Frontiers in Health Informatics
ISSN-Online: 2676-7104
www.healthinformaticsjournal.com
2024; Vol 13: Issue 8
Open Access

Nano-Theraputic Approach for the Osteoarthritis: An Overview.

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Cite this paper as: Smrati Bhardwaj, Naresh Kalra, Wasif Khan (2024) Nano-Theraputic Approach for the Osteoarthritis: An Overview. *Frontiers in Health Informatics, 13* (8), 2554-2563

Abstract:
Osteoarthritis is a debilitating disease involving chronic pain and inflammation of joints culminating in joint immobility. The increase in the aging population and obesity have contributed to the rise in osteoarthritic patients. The disease is characterized by gradual erosion of articular cartilage with loss of collagen type II and proteoglycans attributed to pro-inflammatory cytokines, reactive oxygen species, and proteolytic enzymes. Presently, there are no therapies to curb or reverse osteoarthritis progression. The avascular nature of cartilage causing poor drug penetration and retention coupled with rapid synovial clearance compromises the efficacy of conventional intraarticular injections. There is an urgent need to develop novel therapies that can address the disease on multiple fronts and enhance patient quality of life. This review showcases the incredible potential of nanoparticles in the management of osteoarthritis. The commonly used drugs for the clinical diagnosis and treatment of OA have limitations such as low bioavailability, shorthalf-life, poor targeting, and high systemic toxicity. With the application of nanomaterials and intelligent nanomedicines, novel nanotherapeutic strategies have shown more specific targeting, prolonged half-life, refined bioavailability, and reduced systemic toxicity, compared to the existing medications. In this review, we summarized the recent advancements in new nanotherapeutic strategies for OA and provided suggestions for improving the treatment of OA.
Key Words: *Nanotechnology, Nanotherapeutic Strategies, Nanoparticle, Osteoarthritis*.

INTRODUCTION:

Osteoarthritis (OA) is an incapacitating disease involving chronic pain and inflammation of joints culminating in a compromised quality of life [1]. The World Health Organization (WHO) has included osteoarthritis as one of the three killers of human health [2]. WHO has declared 2021–2030 as the decade of healthy aging emphasizing the need to focus on diseases like osteoarthritis which strongly impact functional capacity and quality of life [3]. Osteoarthritis is the second leading musculoskeletal disorder after low-back pain in Disability Adjusted Life Years (DALYs) calculation in the geriatric population [4]. The growth of the elderly population coupled with the enhanced occurrence of obesity is responsible for the upsurge in osteoarthritis cases [5]. It is expected that by 2030, around 25 % of the adult population will suffer from osteoarthritis [6]. Osteoarthritis may affect the knee, hips, hand, and spine [6]. Osteoarthritis cases are projected to increase by 74.9 % for the knee, 48.6 % for the hand, 78.6 % for the hip, and 95.1 % for other kinds of osteoarthritis by 2050 in comparison to cases in 2020 [3]. Osteoarthritis involves gradual

degeneration of articular cartilage, long-lasting pain, and joint immobility [7]. These symptoms culminate in poor quality of life and pose a socioeconomic burden [8].

Gastrointestinal annoyance, renal malfunctioning and enlarged cardio vascular risk were also connected with RA [9]. RA development seems to be stronger for men's connected with cigarette smoking than women's. The incidence of RA is unrevealed, but it is supposed that the environmental factors may add to its development in hereditarily susceptible individuals [10]. The genetic components and environmental factors affect the various types of cells (including B cells, T cells, macrophages/ synoviocytes) have been identified as key regulators for RA immunological events over the years following immune response and studies [11]. The linkages between environmental factors and the genetics of patients are correlated with the development of RA. Coffee/alcohol consumption, oral contraceptive use, birth weight abnormalities and breast feeding were more significant environmental risk factors for RA development [12].

Nanoparticles for the treatment of RA:

Nanoparticles are spherically shaped particles [13]. The size, surface characteristics and morphology of nanoparticles possess essential role towards the biodistribution of nanoparticle for RA treatment. Nanoparticles (NPs) are utilized as therapeutic/imaging agents, for theranostic applications. The encapsulated drug containing particles helps to afford targeted delivery/controlled release of encapsulated drugs. Physicochemical properties associated with, passive targeting of drugs for RA treatment, includes particle size, charge shape and surface characteristics. Especially, nanoparticles due to their biocompatibility and biodegradability properties hold its vital role in pharmaceutical industries. Nanoparticles conjugated with specific ligand targets and facilitate cellular penetration. The most commonly reported liposomes, micelles, metallic nanoparticles, and polymeric nanoparticle affords efficient delivery towards the treatment of RA. Nanoparticles can be taken by systemic circulation through different process such as adsorption, ligand receptor attachment, covalent coupling, and internalization.

