

NOVEL DRUG DELIVERY SYSTEMS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT:

Rheumatoid arthritis (RA) is a persistent autoimmune disease which affect joints on both the sides of the body in a symmetrical manner. Currently there's no complete cure for RA, as most treatments focus on relieving the symptoms linked to the condition and stop further progression of RA. Presently, a variety of conventional drugs like Nonsteroidal Anti-inflammatory agents (NSAIDs) and Disease Modifying Anti-Rheumatic Drugs (DMARDs) and corticosteroids to treat RA. Nevertheless, these compounds show certain drawbacks such as low solubility, gastrointestinal disturbances, high first pass metabolism, degradation by gastric enzymes, interaction with food and toxicity and low bioavailability. These potential problems can be addressed by utilizing novel drug delivery systems (NDDS). Several NDDS at various stages of development for use in RA are solid lipid nanoparticles, microspheres, liposomes, ufasomes, spanlastics, emulgels, microneedles, dendrimers and microemulsions. These systems deliver the conventional drugs safely to the site of action thereby avoiding damage to other organs. Moreover, these systems are able to overcome most of the shortcomings as mentioned above. This review attempts to summarize the several NDDS that leverage such technologies to tackle the therapeutic complications related with RA. The advantages and limitations of these NDDS along with their application are presented.

Keywords: Rheumatoid Arthritis (RA), NDDS, Disease Modifying Anti-Rheumatic Drugs (DMARDs), NSAIDs, Corticosteroids, Interleukin.

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INTRODUCTION:

Rheumatoid Arthritis (RA) is long term immune mediated condition manifested by inflammation of synovial joints, resulting in the deterioration of articular cartilage, bone damage and related defects.¹ Besides damage to the joints, RA also damages various organs and systems like kidney, heart, eye, skin, nervous system and digestive system, etc.² Initially it affects peripheral joints then as the condition advances it slowly affects larger joints. Common symptoms of RA are fatigue, fever, joint stiffness in the morning and tender and warm joints.³ Its prevalence is predominant in females than in males and may occur in any age group.⁴ There are some differences in development of tenderness and swelling, as tenderness mostly occurs in proximal joints such as shoulders, knees and elbows, while swelling occurs in peripheral joints like metacarpophalangeal joints.⁵ In the synovium there is

presence of various immunological cells like B cells, T cells and macrophages - that following activation produce cytokines, Interleukins and TNF- α , responsible for inflammation and swelling. The subsequent release of these mediators activates enzyme metalloproteases and induces osteoclast production, leading to bone erosion in addition to the stiffness in bone, pain and swelling.⁶

As discussed above, RA is a complex, multi-dimensional and multifactorial disease, and so far, there is no cure for RA. The objective of the treatment for RA is to reduce pain and inflammation, decrease swelling and protect other joints from damage.⁷ Four types of drugs are currently use to manage the disease and these are Glucocorticoids, Biologicals, Nonsteroidal Anti-inflammatory agents (NSAIDs) and Disease Modifying Anti-rheumatic Drugs (DMARDs). Each of these agents have their

limitations for example glucocorticoids results in osteonecrosis and atherosclerosis, biologicals are costly and require hospitalization for administration, NSAIDs cause gastrointestinal diseases and cardiovascular disease and DMARDs are slow acting and hence co-prescribed with another drug and may result in pneumonia and hepatotoxicity.⁸ Various novel drug delivery system are being extensively researched and developed to surmount the failure of conventional systems. These systems deliver the drug to the specific site and hence reduce systemic side effects. Moreover, due to targeted drug delivery there is a reduction in the dosing frequency.⁹ Now-a-days researchers are focusing on topical route of drug administration to overcome drawbacks associated with oral route. To enhance the drug permeation across the skin various nanosized drug carriers have been developed. These carrier systems show enhanced entrapment efficiency, are relatively non-toxic and demonstrate great potential to reach site of inflammation.¹⁰

Pathogenesis:

Rheumatoid arthritis is complex disorder which involves several mechanisms that trigger an auto-immune response resulting in joint damage. There are interactions between various cells which cause inflammation of synovial tissues. B cells produce autoantibodies while T cells activate macrophages leading to an excess secretion of inflammation producing cytokines. Various cytokines and chemokines are released by the activated T cells and B cells. These released cytokines further result in synovial fibroblast stimulation.¹¹ The cascade of events results in hyperplasia in synovial cells. The osteoclast laden zone of synoviocytes and enzymes (matrix metalloproteinases) released by various cells (Neutrophils, Chondrocytes and Synoviocytes) causes further degradation of bone.¹² Collectively these factors including activation of synovial cells results in deterioration of joints and swelling associated with RA.¹³ A simplified schematic representation of the pathway is presented in **Figure 1**.

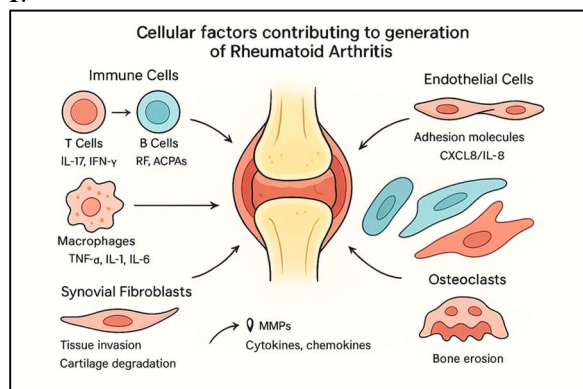


Figure 1. Pathogenesis of Rheumatoid Arthritis

Genetic Factors:

