

Current reviews depicting therapeutic potential of novel drug delivery system in rheumatoid arthritis

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ABSTRACT

Modern advancement in science and technology has altered the way we detect, treat and prevent different diseases in all aspects of human life. Rheumatoid Arthritis (RA) is chronic progressive autoimmune disease in which body's immune system has role to protect the health by attacking foreign bacteria but the virus mistakenly attacking the joints as a result thickened synovium, pannus formation, & destruction of bone, cartilage occurs. Researchers are still researching but are unable to know the exact reason for the disease. Although, it is believed that genes and environmental factors play an important role in the development of RA. In this review the pathophysiology, predictors and factors involved in pathogenesis of RA have been investigated. The conventional drug therapeutic agents and emerging novel drug delivery system (NDDS) like nanoparticles, dendrimers, micelles, microspheres, liposomes and so on are discussed, as these are the tools which show promising effect in overcoming the limitations associated with conventional drug delivery systems. Although several NDDS have been used for various purposes, liposomes have been focused and found to have its potential applications in RA diagnosis and therapy. In addition, the therapeutic effectiveness, and challenges for RA by using these novel drug delivery systems have been reviewed along with its future perspectives.

1 Introduction

Rheumatoid Arthritis is a dependable, auto-immune condition that first influences joints and then spreads among different organs. If left untreated, several consequences such as rheumatoid vasculitis, and irreversible joint damage arthroplasty may develop resulting in severe disability and early death [1]. The auto-response of various insusceptible modulators, such as plasma cells and cell Division, leads to joint injury. It begins by attacking th6fe synovium's membranes before moving on to the nearby structures. Sinusitis is brought on by the actuation of mast cells, macrophages, Thymus cells (T cells), plasma cells, B Lymphocytes, and angiogenesis of cells [2]. However, new therapies with better results have been developed as a result of breakthroughs in our knowledge of the disease's etiology. The current therapeutic approach, which reflects this advancement, involves starting intensive therapy as soon as a diagnosis is made and escalating the medication in the goal of clinical remission while being guided by an evaluation of the disease activity [3].

For the treatment of RA, a number of significant medications including glucocorticoids, DMARDS, NSAIDS, and biological medications are employed. However, regular dosage is used to enhance the therapeutic benefits due to limited bioavailability and high clearance rates[4].Rheumatoid Arthritis leading to severe disability and early death. Chronic synovial membrane inflammation brought on by RA results in extra-articular disease symptoms such as periarticular bone erosion, articular cartilage degradation, and irreversible abnormalities. Aging is the most significant threat for the emergence of Rheumatoid Arthritis. According to estimates, RA affects 1% of the world's population, with women experiencing 2-3 times as many cases as males. The prevalence of RA in India is 0.28 to 0.7%, which is comparable with the frequency of already developed countries [5]. Various predictors behind the RA are represented in Figure1.

