a mixture of solid lipids dispersed within inner cores. Nanostructured lipid carriers are created from a combination of solid and liquid lipids within the cores. Note: PEG stands for polyethylene glycol.

d. Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) have emerged as a promising approach for enhancing the cutaneous delivery of both hydrophilic and lipophilic drugs, outperforming conventional vehicles. These spherical colloidal systems typically have an average diameter ranging from 40 to 1000 nm. SLNs comprise a high- melting-point lipid core surrounded by surfactants, and they are sometimes coated with hydrophilic polymers to enhance their colloidal stability. The lipid matrix can include

materials such as beeswax, stearic acid, cholesterol, glyceryl stearate (both mono- and tri-), solid paraffin, and behenic acid. Various other components, including surfactants, co- surfactants, preservatives, cryoprotectants, and charge modifiers, are also utilized in the preparation of SLNs.[31]

SLNs offer numerous advantages: they exhibit high physical stability, minimal skin irritation, controlled drug release, protection of sensitive drugs from degradation, and excellent in vivo tolerability.[32] They are particularly effective in increasing the bioavailability of poorly soluble drugs and achieving targeted therapy through the incorporation of specific targeting ligands on their surfaces. Upon topical application, SLNs enhance skin hydration and adhesion. They form a monolayer on the skin, which provides occlusive properties, thereby reducing moisture loss. This process decreases corneocyte packing and opens intercorneocyte gaps, facilitating the penetration of the drug into the deeper layers of the skin. [33]

e. Nanoemulsions

Nanoemulsions (NEs) are transparent, isotropic, and kinetically stable colloidal dispersions with particle sizes below 200 nm. They typically comprise emulsified oil, water, and amphiphilic molecules [34]. NEs are extensively utilized as drug delivery systems, particularly for poorly soluble and permeable drugs such as MLX, EXB, and CLX, as they enhance drug solubility, loading capacity, and, ultimately, bioavailability. The small droplet size enables effective skin penetration, improving drug delivery while circumventing chemical or enzymatic degradation in the gut and avoiding the first-pass metabolism associated with oral administration [35].

{B} POLYMERIC BASED NPs

Polymeric nanoparticles (NPs) are currently under investigation as a potential therapeutic option. The development of these nanoparticles involved the use of betamethasone disodium phosphate (BSP), [36] polylactic acid, and monomethoxy polyethylene glycol (PEG)-polylactide block copolymers, which were evaluated for their efficacy in reducing inflammation [37]. The results indicate that these nanoparticles are effective anti-inflammatory agents. The increased permeability at the site of injury facilitates the accumulation of BSP. Furthermore, the absence of PEG leads to an increase in macrophage activity, which promotes the hydrolysis of polymers, thereby releasing BSP from the cells.[38]

Polymeric systems offer numerous advantages, including enhanced stability in the bloodstream, controlled drug release, targeted delivery to specific sites, improved bioavailability [39], protection against degradation due to pH and enzymatic activity, and overall nontoxicity and biodegradability. [40] The accumulation of inflammatory mediators, such as cytokines and macrophages within synovial cells, is a significant trigger for the autoimmune response observed in rheumatoid arthritis (RA).[41] Polymer-based materials can be effectively utilized to deliver antirheumatic medications and immunosuppressive cytokines, such as IL-23 and TNF-α. [42]

Biopolymeric nanoparticulate drug delivery systems are rapidly advancing, as they strategically protect active molecules from in vivo and in vitro degradation.[43] This technology reduces the administration frequency and enhances circulating levels, thereby allowing for the manipulation of biological activity to optimize therapeutic efficacy.[44] Chitosan, the sole natural polysaccharide exhibiting a positive charge, is extensively employed for the delivery of proteins and nucleic acids[45]. Various methodologies for preparing chitosan nanoparticles using compounds such as sulfate, citrate, and tripolyphosphate have been documented.[46] Nanospheres composed of densely concentrated chitosan molecules have also been reported as potential“fusogens.”The diminutive size of chitosan nanoparticles enables their transit across cell membranes to facilitate drug delivery into the cytosol [47] Duetotheir bioadhesive properties, biodegradability, and

biocompatibility, chitosan nanoparticles (CHNP) are recognized as an effective drug delivery system.[48] The positive charge of CHNP further enhances their absorption, and their ease of delivery via both parenteral and non-parenteral routes renders them a more appealing drug delivery option. [49]