NSAIDs based delivery systems were widely reported for RA, which decrease pain (analgesia) associated with early stage of RA through its anti-inflammatory mechanisms without loss of articular function, additionally; it blocks COX-1 and COX-2 enzymes which play an essential role in the generation of prostaglandins. Drug containing nanoparticle systems were delivered therapeutically to inflamed synovium. Metal oxide nanoparticles reveals various desired characteristics such as drug carriers with incredible higher surface area and huge pore sizes for drug encapsulation, intrinsic biodegradability characteristics due to its labile metal-ligand bonds, and versatile functionality for post synthetic grafting of drug molecules. Rutin stabilized silver nanoparticles elicits anti-inflammatory activity in chronic inflammation by its critical inhibition of the creation of pro-inflammatory cytokines (tumour necrotic factor-α (TNF-α) and interleukin-6 (IL-6). Silver nanoparticles have been also utilized for therapeutic benefits in RA patients [13].

Nanoemulsion for the treatment of RA:

Nanoemulsions are isotropic, transparent systems consisting of oil, water and emulsifier and hold an average diameter of 20–500 nm. Emulsifiers plays essential role in settling nanoemulsions through repulsive electrostatic interactions and steric hindrance. The expansion of an emulsifier is mandatory for the production of smaller sized droplets as it decreases the interfacial tension and surface energy per unit range, between the oil and water phases of the emulsion [14]. Nanoemulsions have been reported to enhance bioavailability and efficacy of most anti-inflammatory agents [15]. Nanoemulsions have been used in food industries as flavored nanoemulsions and in cosmetic industries for skin hydration with ease of application. In

pharmaceutical field, nanoemulsions have been utilized for drug delivery systems especially for parenteral, oral, ocular, and topical administration [16]. In addition to that, nanoemulsions contain building blocks for complex material such as compartmentalized nanoparticles and encapsulated oil droplets [17]. The properties associated with nanoemulsion were, high surface area per unit volume, robust stability, optically transparency, and tunable rheology.

Solid lipid nanoparticle for the treatment of RA:

Solid lipid nanoparticles (SLNs) are colloidal carriers with particle size ranging from 120 to 200 nm, widely utilized for controlled drug delivery which merges the benefits of polymeric nanoparticles and oil in water emulsions. SLNs possess remarkable properties such as a good tolerability, protection of incorporated active compounds against chemical degradation, higher bioavailability with incorporation of both lipophilic and hydrophilic drugs, higher drug loading capacity and relatively safe for biological applications [18]. Due to its unique size range SLNs rarely undergoes blood clearance by the reticulo endothelial system. SLNs were made up of physiological lipids, fatty acids, phospholipids and mono/di/triglycerides. SLNs may be prepared by various techniques such as, high shear homogenization, ultrasound, high pressure homogenization, hot homogenization, cold homogenization, solvent emulsification and evaporation methods. In recent years, greater attention has been focused towards lipid based formulations for the improved oral bioavailability of poorly water soluble drugs using SLNs [19]. The drug carrier combines the advantage of polymeric nanoparticles, fat emulsions and liposome; due to its improved physical stability, low cost, ease of scale-up, and producing [20].

Nanomicelles for the treatment of RA:

Nanomicelles are amphiphilic molecules or surfactant monomers that have a polar head and a lipophilic tail. The properties related with amphiphilic molecules in solution results in developmental structures termed as micelles. These micelles hold internally hydrophobic core and externally a hydrophilic surface [21]. Micelles are generally made up of 50–200 monomers. The parameter which affects the micelle formation was the size of the hydrophobic area of amphiphilic molecule, amphiphile concentration, temperature, and solvent [22]. Polymeric micelle holds the diameter of 10–100 nm. Micellar core serves as a compatible microenvironment with center point for joining water insoluble guest molecules. Hydrophobic molecules can be covalently coupled to the block copolymers or it can be physically incorporated into the hydrophobic micelle core. Solubilization process of nanomicelles leads to enhancement of their water solubility and bioavailability.

Nanocapsules for the treatment of RA:

Nanocapsules are sub-micron sized formulations ranging from 10 to 1000 nm, which contains one or more active materials (core) which forms a protective matrix (shell) [23]. The therapeutic substance may be in the form of liquid/solid/molecular dispersion surrounded by a polymeric membrane. Nanocapsules have recently attracted significant interest due to its protective coating, which is generally pyrophoric and gets effectively oxidized [24-26]. The main advantages of nanocapsules towards drug delivery applications were sustained release property, incremental drug selectivity, improved bioavailability and alleviation of drug toxicity [27]. In addition, polymeric nanocapsules enhance the safety and efficacy of drugs by increasing their aqueous solubility, protecting them from degradation, controlling release, enhancing bioavailability and tissue selectivity [28-31]. The diversified applications of nanocapsules in various fields includes, agrochemicals, genetic engineering, cosmetics, wastewater treatments, adhesive component

applications, delivery of the drug to tumours, radiotherapy and as liposomal nanocapsules in food science/ agriculture [32].