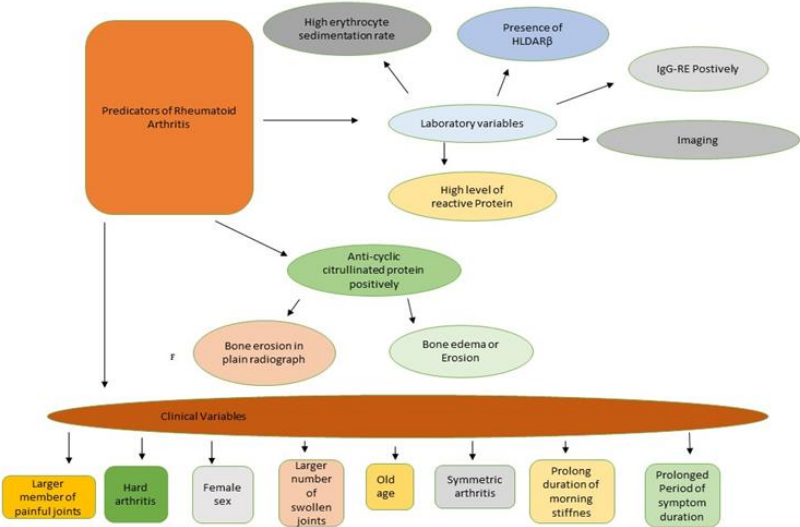


Fig. 1 Pathological factor Rheumatoid Arthritis

1.1Pathological Factor of Rheumatoid Arthritis

The symptoms related to rheumatoid arthritis include joint inflammation caused due to the invasion of the infiltration of the Aggravation cells. The reason behind Rheumatoid Arthritis is complicated process involving the development of Pannus and synovial fibroblast growth leading to invasion of Plasma cells, macrophages, T-cells, and B-cells But it consists of mediators to create a network of interconnected systems, Various cells or the factor like Tumor necrosis factor (TNF), interleukins, and cytokines, factor which regulates the production of Pro-inflammatory Cytokines, which increase production of pro-inflammatory Consequently, goal of therapy is to improve functioning to avoid joint damage capabilities, reducing pain and inflammation in the proper order to continue living a normal life. NSAIDs, DMARDs, biological antirheumatic medications, and corticosteroids have anti-inflammatory and analgesic effects however it does not stop joint deterioration to slow the development [10]. The main classes of medication used to treat RA that show improvement in preventing joint deterioration are DMARDs and biological antirheumatic medicines. Three significant contributors to the pathogenesis below are categories for rheumatoid arthritis [11] as seen in Figure 2 and 3.

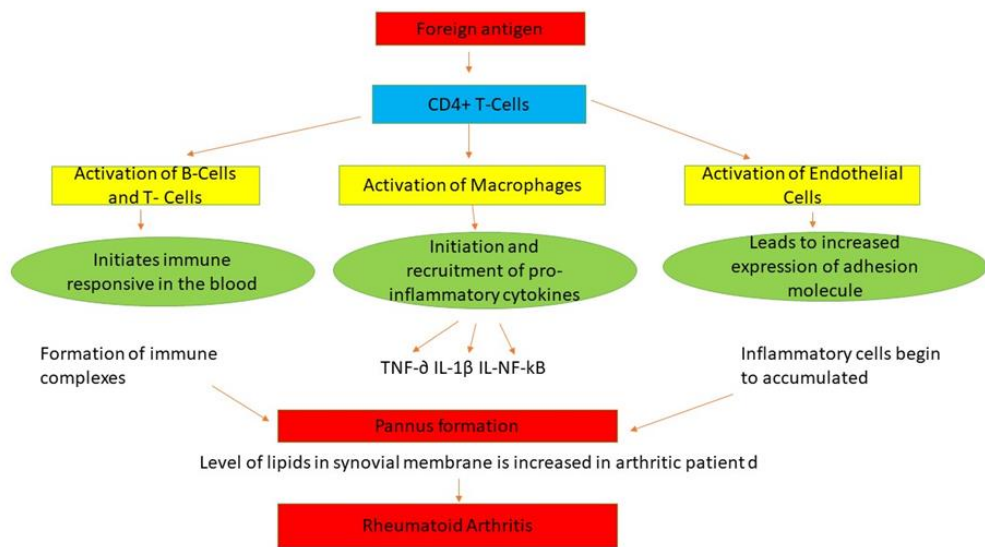


Fig. 2 Pathogenesis of RA

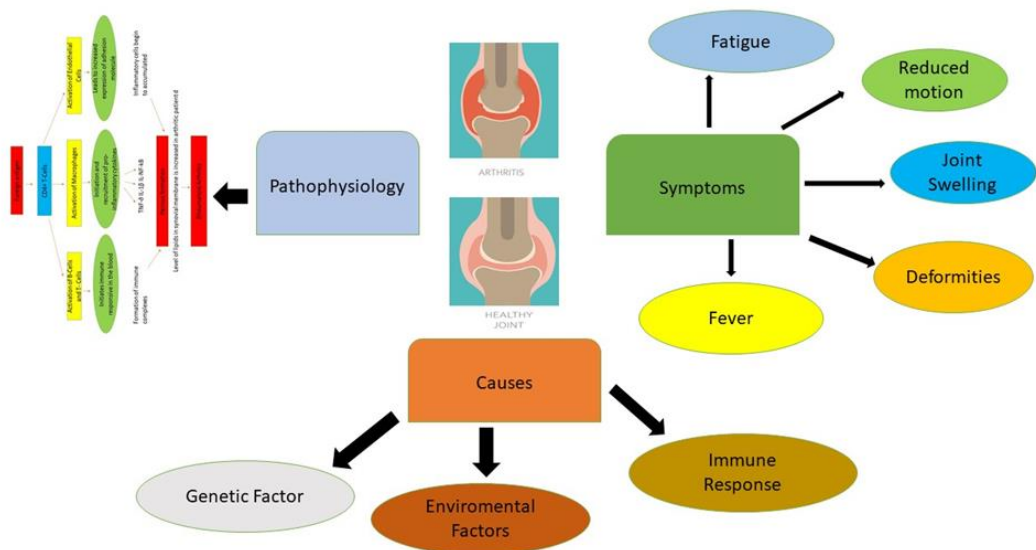


Fig.3 Pathogenesis-related factors for RA

Although the precise pathophysiology of Rheumatoid arthritis is uncertain, according to research, there are numerous inflammatory substances and mediators, such as monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor (TNF), C reactive protein (CRP), interleukins (IL-18 and IL20), and receptor activator. The development of the illness is significantly influenced by matrix MMP-9 (metalloproteinase-9), bond particles, and nuclear factor-B ligand (RANKL) fractalkine [6]. The several recognized elements that are Preclinical RA, genetic variables, and environmental factors can all be generally categorized as contributors in the etiology of RA [7].

