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Review Article

NOVEL NANO THERAPEUTIC MATERIALS FOR THE EFFECTIVE TREATMENT OF RHEUMATOID ARTHRITIS-RECENT INSIGHTS

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ABSTRACT

Recent advances in science and technology and greatly modified the way we stumble on, deal with and prevent special diseases in all components of human lifestyles. Rheumatoid arthritis (RA) is the most not unusual complex multifactorial joint related autoimmune, chronic, severe systemic inflammatory ailment with unknown etiology completed with increased cardiovascular risks. It is regularly associated with critical synovial joint inflammation, autoantibody production, cartilage/bone tissue destruction, cardiovascular, pulmonary, skeletal disorders and massive inflammatory infiltration which might in the end motive extreme disability, huge complications, premature mortality and decreased life quality. Pro-inflammatory cytokines like IL-1, IL-6, IL-8 and IL-10 were dependable for the induction of inflammation in RA patients. It has a global occurrence of around 1% with the incidence among women being 2-3 times extra in men. Preclinical RA, genetic variables, and environmental factors have all been linked to the disease's etiology. Because there is no known cure for RA, the primary goal of treatment is to achieve the shortest possible illness duration and, if possible, rehabilitation. Current clinical remedies of RA display numerous drawbacks which include excessive doses, common administration, speedy metabolism, bad absorption, low responsiveness, higher cost and serious side consequences. These obstacles have inspired extremely good growth of the studies and to enhance those obstacles, nanoparticles that are able to encapsulating and protecting tablets from degradation earlier than they reach the target site *in vivo*, might also function drug delivery structures. Bioavailability and therapeutic bioactivity can be improved, and limited emphasis on damaged joints can be allowed. The current study provides a platform for different lipid nanoparticle methods for RA therapy, using the newly developing field of lipid nanoparticles to improve a targeted theranostic device for RA treatment. This review aims to present the most recent major application of lipid nanoparticles as a biocompatible and biodegradable transport device for improving RA concentration on over free drugs by presenting tissue-specific concentrated on of ligand-controlled drug release by modulating nanoparticle composition. Additionally, we also discuss the pivotal demanding situations to be addressed, as well as destiny views. Therefore, it is feasible to claim that nanoparticles will, within the near future, play a critical role in advanced treatment and affected person-particular cures for human diseases which include RA.

Keywords: Rheumatoid arthritis, Lipid nanoparticle, Inflammation, Drug delivery

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INTRODUCTION

Rheumatoid arthritis (RA) is an infectious condition characterized by inflammation of the chronic joint ultimately leading to serious weakness and premature mortality [1]. RA causes chronic inflammation of the synovial membrane and as the condition progresses, this leads to degradation of the periarticular bone, deterioration of articular cartilage and irreversible deformities along with mania of extra-articular condition [2]. Diverse factors such as disease action, socioeconomic, educational status, body mass index, spirituality, age and gender affects RA patient's quality of life [3]. The global occurrence of RA has been predictable to be approximately 1% and the occurrence of RA in women is 2-3 times higher than in men [4]. In India, the occurrence of RA ranges from 0.28 to 0.7%, which is close to the occurrence in developed nations [5]. People of all age groups are affected by RA, but it is extra prevalent in the 30-50-year-old middle age population [6]. RA can impact any joint within the body (fig. 1). However, it mostly affects proximal interphalangeal, metacarpophalangeal and metatarsophalangeal joints of wrists and knees [7]. It has been noticed that wrist is the very most common affected site in RA. There were also some variations in the occurrence of swelling and tenderness with tenderness occurring more in large joints such as the elbow, shoulder and knee, while swelling happens in small joints such as metacarphalangeal joints [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 is 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]. The number of RA-related symptoms is revealed in fig. 2.

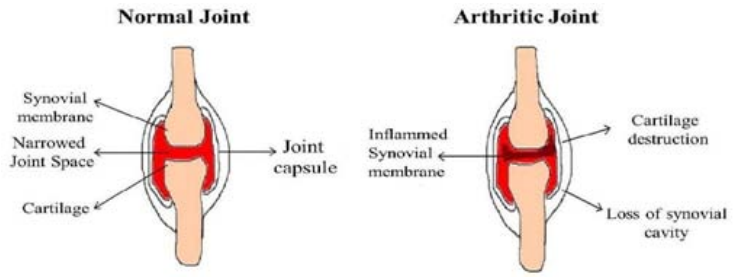

Fig. 1: Comparison between (A) normal and (B) rheumatoid arthritis joints [13]

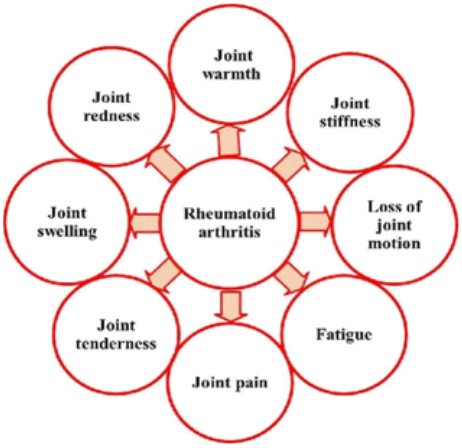

Fig. 2: Symptoms associated with rheumatoid arthritis development [13]

Pathogenesis of RA

Although the exact pathogenesis of RA is unknown, it has been reported that inflammatory mediators such as tumor necrosis factor-, C reactive protein, CD40 L, interleukins, monocyte chemoattractant protein-1, nuclear factor-B ligand receptor activator fractalkine, and metalloproteinase-9 matrix, as well as adhesion molecules, play an important role in the disease's progression [14]. The several well-known variables involved in the pathogenesis of RA may be divided into three categories: preclinical RA, genetic factors, and environmental factors (fig. 3) [15-17].