Targeted nanoparticulate systems for the treatment of R:

Drug delivery systems can be further improved for its therapeutic efficacy and specificity towards the treatment of various disorders using active targeting ligands such as antibody, peptide and polysaccharides. The two modes of targeting were active and passive. In the treatment of RA, the nanoparticulate formulation has been targeted towards the selectively expressed CD44 surface receptors. Mediators such as growth factors, pro-inflammatory cytokines, chemokines, cell adhesion molecules, and proteases plays vital role in the RA development. In this strategy angiogenesis and inflammation were the conditions associated with RA progression. The CD44, CD64, folate receptor-beta (FR-β), vasoactive intestinal peptide (VIP) receptor, and scavenger receptor class A, toll-like receptors, transforming growth factor-beta receptors were over expressed in macrophages. Whereas αvβ3 integrins, E-selectin, vascular cell adhesion molecule-1 (VCAM-1), and intercellular cell adhesion molecule-1 were predominantly expressed during angiogenic conditions [33].

NANOMATERIALS FOR THE DIAGNOSIS OF INFLAMMATORY ARTHRITIS:

Traditional Approaches

The disease is difficult to diagnose as there are more than 100 various kinds of arthritis and among the various disorders affecting the joints, several symptoms are identical [34]. The following classes will usually be defined as arthritis: inflammatory arthritis, degenerative arthritis, infectious arthritis, and metabolic arthritis. [35]. The most common form of arthritis is the inflammatory arthritis [36]. Historically, for the diagnosis of inflammatory arthritis, some common laboratory assays and imaging methods have been carried out. Popular laboratory tests include the detection of blood antinuclear antibodies, arthrocentesis (collection and testing of synovial fluid), complement tests, and blood cell counts (white and red blood cells, and platelets) [37, 38]. For example, the sedimentation rate of erythrocytes or ESR determines how easily red blood cells deposit at the bottom of a test tube. When there is inflammation in the body, the amount of ESR increases [39]. The amount of red blood cells present in a sample of blood is determined by hematocrit or packed cell volume (PCV). Low red blood cell levels (anemia) are frequent in patients with arthritis [40]. The rheumatoid factor (RF) monitors the presence of an antibody in most patients with RA [41]. Interestingly, for inflammatory arthritis, uric acid and CRP increase in gout [42]. On the other hand, biomarkers may allow for the diagnosis of inflammatory arthritis at early stages of the disease. The ACR/EULAR 2010 criteria for the diagnosis of RA focus on the detection of RF and of antibodies against cyclic citrullinated proteins (anti-CCP), while early diagnosis may also include antibodies against carbamylated proteins (anti-CarP), mutated citrullinated vimentin antibodies (anti-MCV), cartilage oligomeric matrix protein (anti-COMP), serum calprotectin, and 14-3-3 eta protein.

Imaging methods, on the other hand, may provide a better understanding of the processes that occur in the joint(s) during inflammatory arthritis. X-rays, ultrasound (US), MRI, and arthroscopy are imaging techniques that can be employed for inflammatory arthritis. X-rays reveal changes in the joints and damage to the bone seen in inflammatory arthritis. In order to see the condition of synovial tissue, ligaments, tendons, and joints, US is based on sound waves without radiation. MRI photographs are even more accurate than X-rays, showing joint damage, including in the muscles and tendons [43]. Arthroscopy consists of a thin tube (arthroscope) carrying a flashlight and a camera to peek through the joint. It is used to diagnose any joint debilitating and/or arthritic alterations, to classify bone disorders and tumors, and to evidence the severity of bone inflammation

and pain [44,45].

All methods have many drawbacks such as low precision, poor image resolution, and high cost, despite the extensive use of conventional methods in the diagnosis of arthritis. However, important progress in nanomedicine has been made recently and new platforms for high precision diagnosis of inflammatory arthritis can be introduced by nanotechnology [46,47].

Nanoimaging

A selection of imaging methods contributes in the diagnosis and evaluation of inflammatory arthritis, although the proper assessment of arthritis, especially in the early stages of the disease, can be problematic [48]. Various studies are therefore ongoing to improve the sensitivity and accuracy of imaging methods to facilitate early stage diagnosis of inflammation arthritis [49]. In the biomedical area, the engineering of nanoscale materials is increasingly used to fulfill this goal [50]. In the following paragraphs, the use of SPIO, gold, polymeric NPs, and multimodal nanomaterials (cerium and silica NPs) will be discussed that could have promising biomedical applications in the imaging of inflammatory arthritis.

