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Review Article

The Therapeutic Potential of Targeted Nanoparticulate Systems to Treat Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a widespread autoimmune inflammatory disease. It implicates damage to bones, cartilage, and joints with uncertain pathogenesis. It is coupled with an elevated risk of cardiovascular complications and human disability. The conventional dosage forms for RA treatment pose numerous problems including poor efficacy, large dosages, frequent administration, limited responsiveness, greater expenses, and severe side effects. The nanoparticulate systems are emerging as a new thought for the diagnosis and treatment of RA. Anti-inflammatory drug-loaded nanoparticulate systems aid in the active and passive targeting of the inflamed region. Improved bioavailability and targetability are achieved by using these systems. In this review, the pathophysiology of RA and its conventional treatment has been discussed. The role of various nanoparticulate systems for passive and active targeting of RA has been reviewed. The authors have summarized the current practices in the typical and novel nanosystems to improve the quality of life in RA patients.

1. Introduction

Arthritis is characterized as the inflammation of one or more joints [1]. There are several signs and symptoms of the disease that include redness of the joints, swelling of the joint and joint discomfort, and joint warmth [2]. Rheumatoid arthritis (RA) and osteoarthritis (OA) are the most frequent forms of arthritis. OA is caused by mechanical wear and tear on joints while RA is classified as an autoimmune disorder [3, 4]. RA tends to impact numerous joints of the body. If left untreated, RA damages bone and cartilage, which makes it difficult for patients to do daily tasks like working or going to social gatherings. This condition is called chronic RA [5]. Figure 1 represents the manifestation of types of arthritis joints. When the tendon is inflamed (tenosynovitis), it results in both the loss of cartilage and the erosion of bone [6]. RA has a heterogeneous clinical response to the different treatments [7]. RA affects around 5 out of every 1000 people and tragically, 80 percent of those affected face disability within 20 years after the early symptoms.

There are several antiarthritic medications on the market today and most of them are relatively expensive, have limited efficacy, and/or have unavoidable adverse effects. Inflammatory drugs are one of the most expensive treatment categories for health care [9]. Nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), disease-modifying antirheumatic drugs (DMARDs), and biological agents are widely prescribed to treat RA. NSAID-induced nephrotoxicity, liver damage, and heart failure are all potential side effects of these treatments, despite their ability to slow the progression of the disease [10, 11]. If medication continues to be ineffective, the only other option is surgery [12–14].

An effective alternative to these outdated therapeutic procedures is required. This review has been focused on

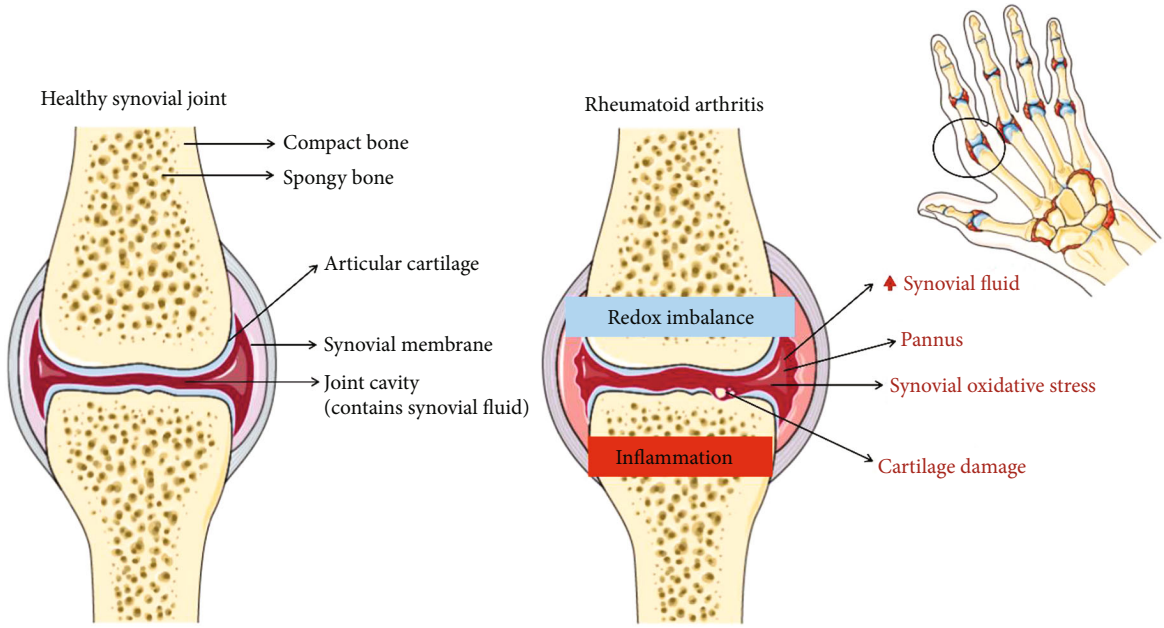

Figure 1: Normal joint vs RA joint. Reproduced from [8].

novel strategies to treat RA. The role of nanotechnology-based nanoparticulate systems will be discussed. The lipid, polymer, metal, inorganic nonmetal, and bionic technology-based nanoparticulate systems will be elaborated. Current progress in different nanodrug delivery systems to treat RA will also be highlighted.