Preclinical RA

In preclinical RA (the period prior to the development of arthritis), it has been reported that there is an enlarged level of disease-related biomarkers, including auto-antibodies in the body [18]. IgM-Rheumatoid factor, RA33, Sa, p68, calpastatin and perinuclear factor [1] are among the various disease-specific auto-antibodies. The rheumatoid factor (RF) plays an significant role in RA pathogenesis. The occurrence of RF is used as a serological criterion for the diagnosis of RA according to the American Rheumatism connection [19].

Genetic factors

RA expansion depends on the genetic background association and a number of environmental factors. Studies in molecular biology established the key role of major genes of the histocompatibility complex (MHC) in disease pathogenesis [20]. In RA, HLA-DRB1 gene was documented as one of the significant genetic associations in MHC, where sequences of shared epitopes within the DRB1 molecule are programmed by specific alles within the clusters DRB1 * 04 and * 01 [21]. Other genetic contributors to the pathogenesis of RA are PADI, CTLA4, PTPN22, CCRS6, CSF2, B3GNT2, PDE2A-ARAP1,

ANXA3, ARID5B, CD83, PLD4, and PTPN2 [22-25].

Environmental factors

The increase of risk of RA has been substantiated by recent research with certain environmental influences. Smoking and alcohol consumption are the most general risk factor [17]. Long-term smoking associates the increased risk of developing seropositive RA [20]. Some other factors rising the risk of developing RA include high sodium ingestion, autoimmune thyroid disease (AITD), atopic dermatitis (AD), schizophrenia, cigarette smoking, and endometriosis [26-32].

Manifestations associated with Rheumatoid arthritis

The major manifestations of RA are categorized in to three, which comprise bone, airway and cardiovascular system. In case of bone manifestations, bones are exaggerated both locally and systemically. Local factors that stimulate osteoclasts result in increased bone resorption and have released these osteoclasts from inflammatory and fibroblastic pannus cells [34]. RA patients were usually vulnerable to bisphosphonate treatment for osteoporosis or for the reduction of glucocorticoid-mediated degradation of bone. Airway symptoms of RA include cricoarytenoid arthritis, pulmonary fibrosis and mild airway disorder, usually known as bronchiolitis and disruptive lung function abnormalities. In RA cases, lung disease is the highest mainly in male seropositive smokers. The risk of mortality in RA patients is 40 % higher, leading to an increased incidence of cardiovascular disease with a high level [35].

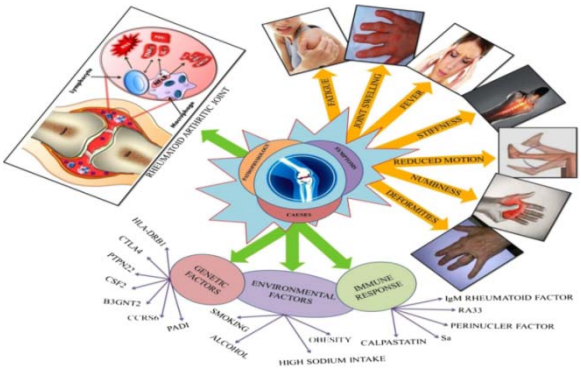

Fig. 3: Factors involved in pathogenesis of rheumatoid arthritis [33]

Treatment options for Rheumatoid arthritis

Curing RA is still out of our reach at present [36, 37]. Nonsteroidal anti-inflammatory medicines (NSAIDs), glucocorticoids (GCs), disease-modifying anti-rheumatic drugs (DMARDs), and biological agents are the most widely utilized treatment methods [11, 38]. NSAIDs (such as ibuprofen and celecoxib) could quickly decrease pain and inflammation by inhibiting cyclooxygenases. However, they are no longer considered to be first-line treatments because of their incapacity to stop joint damage and variety of side effects such as gastrointestinal bleeding, renal dysfunction and cardiovascular disease risk. GCs including prednisolone (Pred), dexamethasone (Dex) and budesonide (Bud) include a potent anti-inflammatory ability and are broadly used in treating active RA, while side effects such as immunosuppression, osteoporosis, hyperglycaemia and hypertension associated with the amount cannot be unnoticed while long term therapy. DMARDs such as methotrexate (MTX) can gradually reduce joint damage and control the disease progression. They have been exposed to provide a more approving outcome in patients. In clinical application, a mishmash of several DMARDs or DMARDs with other types of agents has been demonstrated to be beneficial to arthritis remission [39-42]. The development of biotechnology has promoted the expansion of biological agents in RA treatment. This class includes cytokine antagonists (such as infliximab, a TNF-α inhibitor), B-cell depleting agents (such as rituximab), T-cell costimulation modulators (such as abatacept) and kinase inhibitors (such as JAK inhibitors). Even though the high effectiveness in clinical use, nearly 30% of patients still explain low responsiveness. In addition, diverse problems are associated with current biological therapies, such as elevated costs and risk of serious bacterial infections [36, 38, 39, 43-45]. Despite this narrow clinically used therapeutics in RA, academic research has provided numerous promising therapeutic targets. The components participating in RA incidence and progress, such as diverse cytokines, linkage molecules, proteases and numerous cells including monocytes, FLS, VEC and osteoclasts, might be developed as potential therapeutic targets. In exacting, many endogenous anti-inflammatory molecules or cells survive in the human body, for example, anti-inflammatory cytokines (IL-4, IL-10), numerous kinds of microRNA (miR-23b), receptor antagonists, or regulatory T cells (Treg) and M2 type macrophages. In the inflammatory milieu, the balance between usual immune response and inflammatory cascade breaks down. These endogenous anti-inflammatory agents are actually insufficient to counterbalance the huge complicated inflammatory network. Mimicking the action of such natural

