Int. J. Sci. R. Tech., 2025 2(7)
A Multidisciplinary peer-reviewed Journal
www.ijsrtjournal.com [ISSN: 2394-7063]

Original Article

Nanomedicines Used in The Treatment of the Rheumatoid Arthritis

Aditya Jagatap*, Mayuri Kalokhe, Aniket Gavali, Manali Bavadekar

Dr. Shivajirao Kadam College of Pharmacy, Kasbe Digraj

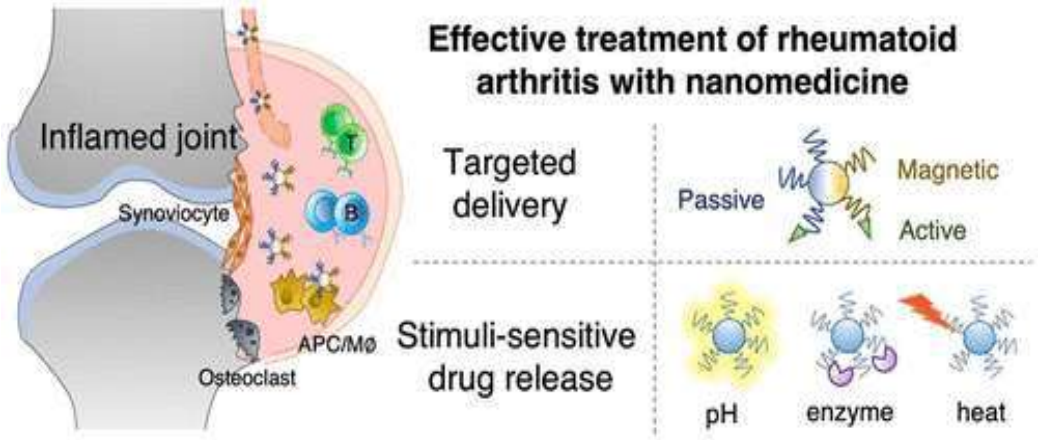
ABSTRACT

Rheumatoid arthritis(RA) is an autoimmune disorder that affects the joints. Various medications successfully alleviate the symptoms of RA in clinical. Still, few therapy strategies can cure RA, especially when joint destruction begins, and there is currently no effective bone-protective treatment to reverse the articular damage. Furthermore, the RA medications now used in clinical practice accompany various adverse side effects. Nanotechnology can improve the pharmacokinetics of traditional anti-RA drugs and therapeutic precision through targeting modification. Although the clinical application of nanomedicines for RA is in its infancy, preclinical research is rising. Current anti-RA nano-drug studies mainly focus on the following: drug delivery systems, nanomedicines with anti-inflammatory and anti-arthritic properties, biomimetic design with better biocompatibility and therapeutic features, and nanoparticle-dominated energy conversion therapies. These therapies have shown promising therapeutic benefits in animal models, indicating that nanomedicines are a potential solution to the current bottleneck in RA treatment. This review will summarize the present state of anti-RA nano-drug research.

Keywords: Nanomedicines, Treatment, Rheumatoid Arthritis

INTRODUCTION

Nanomedicine offers promising approaches for rheumatoid arthritis (RA) treatment by enhancing drug delivery and reducing side effects. Nanomaterials like nanoparticles (polymeric, lipid, metallic, and inorganic) are used to encapsulate or adsorb drugs, targeting inflamed tissues and improving drug solubility, circulation time, and controlled release.



Nanoparticles for the management of RA

Nanoparticles are particles in spherical form [39]. Nanoparticles' thickness, surface heterogeneity and morphology play an important role in the biodistribution of nanoparticles for the treatment of RA [53]. Nanoparticles (NPs), for theranostic applications, are used as therapeutic/imaging agents. The encapsulated particulate material aims to provide a controversial distribution/controlled discharge of encapsulated products. Physicochemical properties connected with, Passive targeting of RA treatment