2. Role of Nanoparticulate Systems in RA Treatment

Nanotechnology has revolutionized every field of applied science. Nanoparticulate systems have attracted attention for their potential to explore a variety of anti-inflammatory drug-loaded nano formulations [15]. Table 1 includes some of the nanoparticulate systems reported for the treatment of RA.

Many researchers have been working on the development of various nanoparticulate systems for treating RA by either directly or indirectly targeting the area of inflammation. Improved bioavailability, targetability, and enhanced therapeutic action are the main advantages of these systems. Prolonged circulation time is achieved by pegylated nanoparticulate systems. Additionally, smart nanoparticulate systems have been designed that release the therapeutic agent only when a trigger or stimulation is encountered. The graphical representation of such systems has been represented in Figure 2. Mahtab et al. discovered the enhanced permeability and retention (EPR) effect that provided a crucial push intended for extensive research into the application of nanoparticulate systems. Passive targeting mainly depends on the EPR effect. Angiogenesis (newly created blood vessels) is critical in chronic inflammatory diseases like RA because of local hypoxia and growth factor generation at inflamed joints. Active targeting following systemic delivery can be accomplished by coating nanoparticulate systems with a targeting moiety. As the disease progresses, angiogenesis and inflammation are the most prominent features. Growth factors, cytokines, adhesion molecules, and proteases have all been implicated in the formation of angiogenesis in various ways. The vascular endothelial growth factor (VEGF) and angiopoietin play a key function in the hypoxia-VEGF system. The endothelial cell surface is also overexpressed with many adhesion molecules, including integrin v3, E-selectin, vascular cell adhesion molecule-1 (VCAM-1), and intercellular cell adhesion molecule-1. Inflamed synovial membranes are rich in macrophages, which have a wide range of proinflammatory properties and contribute significantly to inflammation and joint damage. The selective delivery of nanomedicine by binding to a specific receptor could switch off their complicated connections with other cells and improve the condition of RA while preserving the basic functions of resting macrophages. CD44, CD64, folate receptor-beta (FR-), vasoactive intestinal peptide (VIP) receptor, scavenger receptor class A, toll-like receptors, transforming growth factor-beta receptors, etc. were observed to be over-expressed on activated macrophages [31]. The antibodies or other specialized adhesion molecules (e.g., selectins) are bound to the surface of nanoparticulate systems [32]. Redox-responsive clustered Fe_3O_4 nanoparticles (NPs) were produced in a study. Fe_3O_4-based nanoclusters (NCs) of these NPs were produced following laser irradiation to exhibit adjustable r1 and r2 relativities, thereby enabling enhanced dual-mode T1/T2-weighted MR imaging of inflammatory arthritis [33].

3. Synthetic Nanoparticulate Systems

Based on the particle integrity, the synthetic nanoparticulate systems can be categorized into two major categories: the nonrigid nanoparticles, which include liposomes and solid

Table 1: Nanoparticulate systems for the treatment of RA.

Nanoparticulate system	Drug	In vivo model	Outcome	Ref
Liposome (nonrigid nanoparticulate system)	Dexamethasone	Rats with adjuvant-induced arthritis	Significantly down-regulated serum proinflammatory cytokines including tumor necrosis factor-α and interleukin-1β when compared to free dexamethasone	[16]
Liposome/gold nanoparticles (hybrid nanoparticulate system)	Ubiquinone	Mice with collagen-induced arthritis	Proinflammatory cytokines were significantly decreased	[17]
Calcium phosphate/liposome-based nanocarrier (hybrid nanoparticulate system)	siRNA and methotrexate (MTX)	Mice model	Blocked the transcription factor NF-kB and reduced the expression of proinflammatory cytokines	[18]
Solid lipid nanoparticles (nonrigid nanoparticulate system)	β-Sitosterol	Complete Fruend adjuvant (CFA)-induced arthritis via a dual pathway in rats	Increased the redox status of synovium {reduced the malonaldehyde (MDA) and increase superoxide dismutase (SOD), glutathione (GSH), and catalase (CAT)} levels, and reduced the cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-2, 6, 16, and 17 and increased level of IL-10, transforming growth factor beta (TGF-β). Reduced the level of cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), vascular endothelial growth factor (VEGF), and NF-κB.	[19]
Chitosan-coated solid lipid nanoparticles (hybrid nanoparticulate system)	Leflunomide	Rats with adjuvant-induced arthritis	Improved joint healing and reduced hepatotoxicity	[20]
Chitosan and hyaluronic acid-based polymeric nanoparticles (rigid nanoparticulate system)	Antibodies	Biological assays	Selectively captured and inactivated the proinflammatory cytokine IL-6	[21]
Ethyl cellulose and Eudragit S-100-based polymeric nanoparticles (rigid nanoparticulate system)	Mefenamic acid	In vitro drug release	Greater stability and controlled drug release for 12 h.	[22]
Poly(lactic-co-glycolic acid) (PLGA)–PEG–folic acid (FA), sodium deoxycholate (SDC), and solutol HS15 (HS15) nanocarriers (rigid nanoparticulate system)	Germacrone	Adjuvant-induced arthritis (AIA) rats	Levels of proinflammatory cytokines (TNF-α, IL-1β) in the rat's inflammatory tissue were significantly reduced	[23]
Polyethylene-glycol (PEG)-fabricated multiwalled carbon nanotubes (rigid nanoparticulate system)	Corticosteroids (triamcinolone)	Biological assays	Significantly inhibited the inflammatory response of fibroblast-like synoviocytes	[24]
Single-walled carbon nanotubes (rigid nanoparticulate system)	Targeted carrier	K/BxN serum transfer (STA) model	Specifically targeted cells homing to or present in arthritic joints	[25]
Hyaluronate–gold nanoparticle/tocilizumab (HA-AuNP/TCZ) complex (rigid nanoparticulate system)	Tocilizumab (monoclonal antibody)	Collagen-induced arthritis (CIA) model mice by ELISA	Reduced levels of inflammatory cell infiltration and cartilage and bone destruction	[26]
Multifunctional dendrimer-entrapped gold nanoparticles (rigid nanoparticulate system)	Codelivery of antioxidant alpha-tocopheryl succinate (α-TOS) and anti-inflammatory anti-TNF-α siRNA	CIA mouse model	Better antioxidative effect and the most significant decrease of mRNA of TNF-α and TNF-α protein in the ankle joints	[27]