inhibitors or promoting their endogenous production would be promising therapeutic approaches. Non-conventional methods comprise herbal treatment. Herbal medicines have always been in concern to promote health since untimely times. The herbal treatment is now days extremely used as a substitute technique for the treatment of RA. This comes under the term corresponding and alternative approach (CAM). The major common herbs used are ginger, curcumin, Boswellia, *C. sinensis*, *U. tomentosa*, *U. guianensis*, *T. wilfordii* hook F, *Linum usitaissimum*, *Arctium lappa* or *Arcticum minus*, *Urtica dioica*, *Willow bark*, resveratrol, guggulosterone, piperine etc. Herbal treatment offers many advantages such as security, less side effects and gives better outcomes. Along with this, the chiropractic treatment is also extensively used [46]. The different nanoparticulate based delivery system adopted by various drugs is showed in table 2. The implication of nanoparticles based formulation for the treatment of RA may afford enhanced bioavailability, increased gathering of drug at the diseased reddened site and extended discharge characteristics. At the superior level these nanoparticulate based formulation may also elicits target capacity potential with specific receptors. Ayurvedic system is classified into 3 subcategories based on their mental and physical composition, known as Prakriti, which are Pitta, Kapha, and Vata. In India, the doctors usually administer ayurvedic medicines along with allopathic medicines, with a scientific approach. This practice is based primarily on spiritual beliefs, and is secret. Herbal medicines can be taken as antimicrobials, anti-inflammatory and antiviral in RA infections, injury healing and fever. Some of the at present available herbs used for arthritis treatment are enlisted in table 1 [47].

Table 1: Various herbs used in RA

S. No.	Plant name	Families and local name	Useful portion
1	*Alpinia galangal* Linn	Zingiberaceae, Arattai, Perarattai	Rhizomes
2	*Anacyclus pyrethrum*	Asteraceae, Akkirakkaram	Roots
3	*Capparis deciduas*	Capparaceae, Senkam, Sirakkali	Roots
4	*Aquilaria agallocha*	Thymeleaceae, Krsnaguru	Wood and Oil
5	*Callicarpa macrophylla*	Verbenaceae, Nallai	Flowers and fruits
6	*Aphanamixis polystachya*	Meliaceae, Malampuluvan	Bark
7	*Argemone Mexicana*	Papaveraceae, Kutiyotti	Whole plant, Latex
8	*Ficus benghalensis*	Moraceae, Alamaram	Latex
9	*Hygrophila auriculata*	Acanthaceae, Nirmulli	Roots, Leaves and Seeds
10	*Fritillaria roylei* Hook	Orchidaceae, Kakoli	Bulbs
11	*Heliotropium indicum* Linn	Boraginaceae, Telkodukka	Whole plant
12	*Holarrhena pubescens*	Apocynaceae, Kutasappalai,	Barks, Seeds and Leaves
13	*Flacourtia jangomas*	Flacourtiaceae, Vaiyyankarai	Fruits
14	*Gossypium herbaceum*	Malvaceae, Panju	Leaves
15	*Justicia gendarussa* Burn	Acanthaceae, Vataikkutti	Roots and Leaves
16	*Mimosa pudica* Linn	Mimosaceae, Tottalcurunki	Whole plant
17	*Kaempferia galangal* Linn	Zingiberaceae, kaccolam	Rhizomes and Leaves
18	*Lantana camara* Linn	Verbenaceae, Arisimalar, Unnicceti	Frutis
19	*Mangifera indica* Linn	Anacardiaceae, Mamaram, Mankai	Roots and Barks
20	*Lilium polyphyllum* D	Liliaceae, Ksirakakoli	Bulb
21	*Naravelia zeylanica* Linn	Ranunculaceae, Vatamkolli	Whole plant
22	*Oroxylum indicum* Linn	Bignoniaceae, Palaiyudaycci	Roots
23	*Tribulus terrestris* Linn	Zygophyllaceae, Nerinci	Whole Plant
24	*Jasminum lanceolarium*	Oleaceae, Makarandam	Leaves and Flowers

Problems associated with conventional dosage forms

The variety of conventional dosage forms obtainable for RA treatment includes tablets, capsules, oral liquids, topical products, parenterals, paediatric/geriatric products, and transdermal patches. Ointment, cream, gels or paste are the topical dosage forms for RA healing. Transdermal patches are topical drug delivery device that spreads drugs non-invasively across the skin. The main drawbacks associated with conventional dosage forms for treating RA were poor compliance with patience, short half-life, low bioavailability and poor solubility, which can be enhanced by customized new dosage forms [48]. The novel dosage form obtainable for RA treatments includes microparticles, nanoparticles, nanoemulsions, nanomicelles, nanodispersions, nanocapsules, nanosuspensions etc.