Studies have suggested various genetic factors to be responsible for RA. Human leukocyte antigen (HLA) contributes 30-50% to RA. Besides this, major histocompatibility complex (MHC) is also involved and consists of dense genes responsible for immune functions. Mostly HLA-DRB1 alleles contributes to genetic risk in RA.¹⁴ Also, Protein Tyrosine Phosphatase non-receptor type 22 (PTPN22), Colony stimulating Factor 2 (CSF2), C-C chemokine receptor 6 (CCRS6), Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA4), Phospholipase D Family Member 4 (PLD4), Protein Tyrosine Phosphatase Non- Receptor Type-2 (PTPN2), Beta-1-3-n- acetylglucosaminyltransferase (2B3GNT2), Annexin A3 (ANXA3), AT- rich interactive domain- containing protein 5B (ARID5B), Cluster of Differentiation 83 (CD83) - genes are additionally involved in progression of RA.¹⁵

Environmental Factors:

Different environmental conditions like, occupation, smoking, drinking and food consumption habits are also risk factors for RA.¹⁶ Exposure to silica, consumption of more amount of coffee are also risk factors for RA.¹⁷ Notably tobacco smoking stands out as a significant risk factor for Anti Citrullinated Peptide Antibodies (ACPA).¹⁸ Smoking interacts with the HLA-DR shared epitope gene, illustrating the gene-environment interaction contributing to RA susceptibility. Smokers carry two copies of SE genes which is responsible for 21 fold greater RA development risk than non-smokers.^{19,20} Moderate alcohol drinking inverses the possibilities of RA, whereas consumption of more amount of sweetened soft drink and salt increases the risk of RA.²¹

Treatment of RA:

As pathogenesis of RA is complex and multifactorial, the therapeutic strategy to treat RA is mostly symptomatic, i.e. to treat the symptoms - to reduce pain, swelling and prevent complications associated with the disease.²² The primary treatment approach for RA is management of disease by NSAIDs, corticosteroids and opioid analgesics while the secondary treatment approach is by DMARDs. The aim of primary treatment approach is to decrease ache and inflamed condition, whereas the goal of secondary treatment approach is to promote abatement by stopping the disease progression.^{23,24}

Corticosteroids:

Corticosteroids are the highly preferred drugs for treating RA. Even though NSAIDs are widely used for relieving pain their use is limited by the cardiovascular and gastrointestinal disorders caused by them.²⁵ Corticosteroids act by enhancing the action of inflammation reducing genes while

decreasing level of inflammation producing genes. Hence, these prevent the release of pro-inflammatory cytokines responsible for immune response.²⁶ Also, these act by decreasing the permeability of blood vessels and reducing vasodilation. However excess use of corticosteroids causes osteoporosis, dyslipidemia, and hypertension.²⁵

DMARDs:

DMARDs are the drugs which slow down the disease progression by interfering with the disease process. Biological DMARDs are sometimes recommended when conventional DMARDs are not effective in treatment of RA.²⁷ By using biological DMARDs the use of glucocorticoids (which shows multiple side effects) is also decreased.²⁸ In case of early RA patients, monotherapy of DMARDs is generally preferred. Triple therapy is sometimes preferred when patient requires short term benefit. An example is the co-administration of Methotrexate with a TNF inhibitor, which has shown better effect in RA.²⁹

NSAIDs:

NSAIDs are used for treating RA because these agents reduces pain, inflammation and swelling associated with RA. NSAIDs inhibit cyclooxygenase-2 (COX-2) mediated conversion of arachidonic acid to prostaglandin and shows anti-inflammatory activity.³⁰ These agents are not used alone because they do not reduce the disease progression.³¹ Moreover, NSAIDs have demonstrated gastrointestinal and cardiovascular side effects. Further, these agents sometimes show serious side effects related to kidney and hypersensitivity.³²

Novel Drug Delivery System for the treatment of Rheumatoid Arthritis

As discussed in preceding section, the current therapies have numerous limitations that restrict their use in the prolonged treatment of RA. Significant research continues to be undertaken to manage these drawbacks and enhance the delivery of therapeutic agents for RA. The various novel drug delivery systems under investigation for RA have been depicted in **Figure 2**. Additionally, some prominent examples of agents and their respective delivery systems have been summarized in **Table 1**. These include various approaches such as solid lipid nanoparticles, microemulsions, dendrimers, emulgels, spanlastics, microneedles etc. Each of these and their relevant application from literature is discussed as follows.

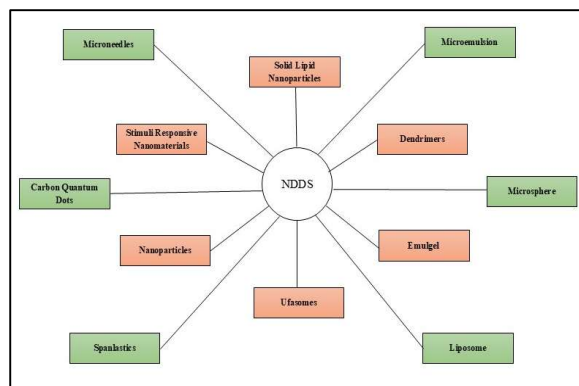


Figure 2. Various Novel drug delivery systems for the treatment of Rheumatoid Arthritis

Solid Lipid Nanoparticles:

Now-a-days numerous biological molecules are used to treat RA; however, these suffer from various downsides like quick metabolism and less absorption and occasionally harsh adverse effects. So solid lipid nanoparticles (SLNs) can overcome these limitations by encapsulating the drug and protecting it from degradation.³³ El-Refaie et al formulated SLNs by using two potent DMARDs (Diacerein (DIA) and Methotrexate (MTX)). Diacerein is prodrug of Rhein (RH) which possess good anti-inflammatory effect. The formulation was evaluated in animal models by using Adjuvant Arthritis Animal (AAA) model. After treatment with MTX-RH-SLN it was observed that there was no ulceration even on the 28th day. Moreover, there was also a decrease in the level of TNF- α .³⁴