Table 1: Continued.

Nanoparticulate system	Drug	In vivo model	Outcome	Ref
Folate/RGD-dual-functionalized mesoporous silica nanoparticles (rigid nanoparticulate system)	Polydatin	CIA model	Joint damages were significantly improved	[28]
Biomimetic exosome (bionic)	Glucocorticoids (dexamethasone sodium phosphate (Dex) nanoparticle (Exo/Dex))	In vitro study and CIA mice	Enhanced endocytosis and excellent anti-inflammation effect against RAW264.7 cells and in vivo model significantly reduced inflamed joints	[29]
Metabolically engineered exosomes (bionic)	Engineered exosomes as a next generation drug for RA	CIA mice model	Promoted M1-M2 macrophage polarization in the bone marrow regions of joints inflamed by RA and reduced the activity of surrounding proinflammatory cells, such as M1 macrophages, activated synovial fibroblasts, and TH17 cells	[30]

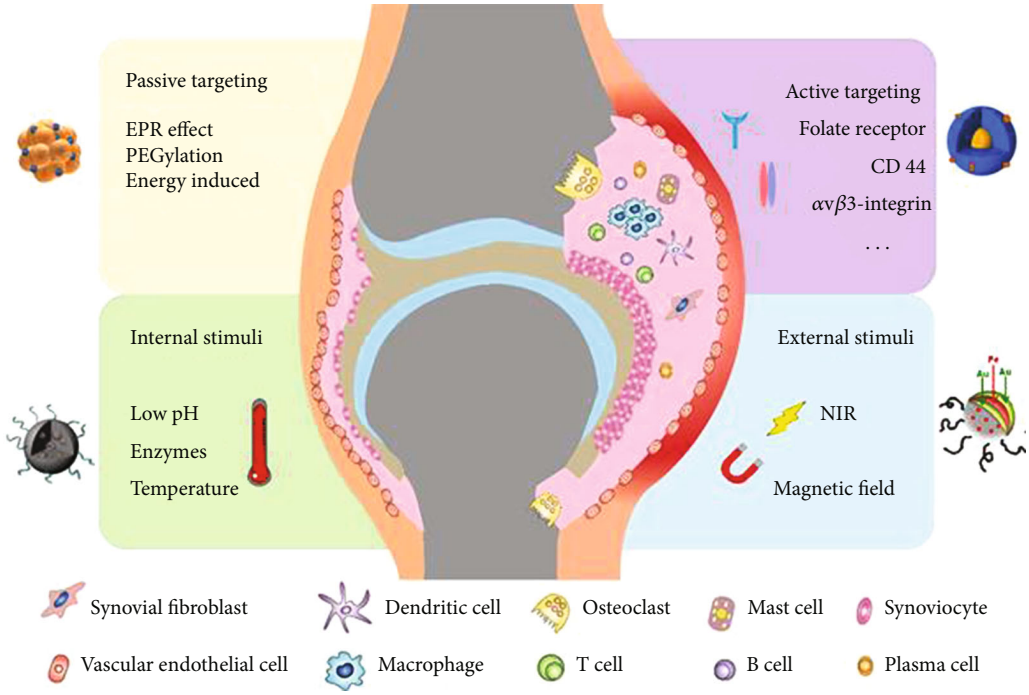

Figure 2: Passive targeting, active targeting, and stimuli-responsive nanoparticulate systems for RA treatment. Reproduced with permission from [34].

lipid nanoparticles, and the rigid nanoparticles, which include polymeric nanoparticles and nanoparticles made of inorganic materials.

3.1. Nonrigid Nanoparticulate Systems. It is well-known that nonrigid nanoparticulate systems have relatively soft structures that are easily disrupted by an external force. The nonrigid nanoparticulate systems include liposomes and solid lipid nanoparticulate systems (SLNs). Nonrigid nanoparticulate systems have an important role in the treatment of RA.

3.1.1. Liposomes. Liposomes are derived from the Greek words "lipo" and "soma," which mean "fat" and "body," respectively. Dr. Alec Bangham and Dr. Horne pioneered the concept of liposomes in 1964. Liposomes are vesicles that can hold hydrophilic (water-soluble) drugs, hydrophobic drugs (water-insoluble), peptides, and nucleic acids effectively. It is possible to compartmentalize a variety of drugs in a single formulation using liposomes. Vesicles made up of lipids and cholesterol are safe, nontoxic, noncarcinogenic, nonthrombogenic, and biodegradable in the natural environment [35].