{C} METALLIC BASED NPs

a. Iron Oxide NPs

Iron oxide nanoparticles (NPs) represent an intriguing nanosystem due to their unique physical properties, biocompatibility, cost-effectiveness, and ability to target specific sites while minimizing damage to surrounding tissues. [50]These magnetic NPs can be co-encapsulated with drug molecules within nanoparticles made from other materials, such as poly (lactic-co-glycolic acid) (PLGA). As a well- defined, biodegradable, and biocompatible polymer, PLGA has garnered significant attention. When iron oxide NPs are co-encapsulated within drug-loaded PLGA nanoparticles, they become shielded from degradation, enabling persistent and controlled drug release. [51] Additionally, it is possible to modify the surface properties of these NPs to enhance stealth and selectivity towards specific cells, organs, or tissues.[52] Moreover, iron oxide NPs can serve as imaging contrast agents, showcasing the application of nanotechnology in medical monitoring and diagnosis. [53]These nanoparticles function as both passive and active targeting imaging agents, typically in the form of superparamagnetic iron oxide nanoparticles (SPIONs), which consist of an iron oxide core coated with hydrophilic dextran or another biocompatible compound to enhance their stability.[54]

b. Silver NPs

Silver nanoparticles (Ag NPs) have been recognized for their anti-inflammatory properties, particularly in reducing the production of proinflammatory cytokines such as TNF-α and IL-6, [55] which can be beneficial for patients with rheumatoid arthritis (RA). Additionally, Ag NPs can lower levels of vascular endothelial growth factor (VEGF), [56] a factor produced by epithelial cells that enhances antigen sensitivity, contributes to physiological abnormalities, and causes plasma proteins to leak into the extracellular space.[57] This, in turn, leads to thickening of the airway wall and heightens T helper type-2 (TH2) cell-mediated inflammation characterized by IL-9, IL-4, IL-5, and IL-13.[58]

Ag NPs inhibit the Src kinase pathway and block Y419 phosphorylation in a dose-dependent manner, which reduces the vascular endothelial permeability induced by VEGF and IL-1β. They also prevent VEGF and IL-1β- induced solute flux while decreasing VEGF-induced cell production.[59] Furthermore, Ag NPs can diminish the expression of hypoxia-inducible factor 1 alpha (HIF-1α), a regulator of proinflammatory gene expression, and possess[60] antibacterial properties. Ultimately, Ag NPs can curtail the secretion of proinflammatory mediators, such as TNF-α, IL-12, and COX-2, at higher concentrations. [61]

c. Gold NPs

Gold nanoparticles (GNPs) are promising nanomaterials with distinct physical, chemical, and optical properties that make them highly valued in nanotechnology and bio-nanotechnology. [62] Their numerous advantageous characteristics including ease of fabrication, high stability, resistance to oxidation, water solubility, plasmon resonance, high surface reactivity, considerable drug-loading capacity, low cytotoxicity, and cost- effectiveness[63] have prompted extensive research and exploration of their potential applications across various fields such as engineering, chemistry, and biomedicine. GNPs, in particular, have emerged as ideal metal nanomaterials for medical applications due to their biocompatibility and inert nature.[64]

Moreover, GNPs can provide therapeutic options beyond traditional gold salts, including enhancing radiotherapy through their preferential absorption of X-rays, thanks to their higher atomic number.[65] The ease of functionalizing GNPs with a variety of molecules further expands their therapeutic

possibilities, enabling innovative approaches to combination therapies and theragnostic.[66] Research has confirmed that GNPs serve as effective carriers for a wide range of therapeutic agents, including antineoplastic drugs, antioxidants, antibiotics,proteins,nucleicacids,andglucose.[67]

Among the various shapes of GNPs, nanospheres and nanorods are particularly favored for biomedical applications due to their well-defined synthesis. The functionalization of GNPs with various therapeutic targeting agents has significantly broadened their application scope.[68] Their successful utilization in numerous biomedical areas—such as diagnostics, therapeutics, vaccine development, drug and gene delivery, imaging, and electrochemical biosensors[69] has been achieved through careful control of particle size and shape during synthesis, as well as appropriate modification with functionalizing groups.[70]

Advantages of Nanoparticle-Based Approaches in treatment of RA

The nanoparticles delivery system is characterized by particle formulations that are dispersed at the nanoscale. The National Nanotechnology Initiative (NNI) defines nanoparticles as structures with dimensions ranging from 1 to 100 nanometers.[71] This specific size range allows for straightforward characterization through visual observation. Typically, nanoparticles exhibit a slightly transparent appearance and demonstrate a reduced precipitating time compared to larger particles exceeding 100 nanometers in size.[72]