Microemulsion:

A microemulsion is a transparent thermodynamically stable, isotropic mixture of two immiscible liquids. It is usually stabilized by use of surfactants and co-surfactants. Qing et al., developed koumine (KME) loaded microemulsion for the treatment of RA. Permeability study was done by using caco-2 cells and an increased permeability in the cytoplasm of KME via the formulated koumine microemulsion (KME-ME) was observed. There was reduction in the arthritis in animals treated with koumine microemulsion (KME-ME) compared to that of the normal saline treated group. Further, major suppression of paw volume ($P > 0.05$) in KME-ME treated animals compared to animals treated with saline was observed.³⁵

Dendrimers:

Dendrimers are highly branched tree-like polymer macromolecular structures used in drug delivery. These have distinct advantages like facile passage of the drug through the biological membrane, targetability and rapid entry into the cell. Dendrimers formulated with poly (amidoamine) are mostly studied. These are used to transport the drug towards

the site of action to manage the pain and inflammation by facilitating the delivery of the drug via ocular, oral, topical and transdermal formulations.³⁶ Oliveira et al., studied poly (amidoamine) dendrimers with anti Tumor Necrosis Factor- α antibodies that targets TNF- α which is responsible for the inflammation observed in RA.³⁷ The formulation containing TNF- α antibodies captures more TNF- α suggesting that the formulation could be used for controlled and sustained delivery of drug. *In-vitro* study revealed that there were no deleterious effects on cells suggesting the formulation possessed histocompatibility and cytocompatibility.³⁷

Microspheres:

Microsphere is a drug carrier system with particle size diameter ranging from 1 micron to 1000 microns. The main benefit of the microsphere system is its ability to provide controlled and targeted drug delivery.³⁸ It releases the drug at targeted site and thereby other tissues remain unaffected. These spheres are made up of proteins or synthetic polymers.³⁹ Khaled et al., formulated prednisolone loaded poly lactic-co-glycolic acid (PLGA) loaded microspheres for treatment of RA in animal models. Arthritis was developed in mice using Freund's complete Adjuvant (FCA) confirmed by a significant difference between the paw volume ($p < 0.005$). The change in the diameter from the beginning of the study to its end was found to be 0.95 ± 0.21 mm and 0.52 ± 0.07 mm respectively for the control (untreated) and the treated groups respectively.⁴⁰

Emulgel:

An emulgel as the name suggests is a formulation composed of an emulsion and a gel matrix. It provides site specific drug delivery to the affected joints by topical administration of the formulation, thereby reducing side effect and increasing therapeutic efficacy.⁴¹ Donthi et al., recently developed a topical emulgel using a multi-kinase inhibitor Dasatinib.⁴² The optimization of the formulation was done by a quality by design (QBD) approach. *In vitro* release studies demonstrated stable drug release for 24 h. Further, there was reduction in the generation of TNF- α in Lipopolysaccharide induced Monocyte Macrophage cell line (RAW 264.7 cells). The prepared emulgel exhibited good spreadability on the skin, thus hydrating the skin resulting in skin swelling and a concomitant enhancement in the permeability through the skin. After applying of the formulation on day 5th of disease induction, there was suppression of arthritis induction ($p < 0.001$). Moreover, a reduction in the paw swelling and redness was also observed.⁴²

Liposomes:

Liposomes are multilamellar vesicular formulations used to deliver the drug topically to the synovial

cavity. As the active ingredient is localized in the synovial cavity; this prevents rapid clearance of the drug. Moreover, this further limits the uptake by other cells and hence undesirable off-target effects associated with the drug are eliminated.⁴³ Jiaqi et al., formulated mannose modified liposomes of Celecoxib as an anti-inflammatory agent. Activation of macrophages is associated with pathophysiology of RA. Mannose binds to mannose receptor on macrophages and releases Celecoxib an anti-inflammatory agent via a targeted drug delivery approach thereby showing efficacy in the treatment of RA.⁴⁴

Ufasomes:

Ufasomes are made up of unsaturated fatty acid, mostly linoleic acid and/or oleic acid. These show property of enhanced permeation, thus are effective in treatment of RA by topical route.⁴⁵ Mittal R. et al., prepared Dexamethasone ufasomal gel by using carbopol 940. Ufasomal vesicles (UF-2) formulated with oleic acid and drug (2:8 ratio) showed an enhanced entrapment efficiency.⁴⁶ The skin partitioning and transdermal permeation was higher with the optimized batch compared to plain drug formulation. A possible reason could be that the surfactant enhanced the permeation of the drug, as the permeability was found to be 4.7 times more than the normal drug preparation. Further, to check anti-inflammatory activity; carrageenan-induced arthritic model was used. It was observed that there was a decrease in the oedema in the ufasomal preparation as compared to marketed formulation.⁴⁶

Spanlastics:

Spanlastics are vesicular drug delivery systems, which are amphiphilic in nature and prepared by using non-ionic surfactants. Due to non-ionic surfactants these are more compatible with our biological membranes and so exhibit no toxicity. These are chemically more stable and exhibit elastic behaviour.⁴⁷ Alaaeldin et al., developed Celecoxib spanlastics with the objective to deliver the drug at the inflamed site. The gel containing celecoxib spanlastics was compared with niosomal gel and it demonstrated a decrease in the size of paw and significant decrease in the Nuclear Factor Kappa B, COX-2 and TNF- α as compared to niosomal gel.⁴⁸

Nanoparticles:

Various types of nanoparticles can be used in formulations to diagnose and treat RA. Nanoparticles are used for the examination and detection of various biomarkers in RA.^{49,50} This nano diagnosis process results in early diagnosis of disease and hence helps in rapid intervention and treatment. This technique is superior in specificity, sensitivity and efficiency.⁵⁰ Silver nanoparticles are mostly used for biomedical purpose because they possess intrinsic anti-

inflammatory activity and can be easily synthesized and modified. If nanoparticles are prepared by using chemical reducing agent, it might be hazardous, due to the toxic nature of the chemicals. However, if herbal extract is used as a reducing agent in the preparation of silver nanoparticles, then it will be advantageous because these are eco-friendly, have low cost, low toxicity and are easy to prepare.⁵¹ PLGA is one of the widely used macromolecular biodegradable polymers employed in the preparation of nanoparticles (NP), as it has potential for the encapsulation of hydrophobic, hydrophilic molecules, proteins and other macromolecules etc. It also shows prolonged release effect. When Collagen type II was encapsulated in PLGA nanoparticle, it showed decrease in the severity of diseases in collagen induced arthritic mice model.⁴⁹

Carbon Quantum Dots:

Carbon quantum dots are fluorescent carbon-based nanomaterials that show excellent optical properties, eco-friendliness, less toxicity, aqueous solubility and biocompatibility and are relatively easy to prepare. Carbon quantum dots have various applications in bioimaging, biosensing and drug delivery etc.⁵² Qiang et al., prepared quantum dots from herbal medicinal agents with dual effect of lubrication and anti-inflammatory action to treat RA. Safflower and *Angelica Sinesis* carbon quantum dots showed great lubrication and anti-inflammatory activity. When used in collagen-induced arthritic rat model these exhibited reduced swelling and reduction in the expression of various inflammation producing cytokines like Tumour Necrosis Factor- α , Interleukin-2, Interleukin-6 etc.⁵³

Stimuli Responsive Nanomaterials:

Stimuli responsive drug delivery system has gained more attention to treat several complex diseases such as RA and cancer. As the name suggests, these stimuli responsive system undergoes physicochemical transformation in response to particular temperature, pH and in presence of certain enzymes.⁵⁴ The normal pH of knee joint is 7.3 and in case of RA the pH at the inflamed knee is decreased to 6.6 due to increased consumption of glucose through glycolysis resulting in lactic acid production and acidosis. After delivery of nanocarriers, due to low pH there is release of drug through the system at specific site, hence it decreases side effect and shows site specific action.⁵⁵ Likewise, there are two parts in enzyme responsive system, one is nanomaterial scaffold (portion sensitive to enzyme) and encapsulated agent linked with carrier with biodegradable bond. Functional groups which are sensitive to enzymes released in pathological condition are incorporated into the nanocarrier system. Therapeutic agent is released upon degradation of this carrier system by different

enzymatic pathways. Enzyme responsive system shows excellent regulation of release as the release of the drug will be dependent on the disease activity. If the disease activity is low then the release of the drug will be less. Additionally, in RA the level of reactive oxygen species increases therefore this change in the redox potential could also be used to regulate drug release. There is change in physical and chemical properties of redox responsive nanomaterial and this contributes in the drug delivery at the site of inflammation.⁵⁶

Microneedles:

Microneedles (MN) are tiny, micron sized needles, which present a physical method for penetration enhancement at the inflamed joint. These deliver the drug into the joint without affecting nerve endings and hence provide painless drug delivery. It shows several benefits such as avoiding first pass biotransformation, as unlike intravenous or oral route of administration the medication is not delivered into the circulatory system. Moreover, it avoids the diffusion of the drug into the healthy tissues and hence there will be no tissue toxicity. Due to these reasons, it requires lower dose as compared to intra articular injection, hence shows better patient compliance.⁵⁷ MN delivers the drug directly into the dermis or epidermis. After penetration the drug does not pass into the blood, but instead it goes into the lymphatic system which is the site for production of proinflammatory cytokines. It shows rapid, sustained and controlled delivery of drugs at inflamed site.⁵⁸ There are various types of MN such as, solid microneedles, coated microneedles, hydrogel microneedles, hollow microneedles etc. prepared by using stainless steel, polymer and silicone material.⁵⁹ Zhao et al., formulated dissolving microneedles for delivery of methotrexate to the inflamed joints. When evaluated in animal study in adjuvant induced arthritis (AIA) rats; these showed a reduction in paw swelling and lowering in release of inflammation-causing cytokines like TNF- α , Interleukin-1 β thereby resulting in decreased synovial and bone destruction.⁶⁰

Limitations of NDDS

As discussed in the preceding section, despite the significant advancements in novel drug delivery systems each of these systems have some inherent limitations. Nanoparticles suffer from low drug loading (10-20%) and instability due to aggregation and oxidation resulting in low joint accumulation. These limitations result in frequent administration via injections thereby reducing patient compliance. Liposomes on the other hand, despite better drug loading (20-30%) rely on passive targeting and may be cleared by the immune system. These are also prone to leakage, oxidation and have some stability

issues. Hydrogels offer localized delivery, but are affected by motion erosion. Transdermal patches despite being low cost haven't been efficacious in overcoming the skin barriers for delivering RA drugs. Microneedles, despite enhancing absorption, face their own challenges: coated types have low payloads while dissolving ones are fragile and moisture-sensitive. Likewise, hollow microneedles risk clogging and mechanical failure, and hydrogel-forming variants may release drugs too quickly followed by insufficient drug levels. Across the different systems low drug loading, stability, handling difficulties and poor drug accumulation pose significant challenges to these novel delivery systems. Moreover, technical issues such as complex manufacturing processes and high manufacturing costs also affect the scalability of these products. Collectively these challenges provide ample scope for researchers to explore and overcome in order to realize the full potential of multiple drug delivery techniques.⁶¹