Nanotechnology

Nanotechnology deals with the exploitation of issues at nuclear level to generate newer novel nano materials due to its capability to produce sophisticated nanomaterials, processes and products selected at nanoscale, which is creating an added increment over the recent years [49]. Lately many techniques were developed to revise the physical phenomena and constructs (typically 1-100 nanometers) of different nanomaterials [50]. The word "smart materials" was used to describe nanoparticles to target drug delivery to individual body organs. Over the last few years, this technology has shielded its way into expanding the future applications of nanoparticles as beauty products. Liposomal technologies have been used to regulate optical properties to advance their solubility and alter their physical properties, provided for hydrophilic vesicles with phosphatidylcholine membrane(s) [51]. Nanomaterials have been used in remedial field for beneficial drug delivery with the focus for treatments of diverse diseases/disorders. Micro and nano scale systems can exploit the efficacy of therapeutic treatments in many ways because they paves the capability to quickly notice and react to disease states frankly at the site by improving the patient's quality of life [52].

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 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 2 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.

Table 2: Nanoparticle based anti-rheumatic arthritic drugs

Drugs	Nano carrier	Therapeutic effects	Reference
MTX	Gold half shell nanoparticle	Anti-rheumatic arthritic effect	[58]
Celecoxib	Solid lipid nanoparticle (Tristearin)	Anti-inflammatory, Anti-rheumatic arthritic effect	[59]
Dexamethasone and MTX	Chitosan Nanoparticles	Anti-inflammatory, Anti-rheumatic arthritic and antioxidant potential	[60]
Curcumin	Carboxy methyl cellulose acetate butyrate (CMCAB)	Anti-rheumatic arthritic effect	[61]
MTX	(Arginine glycine aspartic acid) peptide conjugated gold shell nanoparticle	Anti-inflammatory, Anti-rheumatic arthritic effect	[62]
Tacrolimus	Human serum albumin	Anti-rheumatic arthritic effect	[63]

Solid lipid nanoparticle for the treatment of RA

Solid lipid nanoparticles (SLNs) are colloidal carriers with particle size ranging from120-200 nm, broadly utilized for prohibited drug delivery which merges the benefits of polymeric nanoparticles and oil in water emulsions [64]. SLNs have extraordinary properties such as a good acceptability, protection of incorporated active compounds next to chemical degradation, higher bioavailability with assimilation of both lipophilic and hydrophilic drugs, higher drug loading ability and moderately safe for biological applications [65]. Due to its exclusive size range SLNs hardly undergoes blood clearance by the reticulo endothelial system. SLNs were completed of physiological lipids, fatty acids, phospholipids and mono/di/triglycerides. To make SLNs, a variety of procedures can be utilized, including high shear homogenization, ultrasonic, high pressure homogenization, hot homogenization, cold homogenization, solvent emulsification, and evaporation processes. Lipid-based formulations for enhanced oral bioavailability of poorly water soluble medicines employing SLNs have received more attention in recent years [66]. The drug carrier combines the benefits of polymeric nanoparticles, fat emulsions, and liposomes, including enhanced physical stability, cheap cost, scaleability, and production simplicity [67].

Curcumin-encumbered solid lipid nanoparticles (C-SLNs) for inflammation were created by *Arora et al.,* 2014, to overcome curcumin's low bioavailability [68]. They have an average particle size, product content and capacity of 134 nm, 3.78 mg/ml and 81.92%. They examined how pure curcumin works and C-SLNs in total freund's adjuvant (CFA)-induced arthritic rats. They demonstrated that C-SLNs act as the carrier for the effective delivery of curcumin to patients with RA. They caused C-SLNs to demonstrate their anti-arthritis mechanism through an oxido-inflammatory and immunomodulatory cascade in the model of arthritis induced by CFA. *Peng et al.,* 2016 [69] developed SLNs for the continuous release and transdermal delivery of piroxicam (Pir), as well as highlighting the anti-inflammatory activity of existing SLNs. We found that Pir equipped SLNs had an average 102 nm particle size with a 0.262 PDI and a+30.21 mV charge.

Their optimized formulation, however, showed that Pir-SLNs were formed spherically with higher trapment efficiency (87 percent). They established that SLNs were the best carrier for encapsulation and continued drug release. By reducing the discharge of inflammatory cytokines, Pir-SLNs illustrated the anti-inflammatory responses at edematous site.