There are two primary categories of nanoparticles based on their preparation: nanospheres and nanocapsules. Nanospheres possess a monolithic structure in which the active compound is either actively dispersed throughout the surface or adsorbed onto the surface of the carrier matrix.[73] In contrast, nanocapsules exhibit a membrane- like structure, wherein the active compound is encapsulated within the 'core' of the structure or adsorbed onto the membrane's surface. Nevertheless, classifying nanoparticle complexes strictly as either nanospheres or nanocapsules presents a challenge.[74]

The utilization of nanoparticles offers several advantages due to their diminutive size, which facilitates penetration into intercellular spaces and cell walls, surpassing larger particles in this regard.[75] Furthermore, nanoparticles exhibit the versatility to integrate with other technologies.[76] These particles can effectively encapsulate drugs, safeguarding them from degradation while enhancing targeted delivery. Additionally, nanoparticles enable modifications in drug release profiles and can be produced on a large scale with reproducibility.[77]

The diverse physical and chemical properties of nanoparticles significantly influence the biomedical potential of the encapsulated drugs, impacting factors such as bioavailability and biodistribution.[78] The application of particulate nanomaterials as drug carriers results in the accumulation of nanoparticles within the mononuclear phagocytic system, predominantly located in the spleen and liver.[80]

Consequently, utilizing nanoparticles for targeted liver delivery presents a promising approach for developing therapeutic strategies for liver diseases.[81

Moreover, the surface modification of nanoparticles, particularly with polyethylene glycol (PEG), has been shown to extend their circulation time, diminish in vitro toxicity, and prevent agglomeration, which can lead to the destabilization of nanoparticle suspensions. [82].One significant advantage of drugs formulated as nanoparticles is their excellent storagestability.[83] The reduced Particles of these nanoparticle-based dosage forms minimizes the risks of creaming or sedimentation, as a result of decreased gravitational effects and enhanced Brownian motion.[84] Additionally, the small particle size helps to prevent flocculation, which enables the drugs to be stored for extended periods without compromising their effectiveness.[85].

SUMMARY

Rheumatoid arthritis (RA) is a debilitating autoimmune disorder characterized by chronic joint inflammation, synovial hyperplasia, and systemic involvement of organs. Traditional therapeutic methods, which include non- steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and disease-modifying antirheumatic drugs (DMARDs), primarily focus on symptom management and the attenuation of disease progression. Nonetheless, these approaches are often limited by systemic side effects, a requirement for frequent dosing, and insufficient specificity in targeting affected areas.

Nanotechnology represents a significant advancement in drug delivery systems that effectively address these limitations by utilizing nanoparticles (NPs) to enhance therapeutic outcomes. NPs confer numerous advantages, such as the encapsulation of pharmaceutical agents to safeguard them from degradation, targeted delivery to inflamed tissues, and controlled release profiles. Lipid-based systems, which include liposomes and ethosomes, are particularly noteworthy due to their capacity to incorporate both hydrophilic and hydrophobic drugs, thus improving penetration into inflamed sites. Polymeric nanoparticles exhibit enhanced bioavailability, increased stability within the bloodstream, and the ability to selectively target specific inflammatory mediators, such as cytokines. Additionally, metallic nanoparticles, including gold, silver, and iron oxide, offer unique therapeutic and diagnostic functionalities, such as imaging capabilities and modulation of inflammatory responses.

Each category of nanoparticles presents distinct advantages. For example, liposomes facilitate the accumulation of drugs in synovial tissues via passive targeting mechanisms, while ethosomes promote transdermal delivery with enhanced permeability. Polymeric nanoparticles can achieve a controlled and sustained release of anti- inflammatory agents, thereby reducing the frequency of dosing. Meanwhile, metallic nanoparticles provide the diagnostic benefits by enabling real-time imaging of inflammatory processes while simultaneously delivering therapeutic agents.

Despite the promising results observed thus far, there remain significant challenges to clinical translation. These challenges include ensuring biocompatibility, scaling production processes, and establishing long-term safety profiles. Current research is focused on optimizing nanoparticle formulations as well as integrating passive and active targeting strategies to improve specificity and therapeutic efficacy. Therefore, nanotechnology represents a transformative approach to the treatment of rheumatoid arthritis, with the potential to diminish systemic toxicity, enhance patient adherence, and facilitate superior control over disease progression.