1.2 Pre-clinical cause of Rheumatoid Arthritis

In preclinical RA (the period before the improvement of joint pain or arthritis) it's shown that there is an expansion in the degree of sickness related biomarkers which likewise remember auto-antibodies for the body [8]. There are different sorts of auto-counter acting agents in the body that incorporate immunoglobulin M-Rheumatoid component, Anti-RA33, Sa, p68, calpastatin, and perinuclear factors [9]. Rheumatoid variable assumes a vital part in the pathological process of RA (Rheumatoid Arthritis). According to the American Rheumatism Association, RA is utilized as a serological criterion for the determination or the diagnosis of Rheumatoid Arthritis [8].

1.2.1 Genetics Factor

The interaction between a person's genetic background and other environmental circumstances plays a vital role in the occurrence of Rheumatoid arthritis [12]. Meta-analysis and genome-wide association studies are one of the parameters to determine the genetic features of the RA (GWASs). RA gene therapy has the capacity to effectively and often transfer genes to several joints without causing any damage. Several proteins that carry genetic information include Protein the non-receptor for tyrosine phosphate-22 (PTPN-22), Cytotoxic TNF-induced protein-3 (TNFAIP-3)C-C chemokine and T-lymphocyte antigen-4 (CTL4)CCR-6 is a type six receptor with activator of 4 (STAT4) [11].

1.2.2 Environmental Factor

Recent investigations have shown the relationship between increased risk of RA and a few environmental elements, the two risk factors that are most common are smoking and drinking. Seropositive RA is more likely to develop in person who smoke for an extended period of time. Other risk factors for developing RA include endometriosis, schizophrenia, atopic dermatitis (AD), autoimmune thyroid disease (AITD), high salt intake, and autoimmune thyroid sickness [12]. The etiology of RA is caused by a combination of bacterial and viral infections in addition to hereditary and natural variables. The mechanisms of bacterial and viral infection include the existence of epitope spreads, and articulation of the antigens. The citrulline-explicit pathogenic immune system microorganisms which work against citrullinated protein antibodies (ACPAs) are triggered from B-cells. Additionally, the interaction of ACPA with citrullinated proteins aids in the induction of local inflammation that results in chronic rheumatoid arthritis. Other environmental risk factors that are important for the role pathogenesis of RA include drinking alcohol, smoke, breastfeeding, having a low birth weight, and socioeconomic conditions [13]

2 Convention Therapeutic agents for RA

The reason for RA is obscure. Treatment's primary goal is to reduce the Continuing disease activity and if at all possible to promote recovery. Non-steroidal anti-inflammatory medications, disease modifying anti-rheumatic drugs, corticoids and biologics are the conventional therapeutic agents which are very effective to reduce joint pain and joint damage [14]. Other treatments that are for the RA include radioisotopes, antisense oligodeoxynucleotides and synovectomy using boron neutrons, and enzymes (superoxide dismutase) [15-16]. The conventional rheumatoid arthritis therapy options has been summarized in table 1. There are various different contemporary novel medicine delivery methods for RA in Figure 4.

2.1 Nonsteroidal anti-inflammatory drugs

Ibuprofen, naproxen, and Aspirin are the most used non-steroidal anti-inflammatory also known as NSAIDs which are administered during early stages of rheumatoid arthritis to slow the progression of the condition over time since they exhibit potential left out affecting any articular functioning, anti-inflammatory methods. The NSAIDs have various properties like analgesic properties which reduce the pain. It also has anti-inflammatory activity because of these properties NSAIDs are one of the popular and extensively utilized medications for the Diagnosis of arthritic disease [17]. These are worked by preventing the cyclooxygenase enzyme, which is necessary for production of prostaglandins from arachidonic acid. Most of these which are used as NSAIDs are non-selective cyclooxygenase enzyme inhibitors enzymes, which prevent both COX-1 and COX-2 enzymes from functioning [18]. Intense renal ischemia attributable to prostaglandin hindrance actuated vasoconstriction, changes in pulse, and expanded draining because of platelet restraint are a portion of the unfortunate results [19]. As indicated by reports, non-particular NSAIDs can cause significant upper gastrointestinal related issues like

hole, blockage, and discharge. NSAIDs are still generally utilized medication to treat RA in spite of their raised cardiovascular related dangers, including myocardial localized necrosis and Serious stroke [20].