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

drugs includes particle size, shape of the load and characteristics of outside. Nanoparticles in particular take on their vital role in pharmaceutical industries because of their biocompatibility and biodegradability properties. Nanoparticles paired with specific ligand targets and rendered cellular diffusion simpler [54]. The most commonly reported liposomes, micelles, metallic nanoparticles, and polymeric nanoparticle deliver capable of treating RA. By systemic circulation, nanoparticles can be used through various processes such as adsorption, ligand receptor attachment, covalent binding and internalization [55]. NSAID-based delivery systems have been widely documented for RA, which reduces pain (analgesia) related to early stage RA through its anti-inflammatory pathways devoid of lack of articular function; however, it inhibits COX-1 and COX-2 enzymes that play a necessary role in prostaglandin production. Drug that contains nanoparticles was therapeutically delivered to reddened synovium [39]. Metal oxide nanoparticles show various desirable characteristics, such as drug carriers with extremely higher surface area and large pore sizes for drug encapsulation, intrinsic biodegradability characteristics due to their labile metal-ligand bonds and flexible versatility for post-synthetic drug molecules grafting [56]. Rutin stabilized silver nanoparticles elicits anti-inflammatory involvement in systemic inflammation by its crucial activation of pro-inflammatory cytokine production (tumor necrotic factor-α (TNF-α) and interleukin-6 (IL-6). In RA patients silver nanoparticles were also used for therapeutic benefits [57]. Table shows the numerous nanoparticulate-based delivery systems used by various medicines. The use of nanoparticle-based formulations in the treatment of RA might result in improved bioavailability, greater drug collection at the affected inflamed site, and longer discharge characteristics. These nanoparticulate-based formulations may also stimulate target capacity potential with particular receptors at a higher level.

Drugs	Nano carrier	Therapeutic effects
Curcumin	Indian Gold	Oxido-inflammatory and immunomodulatory cascade
Piroxicam	Glycerol monostearate	Anti-inflammatory effect
Piperine	Glycerol monostearate	Anti-inflammatory effect
Aceclofenac	Glycerol monostearate	Anti-inflammatory effect
Actarit	Stearic acid	Anti-rheumatic arthritic effect
Apigenin	Glyceryl monostearate, tocopheryl polyethylene glycol succinate	Anti-rheumatic arthritic effect
Etofenamate and Ibuprofen	Compritol® 888 ATO	Anti-inflammatory effect
β-Sitosterol	Poly (lactic-co-glycolic acid)	Anti-rheumatic arthritic effect
Nabumetone	Compritol 888 ATO	Anti-inflammatory effect
Celecoxib	Glycerol monostearate	Anti-inflammatory effect
Nabumetone, Ketoprofen, Ibuprofen and phosphotungstic acid	Glycerol monostearate	Anti-inflammatory effect

First-Line Management: NSAIDS and Corticosteroids

The overall goal of first-line treatment is to relieve pain and decrease inflammation. Medications, considered to be fast-acting, are nonsteroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylate (Aspirin), naproxen (Naprosyn), ibuprofen (Advil and Motrin), and etodolac (Lodine). Aspirin is an effective anti-inflammatory for RA when used at high doses, due to the inhibition of prostaglandins. It is one of the oldest NSAIDs used for joint pain. Side effects of aspirin at high doses include tinnitus, hearing loss, and gastric intolerance. There are other NSAIDs that are newer on the market than aspirin and just as effective. In addition, these drugs require fewer doses per day. NSAIDs work by inhibiting cyclo-oxygenase to prevent the synthesis of prostaglandins, prostacyclin, and thromboxanes. Common side effects are nausea, abdominal pain, ulcers, and gastrointestinal (GI) bleeding. These symptoms can be reduced if taken with food, antacids, proton pump inhibitors, or misoprostol (Cytotec), An even newer NSAID called celecoxib (Celebrex) is a selective Cox-2 inhibitor that has less risk of GI side effects [12]. Corticosteroids are a more potent anti-

inflammatory medication than NSAIDs, but they come with greater side effects. For this reason, they are only indicated for a short period of time at low doses, during exacerbations or flares of RA. Intra-articular injections of corticosteroids can be used for the local symptoms of inflammation [13]. They work by preventing the release of phospholipids and decreasing the actions of eosinophils, thereby decreasing inflammation. Their side effects include bone-thinning, weight gain, diabetes, and immunosuppression. Advising the patient to take calcium and vitamin D supplementation can prevent thinning of the bone. Side effects can be reduced by gradually tapering doses as a patient's condition improves. It is important to not abruptly discontinue injected or oral corticosteroids as this can lead to suppression of the hypothalamic-pituitary-adrenal axis (HPA) or flares of RA [14].

Opioid Analgesics

Whittle et al. addressed the question of the use of opioid analgesics for patients with pain due to RA. From their conclusions, weak opioids such as codeine, dextropropoxyphene, and tramadol may play an effective role in the short-term management of pain caused by RA, but the adverse effects outweigh the benefits. They recommend that other analgesics be considered first [16].