CONCLUSION

Nanotechnology is transforming the therapeutic landscape for rheumatoid arthritis by addressing persistent challenges associated with traditional treatments. Nanoparticles (NPs) present innovative strategies for delivering pharmaceuticals directly to inflamed tissues, thereby minimizing systemic exposure and enhancing therapeutic efficacy. Lipid-based nanoparticles, including liposomes and ethosomes, serve as versatile drug delivery platforms characterized by high biocompatibility and the capacity to encapsulate a wide variety of drug types. Polymeric nanoparticles, on the other hand, extend drug stability and facilitate targeted release, while metallic nanoparticles such as gold and silver are notable for their unique dual functionalities in both treatment and diagnostics.

The advantages of these nanoparticle systems encompass reduced dosing frequency, diminished side effects, and improved drug bioavailability, all contributing to a significant enhancement in patients' quality of life. Furthermore, their integration within theranostics merges diagnostic and therapeutic capabilities, providing a more holistic approach to disease management. Nonetheless, challenges such as production scalability, cost- effectiveness, and long-term safety must be addressed to facilitate widespread clinical adoption.

In summary, although still in the developmental phases, nanotechnology possesses considerable potential to redefine the treatment of rheumatoid arthritis by aligning efficacy with precision. Ongoing research,

alongside regulatory approvals and clinical trials will be crucial for translating these advancements into standard clinical practice. By incorporating advanced nanocarrier systems with existing therapeutic strategies, the management of rheumatoid arthritis can achieve a new echelon of effectiveness and patient-centred care.

REFERENCES

1. Hasan AA, Khudhur HR, Hameed AK. Rheumatic autoimmune diseases (focus on RA): prevalence, types, causes and diagnosis. Karbala Journal of Pharmaceutical Sciences. 2022 Jan 1;1(20).
2. Angum F, Khan T, Kaler J, Siddiqui L, Hussain A. The prevalence of autoimmune disorders in women: a narrative review. Cureus. 2020 May 13;12(5).
3. Otón T, Carmona L. The epidemiology of established rheumatoid arthritis. Best Practice & Research Clinical Rheumatology. 2019 Oct 1;33(5):101477.
4. Peng R, Peng Y, Zou Y, Li Z, Zha Z, Zhang H. The basic and research progress of joint barrier dysfunction in joint diseases. Guidelines and Standards in Chinese Medicine. 2025:10-97
5. Moura C da C. Development of multifunctional nanoparticles for targeted therapy and imaging of rheumatoid arthritis [Master's thesis]. Porto: Faculty of Engineering, University of Porto; 2013
6. Fang Q, Zhou C, Nandakumar KS. Molecular and cellular pathways contributing to joint damage in rheumatoid arthritis. Mediators of inflammation. 2020;2020(1):3830212.
7. Masoumi M, Bashiri H, Khorramdelazad H, Barzaman K, Hashemi N, Sereshki HA, Sahebkar A, Karami J. Destructive roles of fibroblast-like synoviocytes in chronic inflammation and joint damage in rheumatoid arthritis. Inflammation. 2021 Apr;44(2):466-79.
8. Royaei M, Tahoori MT, Bardania H, Shams A, Dehghan A. Amelioration of inflammation through reduction of oxidative stress in rheumatoid arthritis by treating fibroblast-like synoviocytes (FLS) with DMF-loaded PLGA nanoparticles. International Immunopharmacology. 2024 Mar 10;129:111617.
9. Dar E, Abbas M, Nazir S, Abbas M. Novel Management, Cure and Complications-Control of Rheumatoid Arthritis with Traditional and Modern Remedies (A Review). Pharmaceutical Chemistry Journal. 2024 Oct;58(7):1020-8.
10. Pawar AT, Baheti AM, Adate-More P, Upaganlawar A. Conventional Therapy for Rheumatoid Arthritis. Frontiers in Arthritis. 2022 Aug 19:26.
11. Prasad P, Verma S, Surbhi, Ganguly NK, Chaturvedi V, Mittal SA. Rheumatoid arthritis: advances in treatment strategies. Molecular and cellular biochemistry. 2023 Jan;478(1):69-88.
12. Ding Q, Hu W, Wang R, Yang Q, Zhu M, Li M, Cai J, Rose P, Mao J, Zhu YZ. Signaling pathways in rheumatoid arthritis: implications for targeted therapy. Signal transduction and targeted therapy. 2023 Feb 17;8(1):68.
13. Zhang RX, Li J, Zhang T, Amini MA, He C, Lu B, Ahmed T, Lip H, Rauth AM, Wu XY. Importance of integrating nanotechnology with pharmacology and physiology for innovative drug delivery and therapy–an illustration with firsthand examples. Acta Pharmacologica Sinica. 2018 May;39(5):825-44.
14. Croitoru GA, Pirvulescu DC, Niculescu AG, Grumezescu AM, Antohi AM, Nicolae CL. Metallic nanomaterials–targeted drug delivery approaches for improved bioavailability, reduced side toxicity, and enhanced patient outcomes. Romanian Journal of Morphology and Embryology. 2024 Jun 30;65(2):145.
15. Dalmo RA, Ingebrigtsen K, Bøgwald J. Non-specific defence mechanisms in fish, with particular reference to the reticuloendothelial system (RES). Journal of fish diseases. 1997 Jul;20(4):241-73.
16. Emami J, Ansarypour Z. Receptor targeting drug delivery strategies and prospects in the treatment of rheumatoid arthritis. Research in Pharmaceutical Sciences. 2019 Dec 1;14(6):471-87.