The targeted delivery of various drugs can minimize their side effects. Methotrexate (MTX) is a commonly prescribed medication for the treatment of RA. MTX was loaded with higher encapsulation efficiency in liposomes (>30%). Experiments in arthritic animals demonstrate that liposomes encapsulating MTX considerably boosted the biological effect [36]. Similar results have been reported with polymerized stealth liposomes as a delivery system for the enhanced anti-inflammatory effect of dexamethasone for the treatment of RA. It was shown that the polymerized stealth liposomes remained stable in blood vessels for a substantial amount of time. Cells were able to metabolize these without inflicting any serious damage. Upon injection into arthritic rats, polymerized stealth liposomes with dexamethasone displayed prolonged circulation and accumulated primarily in the affected joints. The in vivo animal study confirmed suppressing of the proinflammatory cytokines (TNF- and IL-1A) in joint tissues, thereby, decreasing joint swelling, and slowing down the progression of RA [37]. In another study, folate conjugated double liposomes containing prednisolone and MTX were used to target RA. The folate receptor is well-known to be expressed at a higher level in inflamed cells than in normal cells. Both drugs were shown to have a larger concentration in inflamed joints than in noninflamed joints [38]. The thermosensitive liposomes can further enhance the targeted drug delivery. Sinomenine hydrochloride (SIN-TSL) was loaded into a unique thermosensitive liposome created using a pH gradient technique. When the temperature was increased from 37 to 43°C, the rate of drug release was significantly faster than at 37°C. SIN-TSL with microwave hyperthermia increased anti-RA effects in both in vitro and animal studies [39].

T-helper type-17 (Th17) cells are dramatically increased by the proinflammatory cytokine interleukin-23 (IL-23) in the conditions like RA. Biofunctionalized liposomes were studied by Lima et al. to deliver anti-IL-23 antibodies (Abs) effectively. Systemic administration of Abs is limited by the risk of significant side effects and the short half-life of these Abs. A liposomal immobilization technique was used to improve the therapeutic efficacy of anti-IL-23 Abs. Because of the anti-inflammatory and antioxidant capabilities, gold nanoparticulate systems (AuNPs) were loaded into

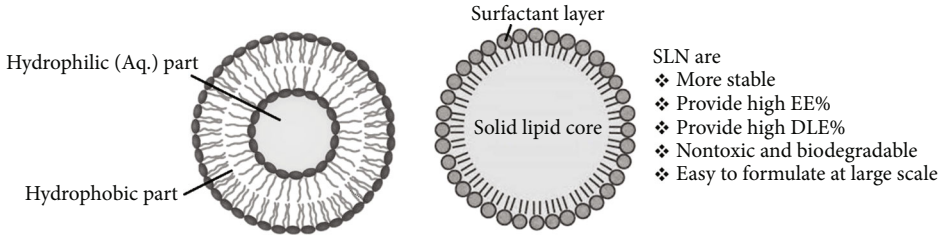

Figure 3: Schematic presentation of the complete structure of solid lipid nanoparticulate systems with advantages over liposomes.

the liposomes. Tests on human articular chondrocytes, macrophages, and endothelial cells showed their hemocompatibility and cytocompatibility. These liposomes significantly reduced the synthesis of IL-17A by peripheral blood mononuclear cells from healthy donors and RA patients who had been driven to Th17 differentiation [40]. Gouveia et al. reported a synovial cell-targeted drug delivery approach using hyaluronic acid (HA) conjugated pH-sensitive liposomes. The CD44 is overexpressed in synovial cells and HA has a high affinity for CD44. The caveolae- and clathrin-dependent endocytosis enables the selective uptake of lipids. The acidic environment caused the breakdown of these pH-sensitive liposomes. Prednisolone was released into the cytosol through intracellular compartments in a regulated manner, minimizing the off-target distribution of the drug. It was found that combining these two approaches (HA and pH) boosted prednisolone's bioavailability and improved its focused therapeutic efficiency while decreasing its well-known adverse effects [41]. Fibroblast-like synoviocytes (FLS) have been identified as a major contributor to RA etiology by numerous studies. FLS increases the progression of RA by producing tumor-like growth and the production of pannus in the joints. Berberine (BBR) has recently been discovered to be a powerful activator of miR-23a, which results in downstream suppression of inflammatory kinases such as ASK1 and GSK-3 in RA disease. Drug-loaded nanoparticulate systems including herbal bioactive substances like berberine have also been developed. PEGylated liposomal berberine and PEGylated liposomal miR-23a were used as therapeutic targeting of an adjuvant-induced arthritic disease model. In the study, raised anti-inflammatory action was achieved. The liposomal formulations employed in this study increased the drug's steady-state distribution, resulting in anti-inflammatory activity, decreased pannus development, decreased cartilage deterioration, and decreased bone erosion. BBR absorption suppressed the Wnt1/-catenin pathway by altering several parameters associated with the clinical complication of rheumatoid arthritis disease, potentially via increasing miR-23a levels [42].