Second-Line Management: Disease-Modifying Antirheumatic Drugs

The overall goal of second-line treatment is to promote remission by slowing or stopping the progression of joint destruction and deformity. Medications are considered to be slow-acting because they take from weeks to months to be effective. Disease-modifying antirheumatic drugs (DMARDs) can also reduce the risk of developing lymphoma that can be associated with RA [17]. Methotrexate (MTX) is the initial second-line drug (also considered an anchor drug). It is an analog to folic acid that competitively inhibits the binding of dihydrofolic acid (FH2) to the enzyme that is responsible for converting FH2 to folinic acid (FH4). Without FH4, the metabolism of purine and pyrimidine is impaired, and the synthesis of amino acids and polyamine is inhibited. MTX is an immunosuppressive drug that requires regular blood tests due to its side effects, i.e., liver problems, cirrhosis, and bone marrow deterioration. Folic acid supplementation can reduce the risk of side effects. It is an effective DMARD, has a lower incidence of side effects than other DMARDs, and has dosage flexibility, meaning that doses can be adjusted as needed [18]. Until now, there is convincing data showing the benefits of combinations of conventional synthetic DMARDs over MTX monotherapy. However, biological and synthetic DMARDs in combination are reported to be better than MTX but with more side effects and greater costs [11, 14, 19]. Hydroxychloroqyine (Plaquenil) is an antimalarial drug and can be used for long-term treatment of RA. This drug decreases the secretion of monocyte-derived proinflammatory cytokines. Common side effects include problems in the GI tract, skin, and central nervous system. The eyes, in particular, can be affected when this drug is taken at high doses. Patients on this medication require routine consultation with an ophthalmologist [20]. Sulfasalazine (Azulfidine) is a DMARD typically used in the treatment of irritable bowel disease. Combined with anti-inflammatory medications, this DMARD can be used to treat RA. The mechanism of action of this drug in the treatment of RA has not been identified. It is thought that sulfapyridine, a reduced form of the medication after administration, may reduce secretions of interleukin (IL)-8 and monocyte chemoattractant protein (MCP). This drug has side effects of GI and central nervous system symptoms as well as rash. It is usually well-tolerated among patients, but should be avoided in patients with sulfa allergies since it contains sulfa and salicylate compounds [21]. Gold salts, such as aurothioglucose (Solganal), auranofin (Ridaura), gold sodium thiomalate (Myochrysine), and D-penicillamine (Depen and Cuprimine) have been used frequently in the treatment of RA. These DMARDs require frequent blood and urine tests due to damage to the bone marrow and kidneys. They have not been used recently due to the more effective treatments, particularly MTX. Other immunosuppressive medications like azathioprine (Imuran), cyclophsphamide (Cytoxan), chlorambucil (Leukeran), and cyclosporine (Sandimmune) can be employed but are typically reserved for patients with very aggressive RA or complications of the disease [22, 23].

CONCLUSION

There is increasing understanding of the pre-RA stage of disease development, which has already driven the completion or development of multiple clinical prevention trials. Importantly, growing interest in this area and the huge potential for improvements in the public health impact of this disease is driving even more studies in understanding the biology of disease development and developing effective preventive interventions; efforts are also underway in other rheumatic autoimmune diseases such as systemic lupus erythematosus and psoriatic arthritis. Further, there is now an approved preventive intervention in type 1 diabetes, which is a disease that has a model of development similar to RA. It is exciting to see the field moving forward to a point where rheumatologists can include in clinical care the discussions around prediction of the clinical onset of RA, and potentially of other rheumatic diseases, as well as the use of potentially soon-to-be-approved preventive interventions. -Nanomaterials have great promise as theranostic agents for RA. Drugs may be delivered to inflamed joints using nanomaterials, which can also provide imaging data at the same time. The use of nanomaterials for RA theranostics has a number of benefits. The effectiveness of medicine delivery can be increased by using nanomaterials since they can be made to target certain cells or tissues. They can also be used to image the illness, which can be useful for tracking RA development and evaluating how well a medication is working. The accuracy of using nanomaterials for diagnosing RA is highly dependent on selecting biomarkers. However, currently developed biomarkers have lower diagnostic accuracy than imaging assays such as X-rays. Biomarkers frequently indicate conditions other than RA. This limitation of specific markers is one of the barriers in developing nanomaterials for the early detection of RA. On the other hand, if detection depends on using tools such as X-rays, it often creates a high time gap between disease occurrence and detection time, increasing the risk of disease. In addition, the lack of reliable biomarkers for accurately diagnosing RA constrains the effectiveness of nanomaterial-based biosensors, which are primarily advantageous in predicting joint pain. In clinical practice, a physical examination of the joints is still necessary to confirm the presence of inflammatory synovitis, leading to duplicated efforts. Thus, this limitation emphasizes the significance of developing specific biomarkers tailored and designed for the diagnosis of RA in the future. Lastly, implementing automation for RA theranostics is definitely a possibility, although there are not many RA theranostic situations in the real world at the moment. As research advances, we can expect further automation and integration of nanomaterials for precise and successful RA therapy.