17. Liu P, Chen G, Zhang J. A review of liposomes as a drug delivery system: current status of approved products, regulatory environments, and future perspectives. Molecules. 2022 Feb 17;27(4):1372.
18. Klojdová I, Milota T, Smetanová J, Stathopoulos C. Encapsulation: a strategy to deliver therapeutics and bioactive compounds?. Pharmaceuticals. 2023 Feb 27;16(3):362.
19. Musumeci T, Bonaccorso A, Carbone C. Basic concepts of liposomes: Components, structures, properties and classification. In Liposomes in Drug Delivery 2024 Jan 1 (pp. 19-48). Academic Press.
20. Nsairat H, Khater D, Sayed U, Odeh F, Al Bawab A, Alshaer W. Liposomes: structure, composition, types, and clinical applications. Heliyon. 2022 May 1;8(5).
21. Safaeian Laein, S., Katouzian, I., Mozafari, M.R., Farnudiyan-Habibi, A., Akbarbaglu, Z., Shadan, M.R. and Sarabandi, K., 2024. Biological and thermodynamic stabilization of lipid-based delivery systems through natural biopolymers; controlled release and molecular dynamics simulations. *Critical Reviews in Food Science and Nutrition*, *64*(22), pp.7728- 7747.
22. erreira-Silva M, Faria-Silva C, Viana Baptista P, Fernandes E, Ramos Fernandes A, Corvo ML. Liposomal nanosystems in rheumatoid arthritis. Pharmaceutics. 2021 Mar 27;13(4):454.
23. Bruno MC, Cristiano MC, Celia C, d'Avanzo N, Mancuso A, Paolino D, Wolfram J, Fresta M. Injectable drug delivery systems for osteoarthritis and rheumatoid arthritis. ACS nano. 2022 Dec 13;16(12):19665-90.
24. Ferreira-Silva M, Faria-Silva C, Viana Baptista P, Fernandes E, Ramos Fernandes A, Corvo ML. Liposomal nanosystems in rheumatoid arthritis. Pharmaceutics. 2021 Mar 27;13(4):454.
25. Abdellatif, A.A., Mohammed, H.A., Khan, R.A., Singh, V., Bouazzaoui, A., Yusuf, M., Akhtar, N., Khan, M., Al-Subaiyel, A., Mohammed, S.A. and Al-Omar, M.S., 2021. Nano-scale delivery: A comprehensive review of nano-structured devices, preparative techniques, site-specificity designs, biomedical applications, commercial products, and references to safety, cellular uptake, and organ toxicity. *Nanotechnology Reviews*, *10*(1), pp.1493-1559.
26. Natsheh H, Touitou E. Phospholipid vesicles for dermal/transdermal and nasal administration of active molecules: The effect of surfactants and alcohols on the fluidity of their lipid bilayers and penetration enhancement properties. Molecules. 2020 Jun 27;25(13):2959.
27. Abdallah MH, Shahien MM, El-Horany HE, Ahmed EH. Modified Phospholipid Vesicular Gel for Transdermal Drug Delivery: The Influence of Glycerin and/or Ethanol on Their Lipid Bilayer Fluidity and Penetration Characteristics. Gels. 2025 May 13;11(5):358.
28. Musumeci T, Bonaccorso A, Carbone C. Basic concepts of liposomes: Components, structures, properties and classification. InLiposomes in Drug Delivery 2024 Jan 1 (pp. 19-48). Academic Press.
29. Alarcon JF, Karusan NR, Presciutti C, Miras J, Magana JR, Guerra-Rebollo M, Borrós S, Ahmad N, Fornaguera C. Revolutionizing rheumatoid arthritis therapy: the potential of lipid nanocarriers. RSC advances. 2025;15(33):27388-402.
30. Shang H, Younas A, Zhang N. Recent advances on transdermal delivery systems for the treatment of arthritic injuries: From classical treatment to nanomedicines. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2022 May;14(3):e1778.
31. Viegas C, Patrício AB, Prata JM, Nadhman A, Chintamaneni PK, Fonte P. Solid lipid nanoparticles vs. nanostructured lipid carriers: a comparative review. Pharmaceutics. 2023 May 25;15(6):1593.
32. Souto EB, Fangueiro JF, Fernandes AR, Cano A, Sanchez-Lopez E, Garcia ML, Severino P, Paganelli MO, Chaud MV, Silva AM. Physicochemical and biopharmaceutical aspects influencing skin permeation and role of SLN and NLC for skin drug delivery. Heliyon. 2022 Feb 1;8(2).
33. Sharma S, Ghosh R, Marianesan AB, Hussain S, Pandey JD, Kumar M. Nanostructured lipid carriers in Rheumatoid Arthritis: treatment, advancements and applications. Inflammopharmacology. 2025 Mar 2:1-8.
34. Wang X, Anton H, Vandamme T, Anton N. Updated insight into the characterization of nano-emulsions. Expert Opinion on Drug Delivery. 2023 Jan 2;20(1):93-114.
35. Maurya R, Vikal A, Patel P, Narang RK, Kurmi BD. Enhancing oral drug absorption: overcoming