3.1.2. SLNs. There has been an enormous amount of attention paid to SLNs since their introduction in 1991, and they have been used as a highly effective method of delivering medications and DNA and targeting therapies [43]. SLNs are made of a solid lipid core, such as triglyceride or stearic acid, as well as waxes and emulsifiers. Numerous methods were studied for the preparation of SLNs, e.g., solvent emulsification/evaporation approach [44, 45]. SLNs may have an edge over other types of nanoparticulate systems because of their high biocompatibility, increased drug loading capacity, and scalability. The drawbacks of the conventional nanocarriers include polymer degradation and cytotoxicity; lack of suitable large-scale production process; insufficient stability; drug leakage and fusion; phospholipid degradation; high production cost; and sterilization problems. The high-melting fat matrix-based SLNs are being developed to overcome the limitations of conventional colloidal carriers including liposomes and polymeric nanoparticulate systems [46]. Figure 3 represents the difference between the liposomes and the SLNs and the advantages of the SLNs. Colloidal drug delivery technologies such as SLNs have been shown to improve drug entrapment, bioavailability, and pharmacokinetic characteristics of hydrophilic and hydrophobic drugs [47].

The targeted drug delivery with minimal burst release has been achieved with the SLNs [43, 48]. Piperine-loaded SLN dispersion to maximize its oral and topical effectiveness was reported. The prepared SLN was given orally and topically to rats with CFA-induced arthritis. Piperine from the SLN gel formulation accumulated in the skin, according to ex vivo results utilizing the Franz diffusion cell. The pharmacodynamic study results revealed that both topical and oral piperine elicited a substantial response when compared to chloroquine suspension administered orally [49]. The FDA has approved leflunomide (LEF) for use in the treatment of RA. However, a wide range of gastrointestinal side effects, including nausea, diarrhea, vomiting, and stomatitis have been attributed to oral LEF treatment. After the application of chitosan (CS) on the surface of the SLNs, folic acid was added (FA). As compared to oral LEF suspension in rats with adjuvant-induced arthritis (AIA), the oral treatment of FA-CS-SLNs resulted in increased joint healing and decreased hepatotoxicity [20].

The SLNs provide oral as well as topical drug delivery. Piroxicam is an effective anti-inflammatory, antipyretic, and analgesic medication; nevertheless, its oral administration for extended periods is limited due to a variety of gastrointestinal adverse effects. SLNs containing piroxicam were prepared using the solvent emulsification/evaporation process. Using guinea pig skin placed on a modified Franz diffusion cell, the in vitro penetration of piroxicam through the SLN-based nanoparticulate system was evaluated. SLN formulations showed improved skin permeability [50]. Curcumin (CUR) is a natural product that has anti-inflammatory properties. Jeevana and Muni developed SLNs to increase the solubility of CUR. The CUR content of SLNs

was reported to be 98.7-99.3%. These results indicated minimal CUR loss during the SLN production process. Ex vivo tests on goat skin showed that SLN topical gel released a significant amount of CUR (76.93%) within 30 minutes of being applied to the skin membrane. Similarly, in the in vivo application, an X-ray radiographic study of untreated rats revealed abnormalities in the hind paws. The treatment with CUR-SLNs prevented these deformities and significantly reduced paw edema in the treated rats [51].

3.2. Rigid Nanoparticulate Systems. Rigid nanoparticles have been shown to have a higher mechanical strength than non-rigid lipid-based nanoparticles published thus far. Rigid nanoparticles are classified into these key subcategories: biodegradable polymeric nanoparticles, carbon nanotubes, and metallic and inorganic nanoparticles.

3.2.1. Polymeric Nanoparticulate (PNP). Solid nanoparticulate, core-shell structures, polymeric micelles, and polyplexes are all examples of biodegradable PNP formulations. Nanoparticulate formulation and synthesis methods are dependent on the polymer and cargo characteristics; however, PNP is most often generated via self-assembly or emulsion in most cases. PNP Polymers may be assembled in a variety of ways, including the formation of complexes of cationic polymers with anionic nucleic acids, as well as the spontaneous formation of micelles when the concentration of amphiphilic block copolymers reaches a threshold micelle concentration. Nanoparticulate may also be created by procedures such as emulsification, in which droplets of one phase are disseminated in another. Solubilized in an organic phase, polymers are often combined with surfactants and ultrasonicated at high power in an aqueous solution to produce nanodroplets [52]. Hardened polymer nanoparticles are formed when the solvent evaporates from the emulsion. They may also be encased in another material to create core-shell nanoparticulate with desirable surface features [53]. PNP is divided into two main categories: Polysaccharides and proteins produced from natural sources. Peptides and polysaccharides may be degraded in the body using enzymes and the breakdown rate can be controlled to get the desired release profile. Dextran, gelatin, poly(L-lysine), chitosan, and alginate are among them [21, 54]. The delivery channels and disease targets may all benefit from synthetic polymers that have desired features such as hydrophobicity and degradation profile. Poly(Lactide-co-Glycolide), poly(-caprolactone), sugar cyclodextrins, and poly(-amino ester) are examples of these polyesters [55].

There are a variety of ways to deliver drugs for the treatment of RA. Targeted drug administration based on stimuli is the most prevalent method. Stimuli from the micro- or macroenvironment can alter the physical properties of stimulus-sensitive polymers [56]. Polymer transitions are influenced by factors such as solubility, hydrophilic/lipophilic balance, solvent interactions, and conductivity. These changes are driven by chemical reactions including acid-base interaction, redox, thermal, or hydrolysis of compounds linked to the polymer chain [57].