REFERENCE

1. G.R. Burmester et al.Novel treatment strategies in rheumatoid arthritisLancet.(2017)
2. J.S. Smolen et al.Treating rheumatoid arthritis to target: recommendations of an international task forceAnn. Rheum. Dis.(2010)
3. S. Ramiro et al.Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritisAnn. Rheum. Dis. (2017)
4. W. Wang et al.Side effects of methotrexate therapy for rheumatoid arthritis: a systematic reviewEur. J. Med. Chem. (2018)
5. R. Heo et al.Dextran sulfate nanoparticles as a theranostic nanomedicine for rheumatoid arthritisBiomaterials.(2017)
6. S. Jafari et al.Methylprednisolone acetate-loaded hydroxyapatite nanoparticles as a potential drug delivery system for treatment of rheumatoid arthritis: in vitro and in vivo evaluationsEur. J. Pharm. Sci. (2016)
7. R. Ulmansky et al.Glucocorticoids in nano-liposomes administered intravenously and subcutaneously to adjuvant arthritis rats are superior to the free drugs in suppressing arthritis and inflammatory cytokinesJ. Control. Release (2012)
8. M. Lorscheider et al.Dexamethasone palmitate nanoparticles: an efficient treatment for rheumatoid arthritisJ. Control. Release (2019)
9. C. Li et al.pH-sensitive polymeric micelles for targeted delivery to inflamed jointsJ. Control. Release (2017)
10. H.M. Khojah et al. Reactive oxygen and nitrogen species in patients with rheumatoid arthritis as potential biomarkers for disease activity and the role of antioxidants Free Radic. Biol. Med. (2016)

11. J Schmitt, K Schwarz, H Baurecht, M Hotze, R Folster Holst, E Rodriguez, YA Lee, A Franke, F Degenhardt, W Lieb, Gieger C, Kabesch M, Nothen MM, Irvine AD, McLean WHI, Deckert S, Stephan V, Schwarz P, Aringer M, Novak N, Weidinger S. Atopic dermatitis is associated with an increased risk for rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes. J Allergy Clin Immunol. 2016;137(1):130-6. doi: 10.1016/j.jaci.2015.06.029, PMID 26253344.
12. RJ Oken, M Schulzer. At issue: schizophrenia and rheumatoid arthritis: the negative association revisited. Schizophr Bull. 1999;25(4):625-38. doi: 10.1093/oxfordjournals.schbul.a033407, PMID 10667736.
13. P Stolt, C Bengtsson, B Nordmark, S Lindblad, I Lundberg, L Klareskog, L Alfredsson, EIRA Study Group. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population-based case-control study, using incident cases. Ann Rheum Dis. 2003;62(9):835-41. doi: 10.1136/ard.62.9.835, PMID 12922955.
14. JE Hart, F Laden, RC Puett, KH Costenbader, EW Karlson. Exposure to traffic pollution and increased risk of rheumatoid arthritis. Environ Health Perspect. 2009;117(7):1065-9. doi: 10.1289/ehp.0800503, PMID 19654914.