Table.1 Application of NDDS in the Treatment of Rheumatoid Arthritis

Drug	Delivery System	Route of Administration	Animal model	Outcome	Ref.
Leflunomide	Nanostructured Lipid Carrier	Oral	Anti gen Induced Rat Model	Reduced Hepatotoxicity by using nanoencapsulated Leflunomide compared to Leflunomide suspension.	62
Koumine	Micro-emulsion	Oral	Collagen Induced	Enhanced absorptiv	35

			ced Arthritis Rat Model	Permeability enhanced accumulation in inflamed joints.	
miR-23b	Dendrimer	Intravenous Injection	Anti gen Induced Arthritis Rat Model	Regulation of the NF- κ B pathway in Hyperplastic synovium demonstrated Anti-inflammatory and antiproliferative action	63
Celecoxib	Spanlastics	Transdermal Delivery	Freund's Complete Adjuvant induced Arthritis	Showed decrease in circumference of Oedema and suppressed Arthritis Markers.	48

Berberine and Sinomenine	Microneedles	Transdermal Delivery	Collagen Induced Arthritis Mouse Model	Decreased expression of CD-68 Positive Macrophage and CD-31 stained blood vessels showed improved antiarthritic effect as compared to monotherapy.	6 4
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CONCLUSION:

The chronic nature of autoimmune disorders gives rise to major challenges in their treatment. This is further complicated by involvement of multiple pathological pathways and the requirement for precise medication to minimize side effects. Currently, there is an increasing interest in using herbal drugs to treat autoimmune conditions such as rheumatoid arthritis (RA). However, traditional herbal compounds often suffer from challenges such as low solubility, limited bioavailability and extensive first-pass metabolism. These challenges can be effectively addressed by incorporating herbal compounds into novel drug delivery systems (NDDS), which provide localized delivery and controlled drug release, ultimately improving their therapeutic potential. In recent years, drug delivery systems have evolved from conventional macro-scale approaches to advanced nanoscale technologies, aiming to enhance therapeutic efficacy through targeted delivery and reduced toxicity. Biodegradable and stimuli-responsive nanocarriers have emerged as critical tools in the management of these conditions,

offering localized, controlled, and site-specific drug delivery. These systems not only lower the rate of traditional drug administration but also enhance overall therapeutic outcomes by strengthening patient commitment to treatment. By targeting inflamed tissues, NDDS minimize circulatory exposure and possible adverse effects. This review attempts to summarize the several NDDS that leverage such technologies to tackle the therapeutic complications related with RA. Select examples highlighting the advantages and limitations of these NDDS have been discussed. Further, as discussed, the challenges associated with each delivery system is unique and paves the way for future research in this exciting area.

CONFLICT OF INTEREST:

The all authors declare that there is no conflict of interest.

REFERENCES:

- (1) Anita, C.; Munira, M.; Mural, Q.; Shaily, L. Topical Nanocarriers for Management of Rheumatoid Arthritis: A Review. *Biomed. Pharmacother. Biomedecine Pharmacother.* 2021, *141*, 111880. <https://doi.org/10.1016/j.biopha.2021.111880>.
- (2) Radu, A.-F.; Bungau, S. G. Management of Rheumatoid Arthritis: An Overview. *Cells* 2021, *10* (11). <https://doi.org/10.3390/cells10112857>.
- (3) Bullock, J.; Rizvi, S. A. A.; Saleh, A. M.; Ahmed, S. S.; Do, D. P.; Ansari, R. A.; Ahmed, J. Rheumatoid Arthritis: A Brief Overview of the Treatment. *Med. Princ. Pract. Int. J. Kuwait Univ. Health Sci. Cent.* 2018, *27* (6), 501–507. <https://doi.org/10.1159/000493390>.
- (4) Zhang, Z.; Gao, X.; Liu, S.; Wang, Q.; Wang, Y.; Hou, S.; Wang, J.; Zhang, Y. Global, Regional, and National Epidemiology of Rheumatoid Arthritis among People Aged 20–54 Years from 1990 to 2021. *Sci. Rep.* 2025, *15* (1), 10736.
- (5) Zodge, A.; Mahamuni, S.; Gaikwad, V. An Overview of Novel Drug Delivery Systems for NSAIDS in the Treatment of Rheumatoid Arthritis. *J. Emerg. Technol. Innov. Res.* 2023, *10* (4), 561–567.
- (6) Dhule, K. D.; Nandgude, T. D. Lipid Nano-System Based Topical Drug Delivery for Management of Rheumatoid Arthritis: An Overview. *Adv. Pharm. Bull.* 2023, *13* (4), 663.
- (7) Yi, J.; Liu, Y.; Xie, H.; An, H.; Li, C.; Wang, X.; Chai, W. Hydrogels for the Treatment of Rheumatoid Arthritis. *Front. Bioeng. Biotechnol.* 2022, *10*, 1014543.
- (8) Han, D.; Chen, Q.; Chen, H. Food-Derived Nanoscopic Drug Delivery Systems for