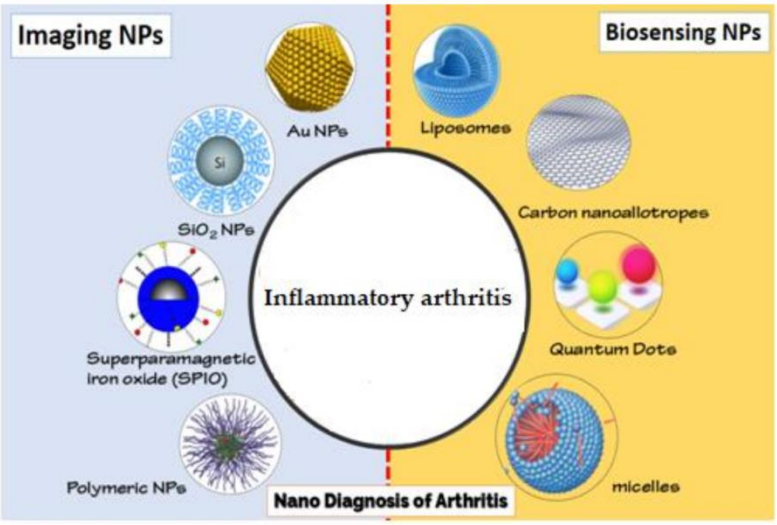

Figure 1: Nanoimagine Techniques

Nanodiagnosis

The prevalence of arthritis since the start of the post-industrial period has alarmingly risen [51]. Historically, the traditional medical diagnosis of arthritis is focused on symptoms of pain and decreased function and computed tomography (joint disturbances) that frequently appear late in the course of the disease [52]. The analysis of biological parameters may be an enticing and realistic alternative. For example, RF and anti-CCP are used for inflammatory arthritis diagnosis based on EULAR 2010 guidelines [53]. The most promising alternative for the future diagnosis and treatment of inflammatory arthritis are actually NPs [54]. Nanomaterials such as quantum dots, carbon nanoallotropes, micelles, and liposomes will be discussed in following paragraphs.

RA is characterized by the development of auto-antibodies, synovial inflammation, and degradation of bones and RF auto-antibodies are the most recognized biomarkers for arthritis as described above. To address this problem, Veigas et al. [55] developed a cost-effective and simple approach to detect and quantitatively measure the RF marker. This colorimetric nanosensor was based on crosslinking of the Au nanoprobe, resulting in extensive accumulation in the vicinity of the pentameric IgM RF. Nanoconjugate accumulation causes a change of color from red to purple that can be easily detected by the unaided eye. A limit of detection (LOD) of 4.15 UA/mL IgM RF was obtained by the nanoplatform.

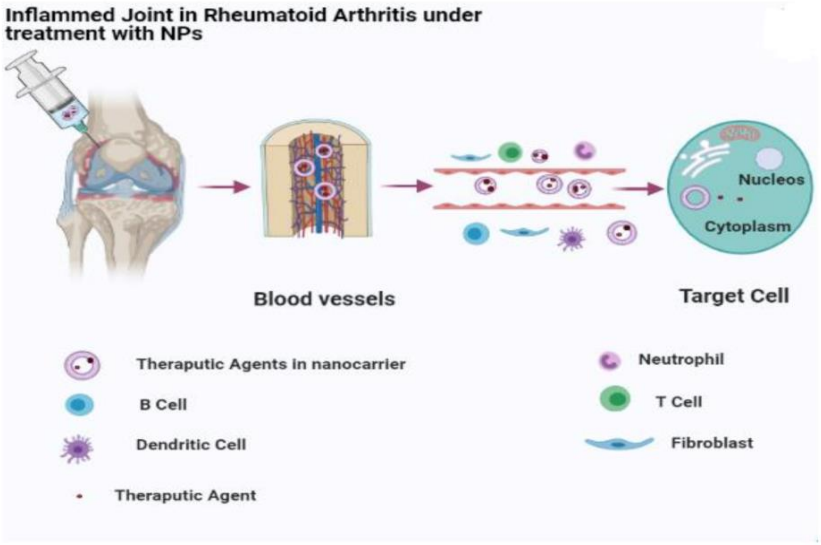

Figure 2: RA treatment with NP's

Polymeric NPs

Polymeric NPs are being prepared from colloidal particles and the diameter ranges considered (1–1000 nm). In fact, polymeric NPs have a great potential in the medical field due to their advantageous properties such as biodegradability, biocompatibility, great synthetic flexibility, ability to be precisely tailored, and appropriate mechanical properties [56]. To prevent the macrophage uptake, the surface of NPs may be sheathed with stealth polymers like PEG, and as the PEG covering density and thickness enhance, the polymeric NP circulation time increases in the blood. Modification of NPs via PEGylation, a process of covalent conjugation that prevents removal from the reticuloendothelial system, or via conjugation with other small molecules (peptides, vitamins, and antibodies) can greatly prolong the circulation time of the systems in the blood and improve the efficacy of the anti-RA drug being delivered, such as NSAIDs, corticosteroids, DMARDs, small interfering RNAs (siRNAs), and therapeutic peptides [57]. Synthetic cationic polymers such as polyethylenemine (PEI), poly-L-lysine (PLL), and dendrimers are usually utilized to deliver nucleic acids such as DNA and interfering RNAs (RNAi) [58]. Among them, PEI is the most frequently employed because of numerous protonated amino functional groups, allowing for a higher cationic charge density at physiological pH that facilitates the attachment of nucleic acids via electrostatic adsorption.