15. HR Harris, KH Costenbader, F Mu, M Kvaskoff, S Malspeis, EW Karlson, SA Missmer. Endometriosis and the risks of systemic lupus erythematosus and rheumatoid arthritis in the Nurses' Health Study II. Ann Rheum Dis. 2016;75(7):1279-84. doi: 10.1136/annrheumdis-2015-207704, PMID 26238146.
16. Sourav Thakur S, Bushra Riyaz B, Akshay Patil A, Amanjot Kaur A, Bhupinder Kapoor B, Vijay Mishra V. Novel drug delivery systems for NSAIDs in management of rheumatoid arthritis: Aan overview. Biomed Pharmacother. 2018; 106:1011-23. doi: 10.1016/j.biopha.2018.07.027, PMID 30119166.
17. CT Kraft, S Agarwal, K Ranganathan, VW Wong, S Loder, J Li J, MJ Delano, B Levi. Trauma-induced heterotopic bone formation and the role of the immune system: A review. J Trauma Acute Care Surg. 2016;80(1):156-65. doi: 10.1097/ TA.0000000000-000883, PMID 26491794.
18. G Jones, P Nash, S Hall. Advances in rheumatoid arthritis. Med J Aust. 2017;206(5):221-4. doi: 10.5694/mja16.01287, PMID 28301793.
19. MI Koenders, WB van den Berg. Novel therapeutic targets in rheumatoid arthritis. Trends Pharmacol Sci. 2015;36(4):189-95.
20. F Yuan, LD Quan, L Cui, SR Goldring, D Wang. Development of macromolecular prodrug for rheumatoid arthritis. Adv Drug Delivery Rev. 2012;64(12):1205-19. doi: 10.1016/j.addr.2012.03.006, PMID 22433784.
21. Van Vollenhoven RF. Treatment of rheumatoid arthritis: state of the art. Nat Rev Rheumatol. 2009;5(10):531-41. doi: 10.1038/nrrheum.2009.182, PMID 19798027.
22. Dolati S, Sadreddini S, Rostamzadeh D, Ahmadi M, Jadidi Niaragh F, Yousefi M. Utilization of nanoparticle technology in rheumatoid arthritis treatment. Biomed Pharmacother. 2016; 80:30-41. doi: 10.1016/j.biopha.2016.03.004, PMID 27133037.
23. Tarner IH, Muller Ladner U. Drug delivery systems for the treatment of rheumatoid arthritis. Expert Opin Drug Deliv. 2008;5(9):1027-37. doi: 10.1517/17425247.5.9.1027, PMID 18754751.
24. Prasad LK, O'Mary H, Cui Z. Nanomedicine delivers promising treatments for rheumatoid arthritis. Nanomedicine (Lond). 2015;10(13):2063-74. doi: 10.2217/nnm.15.45, PMID 26084368.
25. Mitragotri S, Yoo JW. Designing micro- and nano-particles for treating rheumatoid arthritis. Arch Pharm Res. 2011;34(11):1887-97. doi: 10.1007/s12272-011-1109-9.
26. Buch MH, Bingham SJ, Bryer D, Emery P. Long-term infliximab treatment in rheumatoid arthritis: subsequent outcome of initial responders. Rheumatology (Oxford). 2007;46(7):1153-6. doi: 10.1093/rheumatology/kem075, PMID 17478470.
27. Chaudhari K, Rizvi S, Syed BA. Rheumatoid arthritis: current and future trends. Nat Rev Drug Discov. 2016;15(5):305-6. doi: 10.1038/nrd.2016.21, PMID 27080040.
28. Listing J, Strangfeld A, Kary S, Rau R, Von Hinueber U, Stoyanova Scholz M, Gromnica Ihle E, Antoni C, Herzer P, Kekow J, Schneider M, Zink A. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis

Rheum. 2005;52(11):3403-12. doi: 10.1002/art.21386, PMID 16255017.
29. Rao JK, Mihaliak K, Kroenke K, Bradley J, Tierney WM, Weinberger M. Use of complementary therapies for arthritis among patients of rheumatologists. Ann Intern Med. 1999;131(6):409-16. doi: 10.7326/0003-4819-131-6-199909210-00003, PMID 10498556.
30. Chandrasekar R, Chandrasekar S. Natural herbal treatment for rheumatoid arthritis-a review. Int J Pharm Sci Res. 2017;8(2):368.
31. Movahedi M, Beauchamp ME, Abrahamowicz M, Ray DW, Michaud K, Pedro S, Dixon WG. Risk of incident diabetes mellitus associated with the dosage and duration of oral glucocorticoid therapy in patients with rheumatoid arthritis. Arthritis Rheumatol. 2016;68(5):1089-98. doi: 10.1002/art.39537, PMID 26663814.
32. Bahadar H, Maqbool F, Niaz K, Abdollahi M. Toxicity of nanoparticles and an overview of current experimental models. Iran Biomed J. 2016;20(1):1-11. doi: 10.7508/ibj.2016.01.001, PMID 26286636.
33. Xu L, Qi X, Li X, Bai Y, Liu H. Recent advances in applications of nanomaterials for sample preparation. Talanta 2016; 146:714-26.
34. Y Panahi, M Farshbaf, M Mohammad Hosseini, M Mirahadi, R Khalilov, S Saghfi, A Akbarzadeh. Recent advances on liposomal nanoparticles: synthesis, characterization and biomedical applications. Artif Cells Nanomed Biotechnol. 2017;45(4):788-99. doi: 10.1080/21691401.2017.1282496, PMID 28278586.
35. Heloise R, Danhier F, Preat V, Langer R, Anderson DG. Nanoparticle-based drug delivery systems: a commercial and regulatory outlook as the field matures. Expert Opion Drug Delivery 2017;14(7):851-64.
36. E Nogueira, AC Gomes, A Preto, A Cavaco, Paulo A. Folate-targeted nanoparticles for rheumatoid arthritis therapy. Nanomedicine 2016;12(4):1113-26. doi: 10.1016/ j. nano.2015.12.365, PMID 26733257.
37. Q Thao le, Byeon HJ, Lee C, Lee S, Lee ES, Choi HG, Park ES, Youn YS le, HJ Byeon C. Pharmaceutical potential of tacrolimus-loaded albumin nanoparticles having targetability to rheumatoid arthritis tissues. Int J Pharm 2016;497(1-2):268-76. doi: 10.1016/j.ijpharm.2015.12.004, PMID 26657273.
38. S Behzadi, V Serpooshan, W Tao, MA Hamaly, MY Alkawareek, EC Dreaden, D Brown, AM Alkilany, OC Farokhzad, M Mahmoudi. Cellular uptake of nanoparticles: Journey inside the cell. Chem Soc Rev. 2017;46(14):4218-44. doi: 10.1039/c6cs00636a, PMID 28585944.
39. TM Ahmed, BM Aljaeid. Preparation, characterization, and potential application of chitosan, chitosan derivatives, and chitosan metal nanoparticles in pharmaceutical drug delivery. Drug Des Dev Ther. 2016; 10:483-507. doi: 10.2147/DDDT.S99651, PMID 26869768.
40. Rao SD. Rheumatoid arthritis (ra) disease treatment with rutin stabilized nanoparticles, Austin. J Biotechnol Bioeng. 2015; 2(2):1043.
41. Lee SN, Kim HJ, Ha YJ, Park YN, Lee SK, Park YB, Yoo KH. Targeted chemo photothermal treatments of rheumatoid arthritis using gold half-shell multifunctional nanoparticles. ACS. 2012;7(1):50-7.
42. Kishore N, Raja MD, Kumar CS, Dhanalekshmi U, Srinivasan R. Lipid carriers for delivery of celecoxib: in vitro, in vivo assessment of nanomedicine in rheumatoid arthritis. Eur J Lipid Sci Technol. 2016;118(6):949-58. doi: 10.1002/ejlt.201400658.
43. Kumar V, Leekha A, Tyagi A, Kaul A, Mishra AK, Verma AK. Preparation and evaluation of biopolymeric nanoparticles as drug delivery system in effective treatment of rheumatoid arthritis. Pharm Res. 2017;34(3):654-67. doi: 10.1007/s11095-016-2094-y, PMID 28097508.
44. Dewangan AK, Varkey S, Mazumder S. Synthesis of curcumin loaded CMCAB nanoparticles for the treatment of rheumatoid arthritis, IJCEBS; 2015. p. 18-9.
45. Lee SM, Kim HJ, Ha YJ, Park YN, Lee SK, Park YB, Yoo KH. Targeted chemo-photothermal treatments of rheumatoid arthritis using gold half-shell multifunctional nanoparticles. ACS Nano. 2013;7(1):50-7. doi: 10.1021/nn301215q, PMID 23194301.
46. Thao le Q, Byeon HJ, Lee C, Lee S, Lee ES, Choi HG, Park ES, Youn YS. Pharmaceutical potential of tacrolimus-loaded albumin nanoparticles having targetability to rheumatoid arthritis