pH shift has been used to cause the release of integrated therapeutics whenever environmental changes are related to pathophysiological processes such as inflammation [58]. In this context, the idea of using pH-sensitive PNP-carrying therapeutic compounds (NSAIDs, GCs) in RA treatment has great potential. The enhanced angiogenesis that occurs in RA leads to the discontinuity of inflammatory endothelium cells and an increase in vascular permeability. This abnormality may allow nanosystems of the appropriate size to successfully enter inflamed joints [59]. Following enhanced delivery of anti-RA drugs via nanoparticulate systems, low pH vicinity causes the drug to be delivered directly into the affected area of the body. Using this approach, it is possible to increase the efficacy of RA therapeutics by increasing therapeutic selectivity and reducing systemic side effects. Dexamethasone- (DEX-) loaded HAPNPs (HA-coated acid-sensitive PNPs) were examined by Yu et al., for the treatment of RA. PCADK, a polyketide with a high degree of acid sensitivity, was used to make the acid-sensitive polymeric material that comprised egg phosphatidylcholine, polyethyleneimine, and PCADK. As a result of its ability to bind CD44, HA was chosen as a targeting moiety. An average diameter of 150.5 nm was shown to have a pH-dependent drug release characteristic in the nanoparticulate system. HAPNPs demonstrated a strong ability to target activated macrophages because of the presence of HA on the nanoparticulate systems, as demonstrated by cellular uptake experiments. It was also shown that HAPNPs/DEX treatment reduced inflammatory cell infiltration, bone degradation, and cartilage damage in the ankle joints of rat models of AIA [60].

The phase-transition behavior of temperature-responsive polymers is considered while selecting these materials. Polymers with a lower critical solution temperature (LCST) for whom the solubility is influenced by temperature changes are widely used to develop nanocarriers with thermo-responsive properties. Transitional polymers become more soluble, and their components swell due to hydrogen interactions between water molecules and the polymer functional groups. This property makes these polymers suitable for loading drugs below the LCST. During the shift from hydrophilic to hydrophobic, a morphological change occurs from the coil to the globule, due to a change in the temperature. During this transition, the hydrogen bonds and network collapse, resulting in the polymer being insoluble and the water molecules being squeezed out of the polymer. The guest drug molecules are released because of this transformation. Figure 4 depicts the mechanism of action of thermo-responsive drug delivery systems [61].

Drug administration via photo-responsive polymers is based on their ability to absorb light. Upon exposure to light, these polymers change phase. The moieties are responsive to UV, visible, and near-infrared light. These materials are appealing because of their water solubility, biodegradability, and biocompatibility, as well as their ability to manage the spatial and temporal triggering of drug release. Two basic tactics may be utilized depending on the application: one time or repeated on-off active compound release. This is plausible because some materials, when exposed to light,

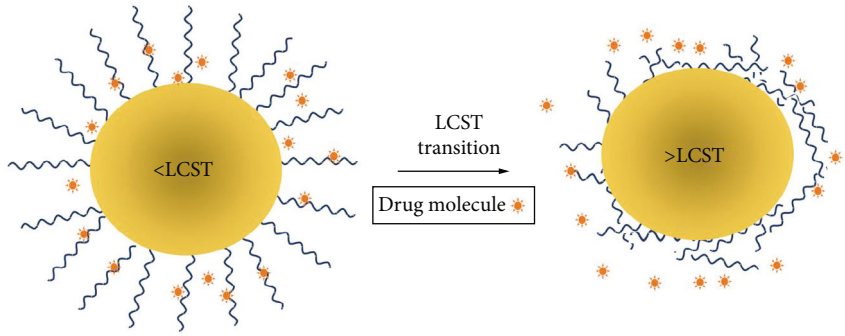

Figure 4: Mechanism of action of thermo-responsive drug delivery system.

can undergo irreversible structural changes, while others when the trigger is removed, can return to their former state [62]. Fomina et al. used a self-immolating quinone-methide system to create degradable nanoparticulate systems made of photo-sensitive polymers. The new photo-sensitive nano system initiated the release of tiny hydrophobic compounds in a controlled burst. As a result of the system's adaptable architecture, the triggering group was responsive to both internal and external stimuli, which offered a lot of promise for RA therapy. Authors of another study described a polymeric substance that was exposed to two-photon absorption, and disassembled in response to near-infrared irradiation, at biologically tolerable levels. Many pendants' protective 4-bromo7-hydroxycoumarin groups were photolyzed, starting a chain reaction that finally destroyed the polymer's backbone by cyclization and rearrangement [63].

Redox-sensitive nanoparticulate systems are another area of interest in the search for new ways to deliver drugs. People's interest in this type of system has been sparked by the redox potential difference between the oxidizing and reducing compartments. Reactive oxygen species (ROS) have a critical role in the pathophysiology of chronic inflammatory arthropathies like RA. ROS are created mostly during oxidative phosphorylation, although they may also be formed during an oxidative burst by activated phagocytic cells. They act as a key intracellular signal that boosts the inflammatory response [8]. Pu et al. reported chitosan-based nanoparticles with dual responses to oxidative stress and reduced pH for curcumin release and its anti-inflammatory applications. This occurred because curcumin and the carrier had Förster resonance energy transfer. It also allowed us to keep tabs on how the intracellular release was progressing. Upon activation, curcumin might effectively neutralize excess oxidants generated by macrophages that had been activated with lipopolysaccharide (LPS). The anti-inflammatory properties of curcumin-loaded nanoparticles were tested on LPS-induced ankle inflammation in a mouse model [64].