physiological and pharmaceutical barriers for improved bioavailability. AAPS PharmSciTech. 2024 Oct 1;25(7):228
36. Iddique R, Mehmood MH, Haris M, Saleem A, Chaudhry Z. Promising role of polymeric nanoparticles in the treatment of rheumatoid arthritis Inflammopharmacology. 2022 Aug;30(4):1207-18.
37. Puricelli C, Gigliotti CL, Stoppa I, Sacchetti S, Pantham D, Scomparin A, Rolla R, Pizzimenti S, Dianzani U, Boggio E, Sutti S. Use of poly lactic-co-glycolic acid nano and micro particles in the delivery of drugs modulating different phases of inflammation.Pharmaceutics. 2023 Jun 20;15(6):1772.
38. Janko C, Civelek M, Cicha I, Spielvogel H, Unterweger H, Alexiou C. Nanoparticles for the treatment of inflammatory conditions. Nanomedicine. 2024 Jan 1;19(2):103-7.
39. Jain KK. An overview of drug delivery systems. Drug delivery systems. 2019 Aug 22:1-54.
40. Ma B, Martín C, Kurapati R, Bianco A. Degradation-by-design: how chemical functionalization enhances the biodegradability and safety of 2D materials. Chemical Society Reviews. 2020;49(17):6224-47.
41. Fang Q, Zhou C, Nandakumar KS. Molecular and cellular pathways contributing to joint damage in rheumatoid arthritis. Mediators of inflammation. 2020;2020(1):3830212.
42. Placha D, Jampilek J. Chronic inflammatory diseases, anti-inflammatory agents and their delivery nanosystems. Pharmaceutics. 2021 Jan 6;13(1):64.
43. Barik SR, Mohapatra RK, Mohapatra PK, Mahal A, El-Ajaily MM. Recent developments in biopolymeric nanoparticles for drug delivery systems: an overview. Micro and Nanosystems. 2022 Jun 1;14(2):92-100.
44. Kutova OM, Guryev EL, Sokolova EA, Alzeibak R, Balalaeva IV. Targeted delivery to tumors: multidirectional strategies to improve treatment efficiency. Cancers. 2019 Jan 0;11(1):68.
45. karayianni M, Sentoukas T, Skandalis A, Pippa N, Pispas S. Chitosan-based nanoparticles for nucleic acid delivery: technological aspects, applications, and future perspectives. Pharmaceutics. 2023 Jun 29;15(7):1849.
46. Jha R, Mayanovic RA. A review of the preparation, characterization, and applications of chitosan nanoparticles in nanomedicine. Nanomaterials. 2023 Apr 7;13(8):1302.
47. de Almeida Soares F. *Development of hybrid nanosystems based on membrane lipids as SPIONs nanocarriers for Staphylococcus aureus biofilms disruption* (Master's thesis, Universidade do Porto (Portugal)).
48. Mikušová V, Mikuš P. Advances in chitosan-based nanoparticles for drug delivery. International journal of molecular sciences. 2021 Sep 6;22(17):9652.
49. Mohammed MA, Syeda JT, Wasan KM, Wasan EK. An overview of chitosan nanoparticles and its application in non-parenteral drug delivery. Pharmaceutics. 2017 Nov 20;9(4):53.
50. Singh P, Pandit S, Balusamy SR, Madhusudanan M, Singh H, Amsath Haseef HM, Mijakovic I. Advanced nanomaterials for cancer therapy: gold, silver, and iron oxide nanoparticles in oncological applications. Advanced Healthcare Materials. 2025 Feb;14(4):2403059.
51. Perinelli DR, Cespi M, Bonacucina G, Palmieri GF. PEGylated polylactide (PLA) and poly (lactic-co-glycolic acid)(PLGA) copolymers for the design of drug delivery systems. Journal of pharmaceutical investigation. 2019 Jul 1;49(4):443-58.
52. Fam SY, Chee CF, Yong CY, Ho KL, Mariatulqabtiah AR, Tan WS. Stealth coating of nanoparticles in drug-delivery systems. Nanomaterials. 2020 Apr 20;10(4):787.
53. Rahman M. Magnetic resonance imaging and iron-oxide nanoparticles in the era of personalized medicine. Nanotheranostics. 2023 Aug 21;7(4):424.
54. Nelson NR, Port JD, Pandey MK. Use of superparamagnetic iron oxide nanoparticles (SPIONs) via multiple imaging modalities and modifications to reduce cytotoxicity: an educational review. Journal of Nanotheranostics. 2020 Dec 9;1(1):105-35.
55. Carvalho-Silva JM, Dos Reis AC. Anti-inflammatory action of silver nanoparticles in vivo: systematic review and meta-analysis. Heliyon. 2024 Jul 30;10(14).
56. Persson CG, Erjefalt JS, Greiff L, Andersson M, Erjefalt I, Godfrey RW, Korsgren M, Linden M,