Bhalekar *et al.*, 2017, formulated piperine charged solid lipid nanoparticles (P-SLNs) by melt emulsification method for RA treatment [70]. They set a regular diameter of 128.80 nm, with 78.71 per cent encapsulation and-23.34 mV charge.

In vivo pharmacodynamic studies in complete freund's adjuvant induced arthritic rats exhibited significant reduction of TNF-α in treated rat which might be the mechanism behind the DMARD action of P-SLNs. *Raj et al., 2015* [71] formed solid lipid nanoparticles (ACF-SLNs) loaded with aceclofenac by injecting glyceryl monostearate as lipid into hydrogels using ultrasonic emulsification technique. They optimized the source of lipid and stirring velocity and defined the average particle size (189 nm), polydispersity index (0.162 nm) and zeta potential (-32.51 mV) for optimized solution.

They have a trap skill of about 85 per cent. *In vivo* tests showed stronger edema reserve with a magnitude of 81 percent after 6 h compared to basic ACF hydrogel tests. Additionally, optimal SLN size and near interaction with the stratum corneum enhanced product deposition in the skin. Hence, they stressed that ACF-SLNs could have beneficial effects for treatment with RA. Injectable actarit loaded solid lipid nanoparticles (A-SLNs) were created by Ye *et al.*, 2008, as a passive targeted agent for the treatment of RA [72]. In this method, A-SLNs were employed to target the spleen and remove the negative consequences (nephrotoxicity) that came with oral delivery. Their optimal formulation had a dimension of 241 nm and a charge of-17.14 mV.

Entrapment efficiency and loading for A-SLNs were found to be 50.87 percent and 8.48 percent, respectively. They found that, in 50 per cent propylene glycol solution, the plasma concentration of A-SLNs was 1.88 times higher than that of the actarit. By comparison, increasing the efficacy of A-SLNs has increased from 6.31 percent to 16.29 percent in spleen, while the drug's renal delivery is greatly decreased following intravenous administration to mice relative to that of the drug solution.

These findings imply that injectable A-SLNs might be a potential inert targeted therapeutic agent for RA therapy, with condensed dosages, reduced dosing occurrence, and reduced toxicity. Table 3 shows the many SLNs-based delivery systems used to deliver a range of medicines. The use of solid lipid nanoparticles in RA formulations might result in a controlled/sustained discharge pattern with fewer dosage frequencies. These solid lipid-based nanoparticles may potentially be able to improve the bioavailability of encapsulated drugs in the treatment of RA.

Recent advancement for the treatment of RA

Recently, nanoformulation approaches based on siRNA, peptides and selective approaches were tried for successful treatment of RA.

SiRNA based nanoparticulate systems for the treatment of RA

The cellular method responsible for silencing of the post-transcription gene that acts on messenger RNA (mRNA) is called RNA interference (RNAi). Silencing achieved with small interfering

RNA (siRNA) is transient; thus new strategies have been developed and reported for longer lasting silencing. Vectors programmed strategy such as short hairpin RNA (shRNA) may be also used for long-term steady cell silencing approach. Due to the outstanding gene silencing potential of RNAi, it has concerned wide attention in terms of high specificity, important effect, minor side effects and simplicity of synthesis. siRNA has the capacity for silencing a precise gene of interest. The issue linked to naked siRNA after systematic administration was nuclease dilapidation that eventually shortens the circulation period of siRNA in the blood stream. Alternatively, siRNA is consumed in the endocytosis mediated by the receptor, thereby emerging from the endosomal compartment with reduced naked siRNA therapeutic output. Such concerns have, however, been resolved lately by the production of products focused on nanotechnology. To provide enhanced protection, the siRNA was encapsulated in fully charged particles that effectively protect against serum degradation and immunological effects off-target. Lately siRNA based delivery systems were utilized for the treatment of RA, particularly providing a capable distribution intoperipherally inflamed tissue [13].

Table 3: Solid lipid nanoparticle based anti-rheumatic arthritic drugs

Drugs	Nano carrier	Therapeutic effects	Reference
Curcumin	Indian Gold	Oxido-inflammatory and immunomodulatory cascade	[68]
Piroxicam	Glycerol monostearate	Anti-inflammatory effect	[69]
Piperine	Glycerol monostearate	Anti-inflammatory effect	[70]
Aceclofenac	Glycerol monostearate	Anti-inflammatory effect	[71]
Actarit	Stearic acid	Anti-rheumatic arthritic effect	[72]
Apigenin	Glyceryl monostearate, tocopheryl polyethylene glycol succinate	Anti-rheumatic arthritic effect	[73]
Etofenamate and Ibuprofen	Compritol® 888 ATO	Anti-inflammatory effect	[74]
β-Sitosterol	Poly (lactic-co-glycolic acid)	Anti-rheumatic arthritic effect	[75]
Nabumetone	Compritol 888 ATO	Anti-inflammatory effect	[76]
Celecoxib	Glycerol monostearate	Anti-inflammatory effect	[77]
Nabumetone, Ketoprofen, Ibuprofen and phosphotungstic acid	Glycerol monostearate	Anti-inflammatory effect	[64]