2.2 Disease-modify anti-rheumatic drugs (DMARDs)

DMARDs are known as slow-acting anti-RA Medications, which were originally used in the 1980s. The treatment term for these medications ranges from 1 to 6 months, and they work by delaying the progression of RA, which reduces joint deterioration. Due to its incredible adequacy, speedy activity, negligible poisonousness, methotrexate has arisen as the most well known DMARD against rheumatic action during the past 20 years. Hepatic cirrhosis, hypersensitive reactions, and retinopathy are limitations [21].

2.3 Corticosteroids

glucocorticoids are taken by approximately 45% to 75% of the patient currently. Dexamethasone and prednisolone are corticosteroids which reduce joint inflammation by releasing phospholipids. Although these medications are provided in the early stages of therapy, regular and repeated usage leads to a number of adverse effects, including hypertension, cardiovascular disease, obesity, and even insulin resistance.

2.4 Opioid analgesic

Opioid usage was widespread and has risen recently in both RA patients and non RA population. More than half of the patients suffering from RA received an opioid prescription, and alarmingly, one in ten received an opioid prescription for the duration of their illness. The results indicate that this opioid use is substantially higher than that of the already opioid-dependent general population, and it is expected to rise in the upcoming years. Opioids used during the RA is highly concerning because the reports released by the research did not support the efficacy of using opioids for the management of chronic pain and also the current study is not able to examine the therapeutic uses of Opioids on the patients [23-24].

2.5 Biological drugs

Biological medicines which inhibit the overproduction of cytokines in the affected region of rheumatic patients, biological drugs also called newer DMARDs. The main working of the Biological drugs is to stop the immune system for making the rheumatic patient more prone to the bacterial and fungal infection [25]. The therapeutic action of these biologic medication divided into various groups, and the group consisting anti-TNF, IL-1 and IL-6 antagonist, cell co-feeling blocker, and B-cell draining agent [26].

3 Novel Drug Delivery System to treat Rheumatoid Arthritis

There are many advantages and drawbacks to regular medication conveyance techniques, including low dissolvability and porousness, unfortunate bioavailability, debasement by GI proteins, first pass digestion, dietary connections, high measurement necessities, and related drug poisonousness. The regular medication techniques which works on the demerits of the regular medication techniques that result in the development of a new drug delivery system which is also called novel drug delivery system. These drugs are target specific which only target the organ of the body, requiring less dose of the drug, also these drugs have less toxicity or poisonous effects. NDDS also solved the problem of low dissolvability and permeation of drugs, and also improved the extent of the drug reaches to the systemic circulation [27]. The benefits and drawbacks of various NDDS along with their respective advantages are shown in Table 2.

The most used drugs during the RA were the first line standard NSAIDs and analgesics. These were trailed by immunosuppressive medications, and these are methotrexate, azathioprine and DMARDs such as salazopyrine and chloroquine which calms the immune system to help to stop it from attacking the body's cells. Other agents, with the various exceptions related to MTX, also have various adverse drug reactions. Leflunomide as well as tacrolimus, two more recent second-line drugs, have been reported to lessen the proliferation of initiates CD-4 T cells, which is an important factor for the pathogenesis of Rheumatic arthritis. Infliximab, adalimumab and anakinra are the new biologics drugs which

provide the knowledge regarding the function of inflammatory mediators in RA. Intra-articular are the drug injection which is a significant advancement for the diagnosis and treatment of RA which ensures a long time period for the drug release so that it distributes the medication directly to the afflicted location. NDDS contain I-a injection of medication that contains such liposomes, nanoparticles, and microparticles are being found to enhance mean residence duration and reduce I-a drug clearance [28]. Detailed discussion of the use of sophisticated nanocarriers and their drug delivery targets in Table 3.

Table 1: Conventional Therapeutic agents to treat rheumatoid arthritis

Drug Classification	Instance	Mechanism of action	Delivery Strategies	Side Effects
Glucocorticoids	Prednisolone, Dexamethasone	Impact on the levels of immunosuppression and inflammatory cytokines	EPR (Enhanced Permeability and retention effect)	osteoporosis, Hypertension, atherosclerosis
NASAIDs (Non-Steroidal anti-inflammatory drugs)	Indomethacin, Diclofenac Sodium	blocking the COXs enzyme	EPR	Kidney failure, Gastrointestinal Disorders
DMARDs-(Disease-modify antirheumatic drug)	Methotrexate	Immunosuppression and Genetic Material Synthesis Inhibition	EPR	Liver and Kidney Failure, Gastrointestinal Reaction
Biological agent	Tocilizumab, Etanercept	TNF- antagonistic, T-cell activation is downregulated	EPR	Gastrointestinal infection, Tuberculosis