Sundler F, Svensson C. Plasma-derived proteins in airway defence, disease and repair of epithelial injury. European Respiratory Journal. 1998 Apr 1;11(4):958-70.
57. Hirose K, Iwata A, Tamachi T, Nakajima H. Allergic airway inflammation: key players beyond the Th2 cell pathway. Immunological reviews. 2017 Jul;278(1):145-61.
58. Hosseinikhah SM, Barani M, Rahdar A, Madry H, Arshad R, Mohammadzadeh V, 58 Cucchiarini M. Nanomaterials for the diagnosis and treatment of inflammatory arthritis. International Journal of Molecular Sciences. 2021 Mar 18;22(6):3092.
59. Yang T, Yao Q, Cao F, Liu Q, Liu B, Wang XH. Silver nanoparticles inhibit the function of hypoxia-inducible factor-1 and target genes: insight into the cytotoxicity and antiangiogenesis. International journal of nanomedicine. 2016 Dec 8:6679-92.
60. Carvalho-Silva JM, Dos Reis AC. Anti-inflammatory action of silver nanoparticles in vivo: systematic review and meta-analysis. Heliyon. 2024 Jul 30;10(14).
61. Panahi Y, Mohammadhosseini M, Nejati-Koshki K, Abadi AJ, Moafi HF, Akbarzadeh A, Farshbaf M. Preparation, surface properties, and therapeutic applications of gold nanoparticles in biomedicine. Drug research. 2017 Nov;11(02):77-87.
62. Goshisht MK, Goshisht A, Bajpai A, Bajpai A. Recent advances in biomedical applications of smart nanomaterials: A comprehensive review. RSC Pharmaceutics. 2025.
63. Rahman M. Magnetic resonance imaging and iron-oxide nanoparticles in the era of personalized medicine. Nanotheranostics. 2023 Aug 21;7(4):424
64. Zhang A, Gao L. The refined application and evolution of nanotechnology in enhancing radiosensitivity during radiotherapy: transitioning from gold nanoparticles to multifunctional nanomaterials. International Journal of Nanomedicine. 2023 Dec 31:6233-56.
65. Puttasiddaiah R, Basavegowda N, Lakshmanagowda NK, Raghavendra VB, Sagar N, Sridhar K, Dikkala PK, Bhaswant M, Baek KH, Sharma M. Emerging nanoparticle-based diagnostics and therapeutics for cancer: innovations and challenges. Pharmaceutics.2025 Jan 7;17(1):70.
66. Anik MI, Mahmud N, Al Masud A, Hasan M. Gold nanoparticles (GNPs) in biomedical and clinical applications: A review. Nano Select. 2022 Apr;3(4):792-828.
67. Liu W, Speranza G. Functionalization of carbon nanomaterials for biomedical applications. C. 2019 Nov 13;5(4):72.
68. Hemdan M, Ali MA, Doghish AS, Mageed SS, Elazab IM, Khalil MM, Mabrouk M, Das DB, Amin AS. Innovations in biosensor technologies for healthcare diagnostics and therapeutic drug monitoring: applications, recent progress, and future research challenges. Sensors. 2024 Aug 8;24(16):5143.
69. Choi SW, Kim WS, Kim JH. Surface modification of functional nanoparticles for controlled drug delivery. Journal of dispersion science and technology. 2003 Jan 7;24(3- 4):475-87.
70. INITIATIVE N. THE NATIONAL NANOTECHNOLOGY INITIATIVE. Rahman M.
Magnetic resonance imaging and iron-oxide nanoparticles in the era of personalized medicine. Nanotheranostics. 2023 Aug 21;7(4):424
71. Guterres SS, Alves MP, Pohlmann AR. Polymeric nanoparticles, nanospheres and nanocapsules, for cutaneous applications. Drug target insights. 2007 Jan;2:117739280700200002.
72. Desai N, Rana D, Patel M, Bajwa N, Prasad R, Vora LK. Nanoparticle Therapeutics in Clinical Perspective: Classification, Marketed Products, and Regulatory Landscape.