3.2.2. Carbon Nanotubes and Nanohorns. Carbon nanotubes (CNTs) are made up of sheets of six-membered carbon atom rings that have been folded into cylinders. Single-walled carbon nanotubes (SWCNTs) have just one layer, whereas multiwalled carbon nanotubes (MWCNTs) have two or more layers (MWCNTs). CNTs are also known as cup-stacked carbon nanotubes and carbon nanohorns [65]. These enticing carbon nanostructures are now being used in a variety of medication delivery methods for the treatment of life-threatening disorders. CNTs have been used to treat inflammatory illnesses like RA, according to many studies.

Kayat et al. investigated the use of folate-anchored CNTs to target an antiarthritis drug, (MTX), to the arthritic inflammatory region. In comparison to naked MWCNTs packed with MTX, as well as free MTX, folate-conjugated MWCNTs significantly enhanced percentage inhibition of RA, biological half-life, and MTX delivery rate. The recent results show that drug-loaded functional MWCNTs may change pharmacokinetics while also providing a steady and optimal drug delivery mechanism [66].

A small interfering RNA (siRNA) targeting the NOTCH1 gene was investigated as a therapeutic carrier for MTX in HiPco- and carboxyl-SWCNTs made by Andersen et al. MTX was covalently attached to the nanotubes after they had been solubilized with PEGylation. A serum transfer mouse model showed that SWCNTs mainly accumulated in joints that were inflamed. They found that both SWCNTs were related to B cells, monocytes, and neutrophils in the blood. Adding MTX to SWCNTs reduced their ability to target immune cells, particularly B cells; however, siRNA alone boosted their ability to target immune cells. Targeting specificity to neutrophils and monocytes was increased when both MTX and siRNA were loaded into carboxyl-SWCNTs, but not to B cells. It was possible to alter the targeting specificity by changing the ratio of MTX and siRNA on SWCNTs [67].

3.2.3. Metallic Nanoparticulate Systems. Metal nanoparticulate have outstanding characteristics, may have numerous functional groups added to them, and are frequently employed in biological applications [68]. Kim et al. developed manganese ferrite and ceria nanoparticle-anchored mesoporous silica nanoparticles (MFC–MSNs) to cure RA. Degenerative features were reduced in the CIA rat model when MFC–MSNs were injected intra-articularly. They have a synergistic effect on scavenging ROS and producing O2, and they may reduce M1 macrophages while polarising M2 macrophages. Furthermore, as a delivery vehicle, monodisperse silica nanospheres may continuously release MTX, enhancing the therapeutic impact as shown in Figure 5 [69].

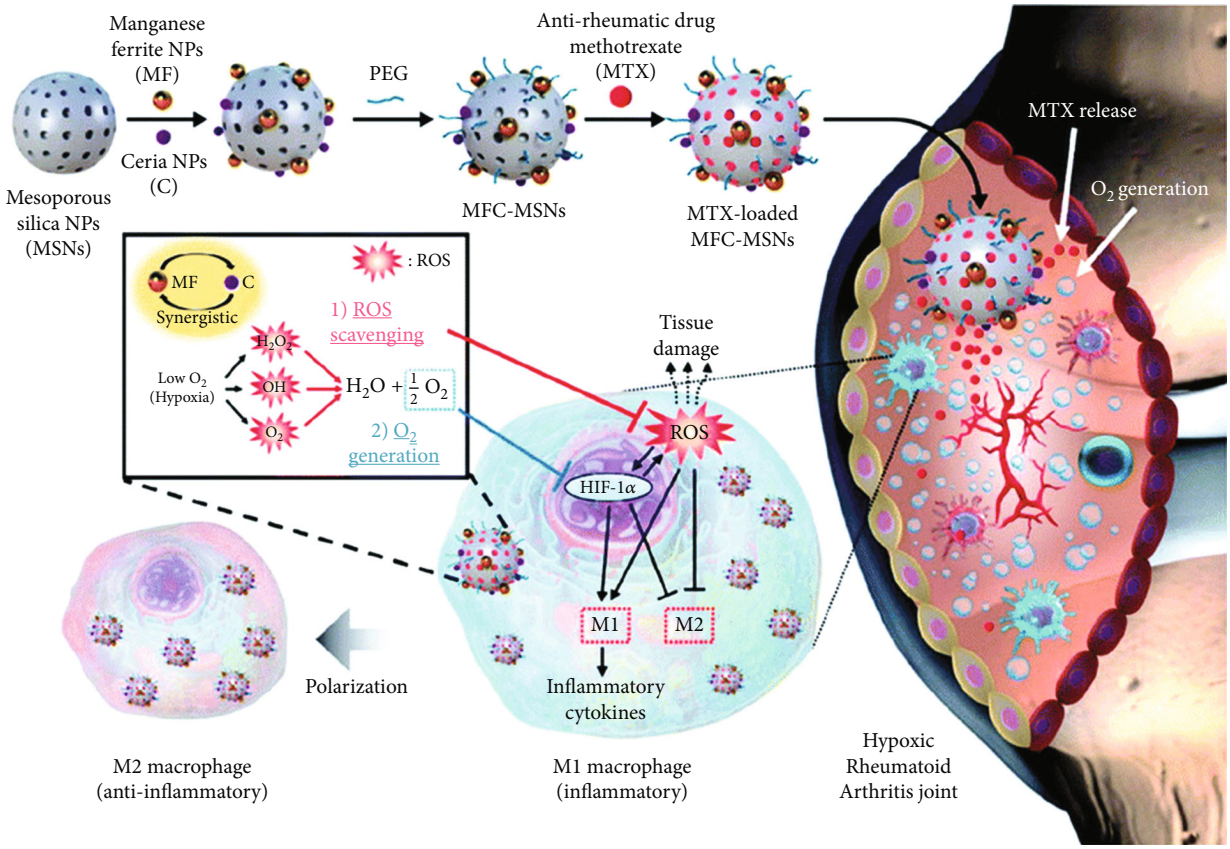

Figure 5: Therapeutic mechanisms of MFC–MSNs in RA treatment. Reproduced with permission from Copyright (2019) American Chemical Society [69].