Table 2: Advantages and Disadvantages linked to several of NDDS

Various Drug delivery system	Advantages	Disadvantages	References
Solid-Lipid Nanoparticles	Good Stability of the Solid Lipid Nanoparticles if its compared to the Liposomes, decreased risk of nephrotoxicity, decreased drug leakage, utilization of biocompatible and physiological lipids that makes SLNs less harmful, assurance of incorporated medicine against compound deterioration and reduced accumulation in kidney	Gelation, lipid polymorphism, and poor drug loading capacity all contribute to drug leakage.	29
Dendrimers	The well-defined branching structure and globular shape of dendrimers' remarkable design bring about a large number of surface gatherings that might be explicitly changed to act as a layout for drug conveyance; improved drug stacking, controlled drug delivery and a lot more prominent medication conveyance to the objective area, less unfavorable outcomes	Functional amine groups which is present on the surface of the compound causing or making it toxic	30-31
Nanoparticles	Rapid absorption and release behavior, the size of the nanoparticle is very less so that it manipulate the size of the particle and surface, easily attain the drug targeting in both active passive process, it enhance the drug-loading capacity of the drug, it also decrease the amount of matrix uses which is important during administration.	Scaling up is challenging	32

Lipogelosomes	Longer retention period; excellent for treating joint disorders locally	leaks of drugs and stability problems	33
Microemulsions	Microemulsions and colloidal dispersions are better at managing inflammation than conventional topical dose forms since they are made of a single optically isotropic and thermodynamically stable framework with drop diameter typically between 10 and 100 nm.	possess poor viscosity, necessitating the use of gelling agents.	34
Emulgels	Larger oedema inhibition, better drug release without causing skin irritation, better penetration compared to commercial gel, higher drug loading capacity, and avoidance of first pass metabolism	contact dermatitis; difficult absorption of big medication particles	35
Microspheres	The main function of the microspores is that it is a kind of controlled release for both of the soluble and insoluble medications and the microsphere is mainly use for the encapsulation.	Less repeatability; stability of core particle may be impacted by the process circumstances	34, 36
Polymeric micelles	High drug effectiveness; also a controlled drug release; excellent physicochemical Balance; it makes the insoluble drug soluble;	Dissociation results from dilution.	37

3.1 Nanoparticles

Nanoparticle systems are employed in the management of rheumatoid arthritis and it’s mostly dependent on polymers. Many scientists employ PLGA nanoparticles to prolong the period that a medicine is in circulation and to regulate how quickly it is released [38]. When administered intravenously to arthritic rats and mice, it is examined that Poly (lactic-co-glycolic acid) Betamethasone is more successful in minimizing the inflamed state than conventional drug glucocorticoids [39]. One of the experiments conducted by Nagei et al. in AIA reported that nano gel ointment contains solid ketoprofen nanoparticles showing anti-inflammatory effect whose mean size is about 83nm. FDA employed both metallic nanoparticles and gold nanoparticles for the management of RA. But for the passive targeting in rheumatoid arthritis, it favours metallic nanoparticles mostly. However, the unfavourable side effect of gold nanoparticles employed to treat RA reveals their general toxicity [40].

In different research carried out by Nagai et al. who formed an IMC ointment containing solid ketoprofen nanoparticles indomethacin (IMC) and investigated its pharmacokinetics. The IMC nanogel ointment was made with Bead Smash 12 and additives. The produced nanoparticles' mean molecule size was determined to be 173 11.6 nm.

In contrast to indomethacin microgel ointment, and it demonstrated mitigation of rise in the paw oedema on the hind foot of AIA rats (adjuvant-induced arthritis rat) [32].Ibuprofen (IBU) nanogel formulation was created by Nagai et al. for topical treatment, and AA rats were used to demonstrate their anti-inflammatory effectiveness. The preparation of the gel-based formulations was done utilizing the bead mill process and ingredients. IBU particle size in the IBU nanogel formulation determined was 208 nm. The inflammation in the hind feet of AA rats was significantly reduced after treatment with the IBU nanogel medications, and this was in contrast to the IBU microgel formulation, which had much greater inhibitory effect to inflammation. Moreover, researchers guaranteed that when contrasted with IBU microgel detailing, IBU nanogel plan gave extraordinarily critical penetrability and aggregation in the skin. After giving AIA rats 0.30 g for the synthesized 5% IBU nanogel for one time daily for 42 days, the researcher did not note any gastrointestinal sores problem. After reviewing the findings, the authors hypothesised that topically applied IBU nanoparticles had an effective therapeutic impact on patients without causing any negative side effects [41]. The various applications of advanced drug delivery nanocarriers in the treatment of RA is discussed in table 3.