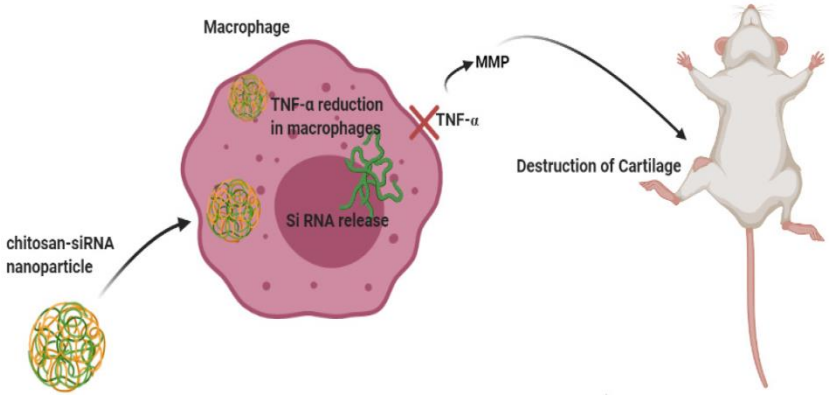

Figure 3: Polymeric NPs

Niosomes.

Niosomes are vesicles with lamellar morphology that are microscopic in size and are mostly composed of nonionic surfactants and cholesterol. They display significant advantages as drug delivery systems due to their ability to support a controlled release of drugs at a targeted site, to their nonimmunogenic properties and biocompatibility, and to their delayed clearance from the environment**.**

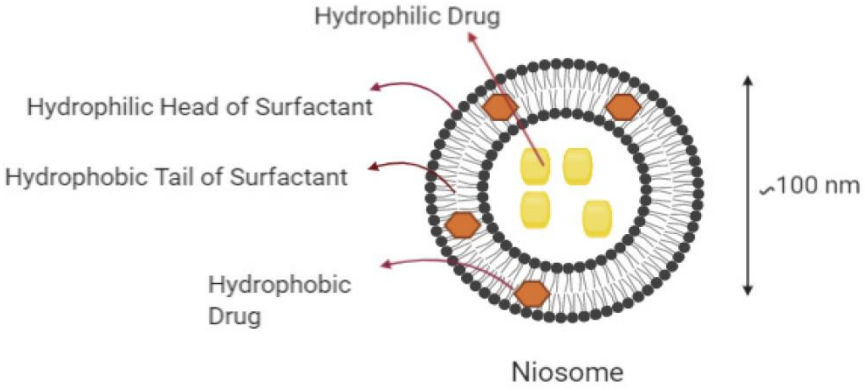

Figure 4: Structure of Niosomes

CONCLUSION:

The natural therapies such as physical therapy, occupational therapy and psychosocial therapy relevantly supports the cure of autoimmune inflammatory diseases RA at present. Eventhough combinatorial therapies are providing a better response, the aspects of selectivity and toxicity to the healthy cells creates a major issues. The future treatment options for RA treatment apart from nanoparticulate formulations may focus towards the development of selective inhibitors of proinflammatory cytokines by the virtue applications of monoclonal antibodies, bioactive peptides and siRNAbased delivery systems. Molecular biology and computational chemistry oriented focussing may offers a better design for developing formulations that specifically target pro-inflammatory cytokines.

Acknowledgment: author is thanks to Lords University, Alwar, Rajasthan, India for provide the facility for the research work and Dr. Naresh Kalra sir and Dr. Wasif Khan sir for their extraordinary support in this these work.

Conflict of interest: Nil.

REFERENCES:

1. S.B. Mello, E.R. Tavares, M.C. Guido, R.C. Maranhao Anti-inflammatory effects of intravenous methotrexate associated with lipid nanoemulsions on antigen-induced arthritis Clinics, 71 (1) (2016), pp. 54-58
2. J. Hoscheid, P.M. Outuki, S.A. Kleinubing, M.F. Silva, M.L. Bruschi, M.L.C. Cardoso
3. Development and characterization of Pterodon pubescens oil nanoemulsions as a possible delivery system for the treatment of rheumatoid arthritis Colloids Surf. A. Physicochem. Eng. Aspects, 484 (2015), pp. 19-27
4. Pathan, M. Mangle, S. Bairagi Design and characterization of nanoemulsion for transdermal delivery of meloxicam Anal. Chem. Lett., 6 (3) (2016), pp. 286-295
5. S.B. Mello, E.R. Tavares, A. Bulgarelli, E. Bonfa, R.C. Maranhao Intra-articular methotrexate associated to lipid nanoemulsions: anti-inflammatory effect upon antigen-induced arthritis Int. J.