tissues. Int J Pharm. 2016;497(1-2):268-76. doi: 10.1016/j.ijpharm.2015.12.004, PMID 26657273.

47. Kumar R, Singh A, Garg N, Siril PF. Solid lipid nanoparticles for the controlled delivery of poorly water soluble non-steroidal anti-inflammatory drugs. Ultrason Sonochem. 2018;40(A):686-96. doi: 10.1016/j.ultsonch.2017.08.018, PMID 28946474.
48. Geszke Moritz M, Moritz M. Solid lipid nanoparticles as attractive drug vehicles: composition, properties and therapeutic strategies. Mater Sci Eng C Mater Biol Appl. 2016; 68:982-94. doi: 10.1016/j.msec.2016.05.119, PMID 27524099.
49. Garg NK, Singh B, Tyagi RK, Sharma G, Katare OP. Effective transdermal delivery of methotrexate through nanostructured lipid carriers in an experimentally induced arthritis model. Colloids Surf B Biointerfaces. 2016; 147:17-24. doi: 10.1016/j.colsurfb.2016.07.046, PMID 27478959.
50. Chavan D, Gangode B, Jadhav A, Patil M, Kshirsagar S. Solid lipid nanoparticles: A modern formulation approach in drug delivery system. IJOD. 2017;5(2):56-70.
51. Arora R, Kuhad A, Kaur IP, Chopra K. Curcumin loaded solid lipid nanoparticles ameliorate adjuvant-induced arthritis in rats. Eur J Pain. 2015;19(7):940-52. doi: 10.1002/ejp.620, PMID 25400173.
52. Peng LH, Wei W, Shan YH, Chong YS, Yu L, Gao JQ. Sustained release of piroxicam from solid lipid nanoparticle as effective anti-inflammatory therapeutics in vivo. Drug Dev Ind Pharm. 2017;43(1):55-66. doi: 10.1080/03639045.2016.1220563. PMID 27498809.
53. Bhalekar MR, Madgulkar AR, Desale PS, Marium G. Formulation of piperine solid lipid nanoparticles (SLN) for treatment of rheumatoid arthritis. Drug Dev Ind Pharm. 2017;43(6):1003-10. doi: 10.1080/03639045.2017.1291666, PMID 28161984.
54. Raj R, Mongia P, Ram A, Jain NK. Enhanced skin delivery of aceclofenac via hydrogel-based solid lipid nanoparticles. Artif Cells Nanomed Biotechnol. 2016;44(6):1434-9. doi: 10.3109/21691401.2015.1036997, PMID 25919063.
55. Ye J, Wang Q, Zhou X, Zhang N. Injectable actarit-loaded solid lipid nanoparticles as passive targeting therapeutic agents for rheumatoid arthritis. Int J Pharm 2008;352(1-2):273-9. doi: 10.1016/j.ijpharm.2007.10.014, PMID 18054182.
56. Gilani SJ, Bin-Jumah MN, Imam SS, Alshehri S, Jahangir MA, Zafar A. Formulation and optimization of nano lipid based oral delivery systems for arthritis. Coatings. 2021;11(5):548. doi: 10.3390/coatings11050548.
57. Mancini G, Gonçalves LMD, Marto J, Carvalho FA, Simoes S, Ribeiro HM, Almeida AJ. Increased therapeutic efficacy of SLN containing etofenamate and ibuprofen in topical treatment of inflammation. Pharmaceutics. 2021;13(3):328. doi: 10.3390/pharmaceutics13030328, PMID 33802592.
58. Zhang F, Liu Z, He X, Li Z, Shi B, Cai F. β-sitosterol-loaded solid lipid nanoparticles ameliorate complete freund's adjuvant-induced arthritis in rats: involvement of NF-κB and HO-1/Nrf-2 pathway. Drug Deliv. 2020;27(1):1329-41. doi: 10.1080/10717544.2020.1818883, PMID 32945205.
59. Chaudhari PM, Ghodake MV. Development and optimization of solid lipid nanoparticle for topical delivery. J Drug Deliv Ther. 2019;9(5):105-21.
60. Shinde SV, Nikam S, Raut P, Ghag MK. Lipid nanoparticles for transdermal delivery of celecoxib: an in vitro and in vivo investigation. Indian Drugs. 2019;56(8):38-48.
61. Chuang SY, Lin CH, Huang TH, Fang JY. Lipid-based nanoparticles as a potential delivery approach in the treatment of rheumatoid arthritis. Nanomaterials (Basel). 2018;8(1):42. doi: 10.3390/nano8010042, PMID 29342965.
62. Purcell WT, Ettinger DS. Novel antifolate drugs. Curr Oncol Rep. 2003;5(2):114-25. doi: 10.1007/s11912-003-0098-3, PMID 12583828.
63. Bleyer WA. The clinical pharmacology of methotrexate: new applications of an old drug. Cancer. 1978;41(1):36-51. doi: 10.1002/1097-0142(197801)41:1<36:aid-cncr2820410108>3.0.co;2-i, PMID 342086.
64. Grim J, Chladek J, Martínkova J. Pharmacokinetics and pharmacodynamics of

methotrexate in non-neoplastic diseases. Clin Pharmacokinet. 2003;42(2):139-51. doi: 10.2165/00003088-200342020-00003, PMID 12537514.