3.2 Solid Lipid Nanoparticles

Kaur et al. performed and evaluated solid lipid nanoparticles loaded with diclofenac which can be applied dermally as well as topically. According to the authors who have worked on this made the SLNs using hot homogenization technique which

is based on microemulsification which had mean size of about 124.0 nm, spherical in shape, and a PDI of 0.294 0.15. the author has also measured the permeation flow, the penetrated quantity and the skin retention which was happened on the upper epithelial surface of the mouse and the values got by the author is like for the permeation flow is was 6.300.09 g/cm²/h, for the penetrated quantity the measurement was 109.990.008g/cm² and the values for the skin retention was 11.740.155. In one of the models called mice air pouch model in which the DIF-loaded SLNs showed that there is a gradual decrease in the weight of the granuloma, volume of the fluid and count of the leucocyte after DIF SLN formulation of the administration. Furthermore the authors also showed the increasing percentage inhibition of oedema in the paw of the rat and the inhibition percentage increased 1.29 and 2.30 times more. After these studies authors suggested that the DIF-SLNs model can be effective for the nanocarriers for the treatment or the management of inflammation related arthritis [5].

3.3 Microemulsion

Microemulsion based topical treatment based on tenoxicam (TNX) formulation was developed by the Gondi et al. which is helpful for the treatment of affected areas of inflammation. For the preparation or formulation of the microemulsion various ingredients were used and some of the ingredients are tween 80 which act as surfactant, co-surfactant (n-butanol and ethanol), and olic acid as an oil. TNX which is demonstrated as the one of the greater mean cumulative percent permeation value and the value is about (p0.001) it means it is very effective if it's compared with the traditional cream and the suspension formulation. The efficacy of the TNX formulation was evaluated by the various inflammatory models and the inflammatory values are air pouch model, cotton pellet granuloma, carrageenan-induced inflammation and xylene induced ear oedema. Microemulsion formulations were the most effective in controlling inflammation than the conventional topical dose forms with the better efficacy compared to the oral formulation. So the studies imply that microemulsion medication is effective for the topical TNX administration to treat the inflammatory disease. [34].

3.4 Dendrimer

Dendrimers, also known as cascade molecules, are multifunctional macromolecules having a regular branching surface. It has a distinctive branching structure as well as a globular form, which results in a large number of surface groups that may be modified to offer an informable instruction for drug delivery, and it can be helpful for the boosting of drug loading. CIA mice were used for the study of the therapeutic effect of dendrimers on macrophage activation. First the methotrexate conjugation consisting of amino groups were administered to the blood circulation of the CIA mice body before administered to the inflammation part of CIA mice. which shows that there is decrease in the weight of the CIA mice body because of the increase on the cationic charge density inside the body. So, there is various advantage of the dendrimers and the advantages are it is having high drug loading capacity, also provide Controlled drug release, also works on the drug delivery to the targeted organ. It's also having demerits and these are cause high toxicity because of the amino function group present on the methotrexate conjugation. [42-43].

The author name chandrasekar has developed a dendrimer which has the goal to deliver the medicine to the targeted area to reduce the inflammation in arthritic rats. The author developed the dendrimer was folate targeted poly ethylene glycol which is also called PEG which conjugates with anionic G3.5 Poly(Amido amine) PAMAM dendrimer. The dendrimer was also helpful in the investigating the bio-distribution pattern in the arthritic rats. The scientists have used a carbodiimide mediated coupling process which is a two-step synthesis process for the synthesis of the Folate PEG PAMAM conjugate. In this synthesis process indomethacin is loaded with the folate conjugates which helps in the investigation. The drug efficiency rose 10 to 20 fold because of the Folate -PEG conjugation and the drug release was shown to be regulated in vitro. The author experienced minor gastrointestinal side effects because the dendrimers lower the absorption of the conjugates in the stomach. The author concluded that the folate PEG PAMAM conjugates have the excellent medication for the effective targeted delivery of anti-arthritic medicines to inflammation with much lesser side effects [31].

3.5 Lipogelosome

Lipogelsomes have anti-inflammatory properties revealed by the author. When the lipogelosome containing diclofenac sodium is administered intravenously it will exhibit anti-inflammatory effectiveness if it is compared with diclofenac product which is topically administered. Furthermore various studies have been performed the studies are histopathology and biodistribution which revealed that alteration in the synovial joints can be treated by the lipogelosome medicated formulation resulted in considerably lower scores (P 0.05) than other joints. It improves the retention time and very effective for the management of the joint problems. However, Lipogelosome has drawbacks such as drug loss and stability concerns [34].

3.6 Microspheres

There are various studies carried out for the microsphere to know the action efficacy of the drug if it is delivered in the form of microspheres.