Targeted nanoparticulate systems for the treatment of RA

Drug delivery systems can be further enhanced with active targeting ligands such as antibody, peptide, and polysaccharides for their therapeutic efficiency and specificity towards the treatment of various disorders. The two aiming modes were active and passive. In the treatment of RA, thenanoparticulate formulation has been beleaguered towards the selectively expressed CD44 surface receptors. Mediators such as growth factors, pro-inflammatory cytokines, chemokines, cell adhesion molecules, and proteases plays essential role in the RA development. In this plan angiogenesis and inflammation were the conditions connected with RA progression. The macrophages over-expressed the CD44, CD64, folate receptor-beta (FR-β), vasoactive intestinal peptide (VIP) receptor, and scavenger receptor class A, toll-like receptors, transforming factor-beta receptor increases. Whereas αvβ3 integrins, E-selectin, molecule-1 (VCAM-1) vascular cell adhesion, and molecule-1 intercellular cell adhesion is expressed more under angiogenic conditions [13].

Peptide based nanoparticulate systems for the treatment of RA

Peptides were lately gaining dedicated interest towards drug delivery for a diversity of therapeutic approaches. Enzymatic proteolysis bioactive peptides derived from natural protein sources (milk, egg, plants, fish, meat etc.) use biological activities for different disorders. Some peptides have the properties of antihypertensive, anti-inflammatory, antidiabetic, anticancer, antimicrobial, and antioxidant. Casein hydrolysate was effective in combating inflammation.

Low bioavailability, metabolic liability, gastrointestinal tract degradation, short absorption, inability to cross epithelial barriers were the problems associated with peptides. To incorporate/assemble the peptides into the nanostructures, solid-phase peptide synthesis, ring-opening polymerization and protein engineering methods were used.

Different types of peptides, such as dipeptides, cyclic peptides, amphiphilic peptides,-helical peptides, and-sheet peptides, have been used in nanoparticulate self-assemblies. Peptide-based delivery methods, mostly from natural sources and synthetic peptides, have recently been used to treat RA [13].

Patents for RA treatment by nanoparticles

Nanotechnologists have been steadily increasing the use of lipid-based nanoparticles as RA treatments. Furthermore, several related patents have garnered wide attention. Table 4 illustrates the recent progression in the field for this purpose [79].

Table 4: Clinical application of nanotherapeutic agents in arthritic diseases

Patent	Lipid nanocarriers	Advantage function
US 20150174069 A1	Dexamethasone sodium phosphate liposome	There is a 10% decrease in one or more of the symptoms of arthritis
WO 2003000190 A2	Glycosaminoglycans liposome	It has a high level of effectiveness in the treatment of osteoarthritis
CN 104688721 A	Paclitaxel liposome	The gel has a therapeutic effect and relieves pain in RA patients
US 20090232731 A1	Cationic liposome	It helps to reduce mononuclear cell infiltration into synovial tissue, pannus formation, and cartilage degradation
US 20160000714	Curcumin solid lipid particles	It provides suppression of cyclooxygenase 2 (COX-2) expression
WO 2017025588 A1	Cyclosporine solid lipid particles	It inhibits interleukin 2 transcription, lowering T lymphocyte activation and proliferation
US 8715736	B2 Nanostructured Lipid Carriers	In RA, it allows for effective skin penetration at the inflammatory site
CN 102225205 B	Tripterine nanostructured lipid carrier	It reduces the inflammation associated with rheumatoid arthritis

Methotrexate

Methotrexate (2,4-diamino-N10-methyl propylglutamic acid, MTX) is one of the major widely studied and effective therapeutics agents accessible to treat many solid tumors, hematologic malignancies, and autoimmune diseases [82]. MTX has played a critical role in the treatment of breast cancer, acute lymphatic leukemia (ALL), osteogenic sarcoma, choriocarcinoma, lung cancer, bladder

carcinoma, brain medulloblastoma, primary CNS lymphoma, and chronic myeloid leukemia [80, 81]. Apart from its original usage as a cancer chemotherapeutic agent, it is now used to treat psoriasis, multiple sclerosis, Crohn's disease, and rheumatoid arthritis, among other illnesses. The Food and Drug Administration (FDA) approved the use of MTX in the treatment of rheumatoid arthritis in 1988, and it is currently regarded the gold standard medication [82–86]. MTX, 2,4-diamino-N10-methyl propylglutamic acid, was first synthesized by Seeger *et al.,* 60 y ago. It is a folic acid analog in which the groups bonded to the C4 carbon and N10 hydrogen are NH2 and CH3. There are three parts in its structure as follows: (1) pteridine ring, (2) p-aminobenzoic acid, and (3) glutamic acid. It is a weak bicarboxylic acid among a molecular weight of 454.5 g/mol ($C_{20}H_{22}N_8O_5$). The drug possess pKa values of 3.8, 4.8, and 5.6 and low permeability (log P = 0.53) [87]. The solubility of MTX in distilled water at 20 °C is 0.01 mg/ml and is pH-dependent. This chemical is easily degraded by heat and light. The degradation of MTX solution is pH-dependent and catalyzed mostly by buffer chemicals in a common acid–base reaction. For greatest MTX persistence, a pH range of 6.6–8.2 is recommended [88]. MTX works as a cancer chemotherapeutic drug by inhibiting dihydrofolate reductase (DHFR) with high similarity, resulting in a decrease in tetrahydrofolates, which are required for purine and thymidilate production. As a result, DNA and RNA synthesis, as well as other metabolic processes, are disrupted [89]. However, MTX does not operate primarily as an antiproliferative drug for the cells responsible for rheumatoid arthritis coupled inflammation. The quick clinical remission seen with low dosage MTX combined with a rapid flare of illness upon medication cessation implies that low dose MTX's mechanism of action is more anti-inflammatory than antiproliferative [89, 90]. In fact, MTX inhibits both dihydrofolate reductase and other folate-dependent enzymes and leads to adenosine overproduction which can induce immunosuppression [91].