Nanomed., 8 (2013), pp. 443-449
6. R. Kumar, A. Singh, N. Garg, P.F. Siril Solid lipid nanoparticles for the controlled delivery of poorly water soluble non-steroidal anti-inflammatory drugs Ultrason. Sonochem., 40 (Pt A) (2018), pp. 686-696
7. R. Arora, A. Kuhad, I.P. Kaur, K. Chopra Curcumin loaded solid lipid nanoparticles ameliorate adjuvant-induced arthritis in rats Eur. J. Pain., 19 (7) (2014), pp. 940-952
8. L.H. Peng, W. Wei, Y.H. Shan, Y.S. Chong, L. Yu, J.Q. Gao Sustained release of piroxicam from solid lipid nanoparticle as an effective anti-inflammatory therapeutics in-vivo Drug. Dev. Ind. Pharm., 43 (1) (2016), pp. 55-66
9. M.R. Bhalekar, A.R. Madgulkar, P.S. Desale, G. Marium Formulation of piperine solid lipid nanoparticles (SLN) for treatment of rheumatoid arthritis Drug. Dev. Ind Pharm., 43 (6) (2017), pp. 1003-1010
10. R. Raj, P. Mongia, A. Ram, N.K. Jain Enhanced skin delivery of aceclofenac via hydrogel-based solid lipid nanoparticles Artif. Cells Nanomed. Biotechnol., 44 (6) (2016), pp. 1434-1439
11. Pfizer. Pfizer value of medicines, Rheumatoid Arthritis and the Value of Treatment Global Policy and International Public Affairs; 2014.
12. Svendsen AJ, Junker P, Houen G, Kyvik KO, Nielsen C, Skytthe A, Holst R. Incidence of chronic persistent rheumatoid arthritis and the impact of smoking: A historical twin cohort study. Arthritis Care Res. 2017;69(5):616-24.
13. . 11. Yang M, Feng X, Ding J, Chang F, Chen X. Nanotherapeutics relieve rheumatoid arthritis. J Control Release. 2017;252:108- 24.
14. McInnes IB, Schett G. Pathogenetic insights from the treatment of rheumatoid arthritis. Lancet. 2017;389(10086):2328-37. doi: 10.1016/S0140-6736(17)31472-1, PMID 28612747.
15. Austin J Rheumatoid arthritis (ra) disease treatment with rutin stabilized nanoparticle Biotechnol. Bioeng., 2 (2) (2015), p. 1043
16. A. Gupta, H.B. Eral, T.A. Hatton, P.S. Doyle Nanoemulsions: formation, properties and applications RSC, 1 (2016), pp. 1-17
17. S.Y. Tang, M. Sivakumar, A.M. Ng, P. Shridharan Anti-inflammatory and analgesic activity of novel oral aspirin-loaded nanoemulsion and nano multiple emulsion formulations generated using ultrasound cavitationInt. J. Pharm., 430 (2012), pp. 299-306
18. M. Geszke Moritz, M. Moritz Solid lipid nanoparticles as attractive drug vehicles: composition, properties and therapeutic strategies Mater. Sci. Eng. C, 68 (2016), pp. 982-994
19. N.K. Garg, B. Singh, R.K. Tyagi, G. Sharma, O.P. Katare Effective transdermal delivery of methotrexate through nanostructured lipid carriers in an experimentally induced arthritis model Colloids Surf. B Biointerfaces, 147 (2016), pp. 17-24
20. D. Chavan, B. Gangode, A. Jadhav, M. Patil, S. Kshirsagar Solid lipid nanoparticles: a modern formulation approach in drug delivery system IJOD, 5 (2) (2017), pp. 56-70
21. S. Nunes, A.R. Madureira, D. Campos, B. Sarmento, A.M. Gomes, M. Pintado, F. Reis
22. Solid lipid nanoparticles as oral delivery systems of phenolic compounds: overcoming pharmacokinetic limitations for nutraceutical applications Crit. Rev. Food Sci. Nutr., 57 (9) (2017), pp. 1863-187.
23. M. Cagel, F.C. Tesan, E. Bernabeu, M.J. Salgueiro, M.B. Zubillaga, M.A. Moretton, D.AChiappetta Polymeric mixed micelles as nanomedicines: achievements and perspectives
24. Eur. J. Pharm. Biopharm., 113 (2017), pp. 211-228
25. S. Bale, A. Khurana, A.S. Reddy, M. Singh, C. Godugu Overview on therapeutic applications of microparticulate drug delivery systems Crit. Rev. Ther. Drug. Carr. Syst., 33 (4) (2016), pp. 309-361