The author name Ramasamy et al. developed an emulsion which is an approach to create the pectin based colon specific microspheres which is also called multi-particulate delivery system. In which eudragit 500 is taken as a coating material which coats the microsphere. The author has observed the various parameters like emulsifier, effect of the polymer, in vivo release and in vitro performance of the drug. The author suggested that the pectin microsphere coated with polymer called eudragit might have worked as a potential carrier for the smooth delivery of the colon specific delivery of aceclofenac in the RA which is based upon the chronopharmacological therapy [44].

Fine chitosan thermosensitive hydrogels in conjugation with alginate microspheres was developed or created by the author name Qi et al.. Works as an intra-article which shows the generated hydrogels anti-inflammatory potential as a drug delivery strategy. In this the author has injected the hydrogels containing glycerophosphate and chitosan in the modified and emulsified microsphere. The developed microsphere containing mixed hydrogels shows more anti-inflammatory activity. The efficacy was checked on the experimental RA induced rabbit which shows that the mixed hydrogels have more anti-inflammatory action than the pure chitosan hydrogels and medication containing substance. By observing the result the author concluded that the mixed hydrogels might be a very effective drug delivery method. [36].

Sanka et al. who created aceclofenac microspheres which are pH triggered delayed-release colon-targeted good at achieving the RA chronotherapy. The authors used the BBD design for the testing of the resultant formulation in rats to check the anti-arthritis efficacy. The expected microspheres encapsulation efficacy and particle size was to be 85.06, 5.85% and 117.36 10.54 respectively. One of the in vivo testing revealed the anti-arthritis effect in the adjuvant induced rats as well as delayed anti-inflammatory action in carrageenan induced rats. The author conclude that the formulation of aceclofenac microsphere is a good option for the chronotherapy action in early morning rheumatoid arthritis symptom. [45].

The DFNa-loaded microsphere was created by the authors name tuncay et al. uses natural polymer for the intra-articular administration. The DFNa-loaded microsphere's main goal is to prolong the duration of the drug in the knee joint. The authors used in vitro criteria for the evaluation of the generated DFNa microsphere formulation in which the authors have evaluated yield value, surface area, particle size, effect of the encapsulation and release of the drug in in-vitro condition and two formulations have been chosen for the in vivo experiment. In-vivo arthritic lesions radiopharmaceuticals ^{99m}Tc-HIG (polyclonal human immunoglobulin) were utilized for the demonstration. The authors induced the arthritic inflammation in the knee of the rat. they injected the DFNa-loaded microspheres into the articular cavity for the determination of the prolonged or the residence time of the microsphere in the induced arthritic inflammation in the rat joints [44].

3.7 Emulgels

Skin irritation testing, stability, pH and in-vitro permeation have been used for the creation of the Emulgels. The authors name Vandana et al. who used the wistar rats in rat they induced the oedema in the hind paw by using carrageenan and developed Nimesulide aloe vera gel. For the testing of the reducing inflammatory property of the created formulation the authors have used the in vivo and in vitro technique for the investigation. . The authors discovered 54% Nimesulide penetration from Nimesulide emulgels compared to 44% from commercialized Nimesulide gel at 30 minutes, indicating greater drug release without the irritation caused in the skin. It also has a greater loading of the drug capacity of 86% more than the commercial medications, making it appropriate for a significant anti-inflammatory impact [30]. Emulgels are useful because they improve medication release at the desired spot while causing no skin irritation. The main disadvantage symptoms are contact dermatitis and limited absorption for bigger medication particles [46].

3.8 Polymeric micelles

Micelles are the drug delivery system used for treatment of RA. Since micelle stability is a significant issue to take into consideration. These were created using PEG phospholipids, which are often used for medication encapsulation, to test the stability and solubility. Vasoactive intestinal peptide Receptor overexpression is the primary cause of synovial macrophage activation. This process is helpful for increasing the solubility of DMARDs. The benefit of employing micelles are less numerous than those of other NDDS, such as improved physicochemical stability, increased pharmacological efficacy, and less toxicity. The greatest disadvantage, however, is dilution that causes disintegration [37].

3.9 Liposomes

To improve the condition of RA, various liposomal system been tried which were given intravenously. Liposomes get accumulated in the synovial tissue of the affected area of the patient. Liposomes such as clondronate-loaded liposomes, lactoferrin-loaded liposomes, immuno-liposomes, cationic liposomes, and superoxide dismutase liposomes were generated [31]. Clondronate is used to encapsulate phosphatidylcholine and cholesterol-based liposomes, which are administered to arthritis-prone rats. These therapeutics reduce inflammation and aid in the prevention of bone resorption. Liposome clondronatewere used to minimize the amount of macrophages in the synovium. In contrast to free drugs, the resulting liposome reduces joint inflammation and toxicity [44]. Liposomes provide a number of benefits, including improved therapeutic index and effectiveness as well as decreased toxicity of the encapsulated drug. The use of liposomes had drawbacks, including high production costs, drug molecule fusion, a short half-life, and decreased solubility [47].