Pathophysiogical approaches for delivery of MTX

Numerous unique characteristics and pathophysiological phenomena of cancers and rheumatoid arthritis can be used as targets or tools for drug delivery, such as angiogenesis [91, 92], improved permeability and retention (EPR) effects [93-95], tissue hypoxia and acidosis [96], and expression of specific antigens and receptors [97-99], and addition of inflammatory cells such as macrophages and T lymphocytes. Angiogenesis not only is necessary for primary tumor growth but also facilitates tumor incursion and metastasis. Tumor microvascular networks have several single pathophysiological features distinguishing them from vigorous blood vessels. These contain extremely dense populations of leaky, tortuous, and primitive microvessels with pericyte covering, basement membrane, and arteriole-venule differences. Rapid angiogenesis leads to high vascular solidity in tumor and inflammatory tissues with great gaps survive between endothelial cells in blood vessels, so tumor, and inflammatory tissues show choosy extravasations of macromolecules compared with normal tissues. Dissimilar the situation with tumor and inflammatory tissues, approval of macromolecules from the interstitial space of normal tissues proceed quickly and gradually via the lymphatic system. Macromolecule clearance in the tumor and inflammatory interstitium is so poor that they stay there for a long period. These phenomena are usually termed EPR effects. On the other hand, because to inadequate blood perfusion, high interstitial fluid pressure, acidosis, and the rapid development of malignant tissues, these peculiar characteristics frequently produce a hypoxic environment. In twist, tissue hypoxia leads to configuration of new imperfect blood vessels. Polymeric conjugates, such as human serum albumin, liposomal conjugates, microspheres, solid lipid nanoparticles, in situ forming hydrogels, polymeric nanoparticles, dendrimers, such as polyamidoamine, polymeric micelles, magnetic nanoparticles, and carrier erythrocyte have all been developed to overcome the drawbacks of MTX therapy. For active targeting, some are further modified with targeting ligands.

Nanoparticles

MTX-loaded polymeric nanoparticles, arranged either by physical entrapment or chemical conjugation were broadly studied to attain sustained discharge pattern, to enhance chemo sensitivity of tumor cell lines or to aim cells/tissues by polymer coating (e. g. Tween 80) or ligand conjugation (e. g. folic acid, LHRH, biotin). *Taheri et al.* prepared MTX-HSA conjugates by carbodiimide reaction. The conjugates were cross-linked with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) to form steady nanoparticles with the mean sizes of 90-150 nm. The nanoparticles were exposed to be more cytotoxic on T47D cells compared to free of charge MTX. Moreover, MTX-HSA nanoparticles decreased the IC50 value of MTX on T47D cells in assessment with free MTX [100]. MTXHSA nanoparticles (MTX-HSA NPs) were coupled with luteinizing-hormone-releasing hormone (LHRH) and used to target 4T1 breast cancer cells in another investigation. *In vivo* investigations in Balb/c mice bearing 4T1 breast cancer tumors revealed that following a single IV injection of free MTX, non-targeted MTX-HAS NPs, and LHRH targeted MTX-HSA NPs, LHRH targeted MTX-HSA NPs demonstrated greater anti-tumor action. The average tumor volume in the LHRH targeted MTX-HSA NPs-treated animals had dropped to 8.67% of the initial tumor volume by 7 d following treatment, whereas the average tumor volume in non-targeted MTX-HSA NPs-treated mice had grown fast and reached 250.7% of the initial tumor volume [101, 102]. Similarly, biotin was taken as targeting agent. By 7 d after single IV injection in the mice model, average tumor volume in the biotin targeted MTX-HSA NPs-treated group decreased to 17.6 % of the initial tumor volume. Biotin targeted MTX-HSA NPs improved the survival of tumor bearing mice and increased their life span [103, 104]. Trastuzumab (TMAB) adorned MTX-HSA NPs were made in another research. It has been demonstrated that precise targeting of TMAB-MTX–HSA nanoparticles can improve MTX therapeutic effectiveness on HER2 tumor cells while reducing MTX adverse effects [105]. Jain *et al.* used a reverse microemulsion technique to make MTX-loaded HSA NPs, which were then chemically crosslinked with glutaraldehyde and FA conjugated through a PEG spacer. *In vitro*, it was discovered that these NPs specifically target folate-receptor overexpressing cancer cells, killing them via S-phase arrest. Circulation duration and tumor-specific localisation of MTX loaded HSA NPs increased after polyethylene glycolylation and conjugation with FA. When compared to non-targeted controls, HSA NPs suppressed tumor development more effectively [106]. *Trapani et al.* used an ionic gelation technique using sodium tripolyphosphate (TPP) to make MTX-loaded chitosan (CS) or glycol chitosan (GCS) nanoparticles for brain administration in the presence and absence of a Tween 80 coating layer. The smallest mean size (125 nm) was reported for MTX-loaded GCS/Tween 80 NPs even as they were about 255 nm for MTX-loaded CS and CS/Tween 80 NPs [107]. In alike study by *Azadi et al.,* minimum mean size of 60 nm with 62 % loading competence was reported. The most cytotoxic NPs against the C6 glioma cell line were GCS-based NPs. Confocal observations revealed that Tween 80-coated fluorescent NPs internalized more than untreated NPs [108]. *Ji et al.* created MTX-loaded CS covalently linked with FA, with TPP as the cross-linking agent, to reduce the toxicity of methotrexate (MTX) and increase the targeting capacity of NPs. The nanoparticles' typical sizes varied from 300 to 400 nm. In phosphate-buffer saline (pH 6.8), the discharge pattern revealed that MTX-loaded nanoparticles exhibited an early burst effect followed by a slow sustained drug release [109]. In another research, MTX was loaded into FA-conjugated O-carboxymethyl chitosan (FA-OCMC) NPs through a crosslinking process between the carboxyl groups of O-CMC and Ca2 ions. The FA-O-CMC nanoparticles had a better encapsulation competence and MTX loading capacity than the FA-CS NPs, while the FA-O-CMC nanoparticles had a smaller particle size. Furthermore, it was discovered that while the initial release of MTX from FA-OCMC nanoparticles was slower, the cumulative release was considerably larger than that of FA-CS nanoparticles [109]. By scattering polymerization (DP) and emulsion polymerization (EP) of n-butyl cyanoacrylate monomer, *Reddy et al.* created poly (butylcyanoacrylate) NPs. In comparison to the DP approach, the EP method produced smaller particles. With increasing monomer concentrations, both kinds of NPs showed an increase in drug entrapment. In 0.1 mol/l HCl, MTX release from DP and EP nanoparticles followed Fickian diffusion, while the technique was shown to be anomalous in phosphate buffer (pH 7.4) [110]. In another work, Gao *et al.* used a mixed polymerization technique to make polybutylcyanoacrylate NPs coated with polysorbate 80 for