Small. 2025 Jun 2:2502315.
73. Behzadi S, Serpooshan V, Tao W, Hamaly MA, Alkawareek MY, Dreaden EC, Brown D, Alkilany AM, Farokhzad OC, Mahmoudi M. Cellular uptake of nanoparticles: journey inside the cell. Chemical society reviews. 2017;46(14):4218-44.
74. Cheon J, Lee JH. Synergistically integrated nanoparticles as multimodal probes for nano biotechnology. Accounts of chemical research. 2008 Dec 16;41(12):1630-40.
75. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering

precision nanoparticles for drug delivery. Nature reviews drug discovery. 2021 Feb;20(2):101-24.
76. Yusuf A, Almotairy AR, Henidi H, Alshehri OY, Aldughaim MS. Nanoparticles as drug delivery systems: a review of the implication of nanoparticles' physicochemical properties on responses in biological systems. Polymers. 2023 Mar 23;15(7):1596
77. Song G, S Petschauer J, J Madden A, C Zamboni W. Nanoparticles and the mononuclear phagocyte system: pharmacokinetics and applications for inflammatory diseases. Current rheumatology reviews. 2014 Apr 1;10(1):22-34.
78. Liu J, Liu J, Mu W, Ma Q, Zhai X, Jin B, Liu Y, Zhang N. Delivery strategy to enhance the therapeutic efficacy of liver fibrosis via nanoparticle drug delivery systems. ACS nano. 2024 Jul 31;18(32):20861-85.
79. Guerrini L, Alvarez-Puebla RA, Pazos-Perez N. Surface modifications of nanoparticles for stability in biological fluids. Materials. 2018 Jul 6;11(7):1154.
80. Wais U, Jackson AW, He T, Zhang H. Nanoformulation and encapsulation approaches for poorly water-soluble drug nanoparticles. Nanoscale. 2016;8(4):1746-69.
81. Chauhan MK, Sachdeva A, Ansari L, Gugulothu D. Manufacturing Process of Nanoparticles. InPharmaceutical Process Engineering and Scale-up Principles 2023 Jul 4 (pp. 151-172). Cham: Springer Nature Switzerland.
82. Mishra DK, Dhote V, Bhatnagar P, Mishra PK. Engineering solid lipid nanoparticles for improved drug delivery: promises and challenges of translational research. Drug delivery and translational research. 2012 Aug;2(4):238-53.
83. Abolmaali SS, Tamaddon AM, Dinarvand R. A review of therapeutic challenges and achievements of methotrexate delivery systems for treatment of cancer and rheumatoid arthritis. Cancer chemotherapy and pharmacology. 2013 May;71(5):1115-30.
84. Silva S, Almeida AJ, Vale N. Combination of cell-penetrating peptides with nanoparticles for therapeutic application: a review. Biomolecules. 2019 Jan 10;9(1):22.
85. Attia MF, Anton N, Wallyn J, Omran Z, Vandamme TF. An overview of active and passive targeting strategies to improve the nanocarriers efficiency to tumour sites. Journal of Pharmacy and Pharmacology. 2019 Aug;71(8):1185-98.