- Treatment of Rheumatoid Arthritis. *Molecules* 2020, 25 (15), 3506.
- (9) Oliveira, I. M.; Fernandes, D. C.; Cengiz, I. F.; Reis, R. L.; Oliveira, J. M. Hydrogels in the Treatment of Rheumatoid Arthritis: Drug Delivery Systems and Artificial Matrices for Dynamic in Vitro Models. *J. Mater. Sci. Mater. Med.* 2021, 32 (7), 74.
 - (10) Syed, A.; Devi, V. K. Potential of Targeted Drug Delivery Systems in Treatment of Rheumatoid Arthritis. *J. Drug Deliv. Sci. Technol.* 2019, 53, 101217.
 - (11) Choy, E. Understanding the Dynamics: Pathways Involved in the Pathogenesis of Rheumatoid Arthritis. *Rheumatology* 2012, 51 (suppl_5), v3–v11.
 - (12) Maeda, K.; Yoshida, K.; Nishizawa, T.; Otani, K.; Yamashita, Y.; Okabe, H.; Hadano, Y.; Kayama, T.; Kurosaka, D.; Saito, M. Inflammation and Bone Metabolism in Rheumatoid Arthritis: Molecular Mechanisms of Joint Destruction and Pharmacological Treatments. *Int. J. Mol. Sci.* 2022, 23 (5), 2871. <https://doi.org/10.3390/ijms23052871>.
 - (13) Babaahmadi, M.; Tayebi, B.; Gholipour, N. M.; Kamardi, M. T.; Heidari, S.; Baharvand, H.; Eslaminejad, M. B.; Hajizadeh-Saffar, E.; Hassani, S.-N. Rheumatoid Arthritis: The Old Issue, the New Therapeutic Approach. *Stem Cell Res. Ther.* 2023, 14 (1), 268. <https://doi.org/10.1186/s13287-023-03473-7>.
 - (14) Newton, J.; Harney, S.; Wordsworth, B.; Brown, M. A Review of the MHC Genetics of Rheumatoid Arthritis. *Genes Immun.* 2004, 5 (3), 151–157.
 - (15) Sharma, S. D.; Leung, S. H.; Viatte, S. Genetics of Rheumatoid Arthritis. *Best Pract. Res. Clin. Rheumatol.* 2024, 38 (4), 101968. <https://doi.org/10.1016/j.berh.2024.101968>.
 - (16) Jiang, X.; Alfredsson, L. Modifiable Environmental Exposure and Risk of Rheumatoid Arthritis—Current Evidence from Genetic Studies. *Arthritis Res. Ther.* 2020, 22 (1), 154.
 - (17) Salliot, C.; Nguyen, Y.; Boutron-Ruault, M.-C.; Seror, R. Environment and Lifestyle: Their Influence on the Risk of RA. *J. Clin. Med.* 2020, 9 (10), 3109.
 - (18) Klareskog, L.; Stolt, P.; Lundberg, K.; Källberg, H.; Bengtsson, C.; Grunewald, J.; Rönnelid, J.; Erlandsson Harris, H.; Ulfgrén, A.-K.; Rantapää-Dahlqvist, S.; others. A New Model for an Etiology of Rheumatoid Arthritis: Smoking May Trigger HLA–DR (Shared Epitope)–Restricted Immune Reactions to Autoantigens Modified by Citrullination. *Arthritis Rheum. Off. J. Am. Coll. Rheumatol.* 2006, 54 (1), 38–46.
 - (19) Ishikawa, Y.; Terao, C. The Impact of Cigarette Smoking on Risk of Rheumatoid Arthritis: A Narrative Review. *Cells* 2020, 9 (2), 475.
 - (20) Liao, K. P.; Alfredsson, L.; Karlson, E. W. Environmental Influences on Risk for Rheumatoid Arthritis. *Curr. Opin. Rheumatol.* 2009, 21 (3), 279–283.
 - (21) Zhang, J.; Wang, X.; Fang, J.; Li, Y.; Yu, Y.; Wang, J.; Sun, B. Contributions of Dietary Patterns and Factors to Regulation of Rheumatoid Disease. *Int. J. Mol. Sci.* 2025, 26 (6), 2674.
 - (22) RINDFLEISCH, I. A.; Muller, M. Diagnosis and Management. *Am. Fam. Physician* 2005, 72, 6.
 - (23) Shams, S.; Martinez, J. M.; Dawson, J. R.; Flores, J.; Gabriel, M.; Garcia, G.; Guevara, A.; Murray, K.; Pacifici, N.; Vargas, M. V.; others. The Therapeutic Landscape of Rheumatoid Arthritis: Current State and Future Directions. *Front. Pharmacol.* 2021, 12, 680043.
 - (24) Gao, Y.; Zhang, Y.; Liu, X. Rheumatoid Arthritis: Pathogenesis and Therapeutic Advances. *MedComm* 2024, 5 (3), e509. <https://doi.org/10.1002/mco2.509>.
 - (25) Liu, D.; Ahmet, A.; Ward, L.; Krishnamoorthy, P.; Mandelcorn, E. D.; Leigh, R.; Brown, J. P.; Cohen, A.; Kim, H. A Practical Guide to the Monitoring and Management of the Complications of Systemic Corticosteroid Therapy. *Allergy Asthma Clin. Immunol.* 2013, 9 (1), 30.
 - (26) Coutinho, A. E.; Chapman, K. E. The Anti-Inflammatory and Immunosuppressive Effects of Glucocorticoids, Recent Developments and Mechanistic Insights. *Mol. Cell. Endocrinol.* 2011, 335 (1), 2–13.
 - (27) Gadzhanova, S.; Roughead, E. Use of Analgesic and Anti-Inflammatory Medicines before and after Initiation of Biological Disease-Modifying Antirheumatic Drugs for Rheumatoid Arthritis. *J. Clin. Pharm. Ther.* 2024, 2024 (1), 8040681.
 - (28) Nilsson, A. C.; Christensen, A. F.; Junker, P.; Lindegaard, H. M. Tumor Necrosis Factor-Alpha Inhibitors Are Glucocorticoidsparing in Rheumatoid Arthritis. *Dan Med Bull* 2011, 58 (4), A4257.
 - (29) Singh, J. A.; Saag, K. G.; Bridges Jr, S. L.; Akl, E. A.; Bannuru, R. R.; Sullivan, M. C.; Vaysbrot, E.; McNaughton, C.; Osani, M.; Shmerling, R. H.; others. 2015 American College of Rheumatology Guideline for the

- Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol.* 2016, 68 (1), 1–26.
- (30) Crofford, L. J. Use of NSAIDs in Treating Patients with Arthritis. *Arthritis Res. Ther.* 2013, 15 Suppl 3 (Suppl 3), S2. <https://doi.org/10.1186/ar4174>.
 - (31) Chang, K.-H.; Hsu, Y.-C.; Hsu, C.-C.; Lin, C.-L.; Hsu, C. Y.; Lee, C.-Y.; Chong, L.-W.; Liu, H.-C.; Lin, M.-C.; Kao, C.-H. Prolong Exposure of NSAID in Patients with RA Will Decrease the Risk of Dementia: A Nationwide Population-Based Cohort Study. *Medicine (Baltimore)* 2016, 95 (10), e3056.
 - (32) Stiller, C.-O.; Hjemdahl, P. Lessons from 20 Years with COX-2 Inhibitors: Importance of Dose-Response Considerations and Fair Play in Comparative Trials. *J. Intern. Med.* 2022, 292 (4), 557–574. <https://doi.org/10.1111/joim.13505>.
 - (33) Chuang, S.-Y.; Lin, C.-H.; Huang, T.-H.; Fang, J.-Y. Lipid-Based Nanoparticles as a Potential Delivery Approach in the Treatment of Rheumatoid Arthritis. *Nanomaterials* 2018, 8 (1), 42.
 - (34) El-Refai, W. M.; Ghazy, M. S.; Ateyya, F. A.; Sheta, E.; Shafek, M. Y.; Ibrahim, M. S.; Ismail, M. M.; Gowayed, M. A. Rhein Methotrexate-Decorated Solid Lipid Nanoparticles Altering Adjuvant Arthritis Progression through Endoplasmic Reticulum Stress-Mediated Apoptosis. *Inflammopharmacology* 2023, 31 (6), 3127–3142.
 - (35) Hu, Q.; Fu, X.-L.; Dong, Y.-Y.; Ma, J.; Hua, J.; Li, J.-T.; Liu, K.-X.; Yang, J.; Yu, C.-X. D-Optimal Design and Development of a Koumine-Loaded Microemulsion for Rheumatoid Arthritis Treatment: In Vivo and in Vitro Evaluation. *Int. J. Nanomedicine* 2023, 2973–2988.
 - (36) Bosch, X. Dendrimers to Treat Rheumatoid Arthritis. *ACS Nano* 2011, 5 (9), 6779–6785.
 - (37) Oliveira, I. M.; Gonçalves, C.; Oliveira, E. P.; Simón-Vázquez, R.; da Silva Morais, A.; González-Fernández, Á.; Reis, R. L.; Oliveira, J. M. PAMAM Dendrimers Functionalised with an Anti-TNF α Antibody and Chondroitin Sulphate for Treatment of Rheumatoid Arthritis. *Mater. Sci. Eng. C Mater. Biol. Appl.* 2021, 121, 111845. <https://doi.org/10.1016/j.msec.2020.111845>.
 - (38) Singh, S.; Devi, A.; Sharma, S.; Sabharwal, S.; Sharma, S.; Dhiman, S.; Chauhan, S. A Review on Microspheres and Its Role in Different Drug Delivery System as a Novel Approach. *Int. J. Pharm. Sci.* 2024, 2 (6), 1112–1126.
 - (39) Yadav, M.; Mandhare, T. A.; Jadhav, V.; Otari, K. A Review on Microspheres as a Promising Drug Carrier. *J. Drug Deliv. Ther.* 2024, 14 (7).
 - (40) Khaled, K. A.; Sarhan, H. A.; Ibrahim, M. A.; Ali, A. H.; Naguib, Y. W. Prednisolone-Loaded PLGA Microspheres. in Vitro Characterization and in Vivo Application in Adjuvant-Induced Arthritis in Mice. *Aaps Pharmscitech* 2010, 11 (2), 859–869.
 - (41) Sinha, A.; Garg, U.; Nagaich, U.; Chaudhary, A.; Pandey, M.; Jain, N. Emulgels: A Promising Topical Drug Delivery System for Arthritis Management and Care. *Pharm. Dev. Technol.* 2024, 29 (1), 25–39.
 - (42) Donthi, M. R.; Saha, R. N.; Singhvi, G.; Dubey, S. K. Dasatinib-Loaded Topical Nano-Emulgel for Rheumatoid Arthritis: Formulation Design and Optimization by QbD, in Vitro, Ex Vivo, and in Vivo Evaluation. *Pharmaceutics* 2023, 15 (3), 736.
 - (43) Kapoor, B.; Singh, S. K.; Gulati, M.; Gupta, R.; Vaidya, Y. Application of Liposomes in Treatment of Rheumatoid Arthritis: Quo Vadis. *Sci. World J.* 2014, 2014 (1), 978351.
 - (44) Si, J.; Guo, R.; Zhang, L.; Liu, W.; Kong, L.; Liu, Y.; Yu, Y.; Zang, J.; Chen, W.; Li, X.; others. Mannose-Modified Celastrol Liposomes Targeted Activated Macrophages for Rheumatoid Arthritis Treatment in Vitro and in Vivo Evaluation. *J. Drug Deliv. Sci. Technol.* 2024, 91, 105185.
 - (45) PA^{TEL}, H. A Vesicular Drug Delivery for Futuristic Drug Delivery Applications: Ufasomes. *Indian J. Pharm. Biol. Res.* 2022, 10 (04).
 - (46) Mittal, R.; Sharma, A.; Arora, S. Ufasomes Mediated Cutaneous Delivery of Dexamethasone: Formulation and Evaluation of Anti-Inflammatory Activity by Carrageenin-Induced Rat Paw Edema Model. *J. Pharm.* 2013, 2013 (1), 680580.
 - (47) Kamath, K.; Jain, S.; Shabaraya, A. Spanlastics: A Modern Formulation Approach in Drug Delivery. *Eur J Pharm Med Res* 2023, 10, 96.
 - (48) Alaaeldin, E.; Abou-Taleb, H. A.; Mohamad, S. A.; Elrehany, M.; Gaber, S. S.; Mansour, H. F. Topical Nano-Vesicular Spanlastics of Celecoxib: Enhanced Anti-Inflammatory Effect and down-Regulation of TNF- α , NF- κ B and COX-2 in Complete Freund's Adjuvant-Induced Arthritis Model in Rats. *Int. J. Nanomedicine* 2021, 133–145.
 - (49) Li, C.; Han, Y.; Luo, X.; Qian, C.; Li, Y.; Su, H.; Du, G. Immunomodulatory Nano-