26. Y. Wang, P. Li, T. Truong-Dinh Tran, J. Zhang, L. Kong Manufacturing techniques and surface engineering of polymer based nanoparticles for targeted drug delivery to cancer Nanomaterials (Basel), 6 (2) (2016), p. pii: E26
27. J.P. Devissaguet, H. Fessi, F. Puisieux, Process for the preparation of dispersible colloidal systems of a substance in the form of nanocapsules. US Patent 5049322 (1991).
28. Radtchenko, G. Sukhorukov, H. Mohwald A novel method for encapsulation of poorly water-soluble drugs: precipitation in polyelectrolyte multilayer shells Int. J. Pharm., 242 (2002), pp. 219-223
29. A. Jager, V. Stefani, S.S. Guterres, A.R. Pohlmann Physico-chemical characterization of nanocapsule polymeric wall using fluorescent benzazole probes Int. J Pharm., 338 (1-2) (2007), pp. 297-305
30. Bernardi, R.L. Frozza, A. Meneghetti, J.B. Hoppe, A.M. Battastini, A.R. Pohlmann, S.S. Guterres, C.G. Salbego Indomethacin-loaded lipid-core nanocapsules reduce the damage triggered by Aβ1-42 in Alzheimer's disease models Int. J Nanomed., 7 (2012), pp. 4927-4942
31. F.A. Dimer, M. Ortiz, C.S. Pase, K. Roversi, R.B. Friedrich, A.R. Pohlmann, M.E. Burger, S.S. Guterres Nanoencapsulation of olanzapine increases its efficacy in antipsychotic treatment and reduces adverse effects JBN, 10 (2014), pp. 1137-1145
32. S.E. Haas, C.C. Bettoni, L.K. de Oliveira, S.S. Guterres, T. Dalla Cost Nanoencapsulation increases quinine antimalarial efficacy against plasmodium berghei in-vivo Int. J. Antimicrob. Agents, 34 (2) (2009), pp. 156-161
33. D.M. Benvegnu, R.C. Barcelos, N. Boufleur, C.S. Pase, P. Reckziegel, F.C. Flores, A.F. Ourique, M.D. Nora, B. da Silva Cde, R.C. Beck, M.E. Burger Haloperidol-loaded polysorbate-coated polymeric nanocapsules decrease its adverse motor side effects and oxidative stress markers in rats Neurochem. Int., 61 (2012), pp. 623-631
34. P. Kothamasu, H. Kanumur, N. Ravur, C. Maddu, R. Parasuramrajam, S. Thangavel Nanocapsules: the weapons for novel drug delivery systems Bio Impacts, 2 (2) (2012), pp. 71-81
35. Bernardi, A.C. Zilberstein, E. Jager, M.M. Campos, F.B. Morrone, J.B. Calixto, A.R. Pohlmann, S.S. Guterres, A.M. Battastini Effects of indomethacin-loaded nanocapsules in experimental models of inflammation in rats Br. J. Pharmacol., 158 (2009), pp. 1104-1111
36. Jo, J.; Tian, C.; Xu, G.; Sarazin, J.; Schiopu, E.; Gandikota, G.; Wang, X. Photoacoustic tomography for human musculoskeletal imaging and inflammatory arthritis detection. Photoacoustics 2018, 12, 82–89.
37. Glaudemans, A.W.; Quintero, A.M.; Signore, A. PET/MRI in Infectious and Inflammatory Diseases: Will It Be a Useful Improvement? Springer: Berlin/Heidelberg, Germany, 2012.
38. Cormode, D.P.; Skajaa, T.; Fayad, Z.A.; Mulder, W.J. Nanotechnology in medical imaging: Probe design and applications. Arterioscler. Thromb. Vasc. Biol. 2009, 29, 992–1000.
39. Dardzinski, B.J.; Schmithorst, V.J.; Holland, S.K.; Boivin, G.P.; Imagawa, T.; Watanabe, S.; Lewis, J.M.; Hirsch, R. MR imaging of murine arthritis using ultrasmall superparamagnetic iron oxide particles. Magn. Reson. Imaging 2001, 19, 1209–1216.
40. Lutz, A.M.; Seemayer, C.; Corot, C.; Gay, R.E.; Goepfert, K.; Michel, B.A.; Marincek, B.; Gay, S.; Weishaupt, D. Detection of synovial macrophages in an experimental rabbit model of antigen-induced arthritis: Ultrasmall superparamagnetic iron oxide–enhanced MR imaging. Radiology 2004, 233, 149–157.
41. Chen, C.-L.; Siow, T.Y.; Chou, C.-H.; Lin, C.-H.; Lin, M.-H.; Chen, Y.-C.; Hsieh, W.-Y.; Wang, S.-J.; Chang, C. Targeted superparamagnetic iron oxide nanoparticles for in vivo magnetic resonance imaging of T-cells in rheumatoid arthritis. Mol. Imaging Biol. 2017, 19, 233–244.
42. Finkelstein, A.; Walz, D.; Batista, V.; Mizraji, M.; Roisman, F.; Misher, A. Auranofin. New oral