65. Cutolo M, Sulli A, Pizzorni C, Seriolo B, Straub RH. Anti-inflammatory mechanisms of methotrexate in rheumatoid arthritis. Ann Rheum Dis. 2001;60(8):729-35. doi: 10.1136/ard.60.8.729, PMID 11454634.
66. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet. 2001;358(9285):903-11. doi: 10.1016/S0140-6736(01)06075-5, PMID 11567728.
67. Tarner IH, Muller Ladner U. Drug delivery systems for the treatment of rheumatoid arthritis. Expert Opin Drug Deliv. 2008;5(9):1027-37. doi: 10.1517/17425247.5.9.1027, PMID 18754751.
68. Rahman LK, Chhabra SR. The chemistry of methotrexate and its analogues. Med Res Rev. 1988;8(1):95-155. doi: 10.1002/med.2610080106, PMID 3278183.
69. Chatterji DC, Gallelli JF. Thermal and photolytic decomposition of methotrexate in aqueous solutions. J Pharm Sci. 1978;67(4):526-31. doi: 10.1002/jps.2600670422, PMID 641762.
70. Genestier L, Paillot R, Quemeneur L, Izeradjene K, Revillard JP. Mechanisms of action of methotrexate. Immunopharmacology. 2000;47(2-3):247-57. doi: 10.1016/s0162-3109(00)00189-2, PMID 10878292.
71. Cutolo M, Bisso A, Sulli A, Felli L, Briata M, Pizzorni C, Villaggio B. Antiproliferative and antiinflammatory effects of methotrexate on cultured differentiating myeloid monocytic cells (THP-1) but not on synovial macrophages from patients with rheumatoid arthritis. J Rheumatol. 2000;27(11):2551-7. PMID 11093433.
72. Hillson JL, Furst DE. Pharmacology and pharmacokinetics of methotrexate in rheumatic disease. Practical issues in treatment and design. Rheum Dis Clin North Am. 1997;23(4):757-78. doi: 10.1016/s0889-857x(05)70359-8, PMID 9361154.
73. Cronstein BN. The mechanism of action of methotrexate. Rheum Dis Clin North Am. 1997;23(4):739-55. doi: 10.1016/S0889-857X(05)70358-6.
74. Koch AE, Distler O. Vasculopathy and disordered angiogenesis in selected rheumatic diseases: rheumatoid arthritis and systemic sclerosis. Arthritis Res Ther. 2007;9 Suppl 2:S3. doi: 10.1186/ar2187, PMID 17767741.
75. Koning GA, Schiffelers RM, Wauben MH, Kok RJ, Mastrobattista E, Molema G, ten Hagen TL, Storm G. Targeting of angiogenic endothelial cells at sites of inflammation by dexamethasone phosphate-containing RGD peptide liposomes inhibits experimental arthritis. Arthritis Rheum. 2006;54(4):1198-208. doi: 10.1002/art.21719, PMID 16575845.
76. Gaffo A, Saag KG, Curtis JR. Treatment of rheumatoid arthritis. Am J Health Syst Pharm. 2006;63(24):2451-65. doi: 10.2146/ajhp050514, PMID 17158693.
77. Levick JR. Permeability of rheumatoid and normal human synovium to specific plasma proteins. Arthritis Rheum. 1981;24(12):1550-60. doi: 10.1002/art.1780241215, PMID 7326067.
78. Levick JR. Microvascular architecture and exchange in synovial joints. Microcirculation. 1995;2(3):217-33. doi: 10.3109/10739689509146768, PMID 8748946.
79. Levick JR. Hypoxia and acidosis in chronic inflammatory arthritis; relation to vascular supply and dynamic effusion pressure. J Rheumatol. 1990;17(5):579-82. PMID 2359066.
80. Halin C, Neri D. Antibody-based targeting of angiogenesis. Crit Rev Ther Drug Carrier Syst. 2001;18(3):299-339. doi: 10.1615/CritRevTherDrugCarrierSyst.v18.i3.20, PMID 11442202.
81. Nagai T, Tanaka M, Tsuneyoshi Y, Matsushita K, Sunahara N, Matsuda T, Yoshida H, Komiya S, Onda M, Matsuyama T. In vitro and in vivo efficacy of a recombinant immunotoxin against folate receptor beta on the activation and proliferation of rheumatoid arthritis synovial cells. Arthritis Rheum. 2006;54(10):3126-34. doi: 10.1002/art.22082, PMID 17009233.
82. Trachsel E, Bootz F, Silacci M, Kaspar M, Kosmehl H, Neri D. Antibody-mediated delivery of IL-10 inhibits the progression of established collagen-induced arthritis. Arthritis Res Ther. 2007;9(1):R9. doi: 10.1186/ar2115, PMID 17261171.
83. Taheri A. Nanoparticles of conjugated methotrexate-human serum albumin: preparation

and cytotoxicity evaluations. J Nanomaterials 2011; 5:1-7. doi: 10.1155/2011/768201

84. Taheri A, Dinarvand R, Ahadi F, Khorramizadeh MR, Atyabi F. The in vivo antitumor activity of LHRH targeted methotrexate-human serum albumin nanoparticles in 4T1 tumor-bearing Balb/c mice. Int J Pharm. 2012;431(1-2):183-9. doi: 10.1016/j.ijpharm.2012.04.033. PMID 22531853.

HOW TO CITE: Aditya Jagatap*, Mayuri Kalokhe, Aniket Gavali, Manali Bavadekar, Nanomedicines Used in The Treatment of the Rheumatoid Arthritis, Int. J. Sci. R. Tech., 2025, 2 (7), 96-104. https://doi.org/10.5281/zenodo.15806607