- Preparations for Rheumatoid Arthritis. *Drug Deliv.* 2023, 30 (1), 9–19.
- (50) Angela, S.; Fadhilah, G.; Hsiao, W. W.-W.; Lin, H.-Y.; Ko, J.; Lu, S. C.-W.; Lee, C.-C.; Chang, Y.-S.; Lin, C.-Y.; Chang, H.-C.; others. Nanomaterials in the Treatment and Diagnosis of Rheumatoid Arthritis: Advanced Approaches. *SLAS Technol.* 2024, 29 (4), 100146.
 - (51) Ren, S.; Xu, Y.; Dong, X.; Mu, Q.; Chen, X.; Yu, Y.; Su, G. Nanotechnology-Empowered Combination Therapy for Rheumatoid Arthritis: Principles, Strategies, and Challenges. *J. Nanobiotechnology* 2024, 22 (1), 431. <https://doi.org/10.1186/s12951-024-02670-7>.
 - (52) Yadav, P. K.; Chandra, S.; Kumar, V.; Kumar, D.; Hasan, S. H. Carbon Quantum Dots: Synthesis, Structure, Properties, and Catalytic Applications for Organic Synthesis. *Catalysts* 2023, 13 (2), 422.
 - (53) Qiang, R.; Huang, H.; Chen, J.; Shi, X.; Fan, Z.; Xu, G.; Qiu, H. Carbon Quantum Dots Derived from Herbal Medicine as Therapeutic Nanoagents for Rheumatoid Arthritis with Ultrahigh Lubrication and Anti-Inflammation. *ACS Appl. Mater. Interfaces* 2023, 15 (32), 38653–38664.
 - (54) Parvin, N.; Joo, S. W.; Mandal, T. K. Biodegradable and Stimuli-Responsive Nanomaterials for Targeted Drug Delivery in Autoimmune Diseases. *J. Funct. Biomater.* 2025, 16 (1), 24.
 - (55) Xie, Y.; Tuguntaev, R. G.; Mao, C.; Chen, H.; Tao, Y.; Wang, S.; Yang, B.; Guo, W. Stimuli-Responsive Polymeric Nanomaterials for Rheumatoid Arthritis Therapy. *Biophys. Rep.* 2020, 6 (5), 193–210.
 - (56) Zhang, M.; Hu, W.; Cai, C.; Wu, Y.; Li, J.; Dong, S. Advanced Application of Stimuli-Responsive Drug Delivery System for Inflammatory Arthritis Treatment. *Mater. Today Bio* 2022, 14, 100223.
 - (57) Guo, P.; Huang, C.; Yang, Q.; Zhong, G.; Zhang, J.; Qiu, M.; Zeng, R.; Gou, K.; Zhang, C.; Qu, Y. Advances in Formulations of Microneedle System for Rheumatoid Arthritis Treatment. *Int. J. Nanomedicine* 2023, 7759–7784.
 - (58) Wendong, Y.; Xingxing, Y.; Xianze, X.; Qiaomei, F.; Yujun, S.; Shanshan, Z.; Zheng, S.; Hairu, X. Nanoformulation-Assisted Microneedle Transdermal Drug Delivery System: An Innovative Platform Enhancing Rheumatoid Arthritis Treatment. *Biomed. Pharmacother.* 2024, 178, 117219.
 - (59) Agarwal, S.; Khare, S.; Gupta, D. Exploring Micro Needles Applications in Rheumatoid Arthritis: Efficacy, Safety, and Patient Benefits. *J. Med. Pharm. Allied Sci.* 2024, 13 (6), 6829–6839. <https://doi.org/10.55522/jmpas.V13I6.6687>.
 - (60) Zhao, W.; Zheng, L.; Yang, J.; Ma, Z.; Tao, X.; Wang, Q. Dissolving Microneedle Patch-Assisted Transdermal Delivery of Methotrexate Improve the Therapeutic Efficacy of Rheumatoid Arthritis. *Drug Deliv.* 2023, 30 (1), 121–132.
 - (61) Mohanty, S.; Panda, S.; Bhanja, A.; Pal, A.; Chandra, S. S. Novel Drug Delivery Systems for Rheumatoid Arthritis: An Approach to Better Patient Compliance. *Biomed. Pharmacol. J.* 2019, 12 (1), 157–170.
 - (62) Zewail, M.; Nafee, N.; Helmy, M. W.; Boraie, N. Coated Nanostructured Lipid Carriers Targeting the Joints—an Effective and Safe Approach for the Oral Management of Rheumatoid Arthritis. *Int. J. Pharm.* 2019, 567, 118447.
 - (63) Han, H.; Xing, J.; Chen, W.; Jia, J.; Li, Q. Fluorinated Polyamidoamine Dendrimer-Mediated miR-23b Delivery for the Treatment of Experimental Rheumatoid Arthritis in Rats. *Nat. Commun.* 2023, 14 (1), 944.
 - (64) Hua, P.; Yang, S.; Yu, L.; Huang, Y.; Chen, M. Natural Product-Integrated Microneedle Patch for Rheumatoid Arthritis Treatment through Anti-Inflammation and Angiogenesis Suppression. *Biomater. Sci.* 2025, 13 (9), 2462–2474.