gold compound for treatment of rheumatoid arthritis. Ann. Rheum. Dis. 1976, 35, 251–257.
43. Ma, J.; Liu, X.; Wang, R.; Zhang, J.; Jiang, P.; Wang, Y.; Tu, G. Bimetallic core-shell nanostars with tunable surface plasmon resonance for surface-enhanced Raman scattering. ACS Appl. Nano Mater. 2020, 3, 10885–10894.
44. Zhao, Y.; Liu, Y.; Li, X.; Wang, H.; Zhang, Y.; Ma, H.; Wei, Q. Label-free ECL immunosensor for the early diagnosis of rheumatoid arthritis based on asymmetric heterogeneous polyaniline-gold nanomaterial. Sens. Actuators B Chem. 2018, 257, 354–361.
45. Fournelle, M.; Bost, W.; Tarner, I.H.; Lehmberg, T.; Weiß, E.; Lemor, R.; Dinser, R. Antitumor necrosis factor-α antibody-coupled gold nanorods as nanoprobes for molecular optoacoustic imaging in arthritis. Nanomed. Nanotechnol. Biol. Med. 2012, 8, 346–354.
46. Sarkar, S.; Levi-Polyachenko, N. Conjugated polymer nano-systems for hyperthermia, imaging and drug delivery. Adv. Drug Deliv. Rev. 2020, 163, 40–64.
47. Chen, J.; Qi, J.; Chen, C.; Chen, J.; Liu, L.; Gao, R.; Zhang, T.; Song, L.; Ding, D.; Zhang, P. Tocilizumab-conjugated polymer nanoparticles for NIR-II photoacoustic-imaging-guided therapy of rheumatoid arthritis. Adv. Mater. 2020, 32, 2003399.
48. Vu-Quang, H.; Vinding, M.S.; Jakobsen, M.; Song, P.; Dagnaes-Hansen, F.; Nielsen, N.C.; Kjems, J. Imaging rheumatoid arthritis in mice using combined near infrared and 19 F magnetic resonance modalities. Sci. Rep. 2019, 9, 14314.
49. Xiao, S.; Tang, Y.; Lin, Y.; Lv, Z.; Chen, L. Tracking osteoarthritis progress through cationic nanoprobe-enhanced photoacoustic imaging of cartilage. Acta Biomater. 2020, 109, 153–162.
50. Rieter, W.J.; Kim, J.S.; Taylor, K.M.; An, H.; Lin, W.; Tarrant, T.; Lin, W. Hybrid silica nanoparticles for multimodal imaging. Angew. Chem. Int. Ed. 2007, 46, 3680–3682.
51. Celardo, I.; Pedersen, J.Z.; Traversa, E.; Ghibelli, L. Pharmacological potential of cerium oxide nanoparticles. Nanoscale 2011, 3, 1411–1420.
52. Gavrilă, B.; Ciofu, C.; Stoica, V. Biomarkers in rheumatoid arthritis, what is new? J. Med. Life 2016, 9, 144.
53. Humby, F.C.; Al Balushi, F.; Lliso, G.; Cauli, A.; Pitzalis, C. Can synovial pathobiology integrate with current clinical and imaging prediction models to achieve personalized health care in rheumatoid arthritis? Front. Med. 2017, 4, 41.
54. Veigas, B.; Matias, A.; Calmeiro, T.; Fortunato, E.; Fernandes, A.R.; Baptista, P.V. Antibody modified gold nanoparticles for fast colorimetric screening of rheumatoid arthritis. Analyst 2019, 144, 3613–3619.
55. Hwang, E.Y.; Lee, J.H.; Lim, D.W. Compartmentalized bimetal cluster-poly (aniline) hybrid nanostructures for multiplexed detection of autoantibodies in early diagnosis of rheumatoid arthritis. Sens. Actuators B Chem. 2020, 321, 128482.
56. Chu, K.-A.; Chen, W.; Hsu, C.Y.; Hung, Y.-M.; Wei, J.C.-C. Increased risk of rheumatoid arthritis among patients with Mycoplasma pneumonia: A nationwide population-based cohort study in Taiwan. PLoS ONE 2019, 14, e0210750.
57. Jia, X.; Wang, C.; Rong, Z.; Li, J.; Wang, K.; Qie, Z.; Xiao, R.; Wang, S. Dual dye-loaded Au@ Ag coupled to a lateral flow immunoassay for the accurate and sensitive detection of Mycoplasma pneumoniae infection. RSC Adv. 2018, 8, 21243–21251.
58. Carroll, M.B.; Fields, J.H.; Clerc, P.G. Rheumatoid arthritis in patients with HIV: Management challenges. Open Access Rheumatol. Res. Rev. 2016, 8, 51.