brain administration. Rats were given nanoparticles with diameters of 70, 170, 220, and 345 nm by IV injection. It was observed that as compared to uncoated nanoparticles, covered nanoparticles may improve drug point in both brain tissues and cerebrospinal fluids and were a simple solution. Seventy-nanometer nanoparticles may carry more medicines into the brain, but the other three size ranges showed no differences [111]. *Cascone et al.* used a simple solvent evaporation process based on a single water-in-oil emulsion and stabilized with glutaraldehyde as a cross-linking agent to produce gelatin nanoparticles with initial different quantities of MTX. The particles were able to discharge MTX via a diffusion-controlled mechanism that was unaffected by the quantity of MTX loaded in the range of 5-15 percent [112].

Future perspectives for the treatment of RA

Natural treatments such as physical therapy, clinical therapy, and psychosocial treatment are currently important for promoting the recovery of autoimmune inflammatory RA diseases. While combinatorial therapies have a better solution, the selectivity and toxicity features of the healthy cells pose a major problem.

Potential treatment options for RA treatment separately from nanoparticulate formulations that rely on the production of proinflammatory cytokine specific inhibitors through virtue applications of monoclonal antibodies, bioactive peptides, and siRNA-based delivery systems. Leaning focusing on molecular biology and computational chemistry may offer a better suggestion for developing formulations intended to target pro-inflammatory cytokines.

CONCLUSION

RA is a pathogenic autoimmune disease that causes bone erosion, deformation, and even physical disability. While the traditional drug formulation would provide an appropriate solution in RA, no single drug therapy or combination therapy has been satisfactorily concluded with serious systemic side effects, frequent administration, tolerance from long-lasting management and high costs. Also with the newer biological therapeutics, there is a need to get better their side effect. To address these issues, extensive attention has been given to the concept of nanoparticles as drug carriers to improve the therapeutic index of drugs. Most of the current studies show improved efficacy when administering a drug in the formulation of nanoparticles as compared to the free drug, mostly in three aspects: selective accumulation, prohibited drug release and condensed systemic toxicity. The newly developed nanocarriers considerably improve the therapeutic effectiveness of present drugs for enhanced RA in experimental models by on the whole dose reduction and higher local drug localization by passive and active drug targeting. Lipid-based nanoparticles are extra advantageous compared to other nanoparticles because of the extra biocompatible and biodegradable nature of their constituents relative to the synthetic polymers establish in other types of nanoparticles. Currently, a multiplicity of lipid-based nanoparticles encapsulated with drugs is clinically approved and commercially obtainable, while lots of more formulations are being investigated in dissimilar stages of clinical trials or are awaiting approval. However, added studies are still necessary to optimize their capability as drug-delivery systems. Lipid-based nanoparticles have the potential to boost anti-arthritic drug effectiveness and safety profile and, more importantly, the result for patients with RA.

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All authors have contributed equally.

CONFLICT OF INTERESTS

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