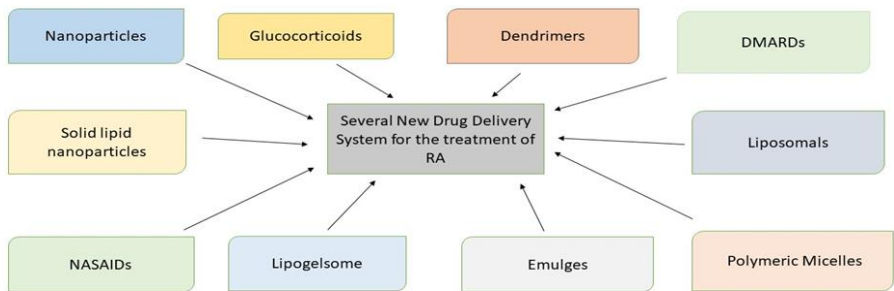


Fig. 4 Several Novel Drug Delivery systems for the treatment of RA

Table 3. various applications of advanced drug delivery nanocarrier in the treatment of RA

S. No	Drug	Delivery System	Target Delivery	Ligand	Route of Administration	In vivo animal model	Beneficial Outcome	Ref.
1.	Betamethasone	Liposomes	FR β expressing macrophages & EPR effect	Folic acid	Intravenous	AIA Rat	The amount of folate and immune cells splenomegaly are decreased, boosting the efficiency	50
2.	Withaferin-A	Liposomes	Synovial Macrophages	P-aminophenyl-D mannopyranoside	Intravenous	AIA Rat	TNF, IL-1, IL-6, MCP-1, and VEGFs were inhibited	51
3.	Methotrexate	Ultra-Deformable Liposome gel	Passive	Na	Topical	AIA Rat	TNF- and IL-1 mRNA levels being suppressed	52
4.	Loperamide	Liposomes	-	-	Topical	AIA Rat	accelerated disease development compared to diclofenac	53
5.	p-Coumaric acid	Liposomes	Synovial macrophages (CD86) & pre-osteoclast (CD51)	4-aminophenyl - D-mannopyranoside	Intravenous	AIA Rat	Inflammatory cytokines and the expression of MMP-9 and NFATc1 are downregulated.	54
6.	Interleukin-27 α	Liposomes	Activates endothelial cells	ART-1 lipopeptide	Intravenous	AIA Rat	Less side effect and maximum efficacy	55
7.	Dexamethasone Palmitate	Liposomes	Peripheral bloodneutrophils	Sialic acid	Intravenous	AIA Rat	Show the anti-inflammatory action and also targeted drug delivery	56
8.	MCL-1 siRNA	Neutral PEGylated liposomes	FR β on activated macrophages	Folic acid	-	Raw 264.7	It cause the slow release into the cell and make sanitize the cell for apoptosis	57
9.	Methotrexate	Micelles	E- selection on Lymphocytes	Sialic acid-dextran-octadecanoic acid	Intravenous	CFA Rat	Reduce the level of urea-nitrogen, aminotransferase, aspartate, creatinine	58,59
10.	Dexamethasone	Acid Labile micelle	Macrophages	Hydrazone linkers	Intravenous	AIA Rat	Better bioavailability and increase circulation time	60,61

11.	Methotrexate and microRNA-124	Hybrid Micelle	FR β on activated macrophages	PEI-LA and mPEG-LA	Intravenous	AIA Rat	Successful distribution of microRNA-124 through endosome escape with synergistic effectiveness	62,63
12.	Co delivery of Dexamethasone and siRNA	Polymetric Hybrid micelles	P65 in macrophages	Polycaprolactone-Polyethyleneimine (PCL-PEI) and Polycaprolactone - polyethyleneglycol (PCL-PEG)	Intravenous	CFA rat	It suppress the Nuclear tanslocation of p65 and ProinflammatoryCytokines	64,65
13.	Indomethacin	Ethosomes	Passive	NA	Transdermal	NA	Enhance skin absorption and permeation	66,67

4 Conclusion

Despite several developments in RA research, neither a single medication nor a combination therapy has shown positive outcomes. By lowering the possibility of an adverse response during traditional therapy, the introduction of the different drug delivery techniques discussed here promises to enhance patient outcomes. However, researchers have created liposomal drug delivery systems and nanotherapeutics to address these new difficulties, offering fresh ideas for treating RA. These techniques outperform traditional RA therapy because of their regulated release, selective accumulation, and lower systemic toxicity. In an experimental setting, the newly created nanocarriers (liposomal formulations) greatly improve the therapeutic efficiency of existing medications for better arthritic remission.

5 References

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