In another study, Kalashnikova et al. created albumin-cerium oxide nanoparticulate that were indocyanine green conjugated (ICG). The nanoparticulate systems were put into the CIA mice's swollen joints, and an in vivo imaging system showed that they accumulated in the affected joints and had a stronger therapeutic impact. This unique albumin-cerium oxide nanoparticulate' targeting and therapeutic impact point us to a new route for arthritis therapy [70]. Lee et al. created a hyaluronate–gold nanocarriers/tocilizumab (HA-AuNP/TCZ) as a combination therapy for RA. In this treatment, AuNP was exploited as a therapeutic carrier that reduced angiogenesis. TCZ is a monoclonal antibody that binds against the interleukin-6 (IL-6) receptor that is exploited as an immunosuppressive treatment in the initiation and progression of RA by interfering with IL-6. HA is well-known for its cartilage-protecting and lubricating qualities. End-group thiolated HA was synthesized by altering HA with cystamine by reductive amination, which was then reduced with dithiothreitol (DTT) (HA-SH) (HA-SH). HA-SH was utilized to chemically modify AuNP, whereas TCZ was employed to physically modify it. In collagen-induced arthritis, the therapeutic effect of the HA-AuNP/TCZ combination on RA was verified [26].

3.2.4. Inorganic Non-metallic Nanomaterials. One of the most often used RA drug delivery techniques is based on injectable silica-based nanoparticulate systems. By using a core–cone structure, Li et al. produced mesoporous silica nanoparticulate systems (MSN-CC) as more convenient, efficient, and long-lasting therapeutic than the previous method of injecting HA. In a rat model of RA, this nanomaterial enhanced the synthesis of HA, reduced synovitis inflammation, and promoted bone repair. Hyaluronan synthase type 2 (HAS2) has high protein loading capacity and good biocompatibility, degradation, and degradability. Functionalized group PEI was applied to the surface of mesoporous silica to load and deliver HAS2. Intra-articular injection of MSN-CC-PEI successfully transported HAS2 into synovial cells and boosted the production of endogenous HA both inside and outside the body [71]. Local percutaneous injection and nano-controlled MTX release were studied by Guo et al. The MTX-mSiO2@PDA system was highly responsive in terms of pH. After 24 hours, the cumulative amount of MTX transferred from MTX-mSiO2@PDA to pH 5.0 receptor fluid via the entire skin was nearly three times larger than the amount transferred to pH 7.4 receptor fluid in vitro local percutaneous injection studies. Further in vivo testing in DBA/1 mice utilizing a CIA paradigm found that the thickness of a mouse's toes fell to roughly 65 percent of its initial level after 27 days of local percutaneous MTX-mSiO2@PDA injection. It was shown that the toe thickness variation of mice administered with MTX-

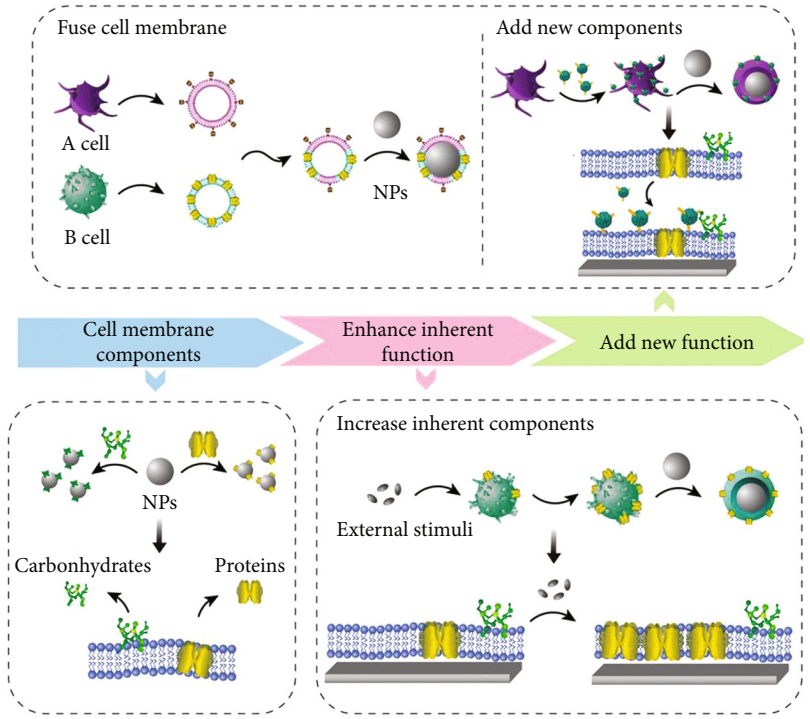

Figure 6: Role of the cell membrane to encapsulate nanoparticulate systems. Reproduced with permission from [78].

mSiO2@PDA through local percutaneous injection was substantially lower than that of animals given MTX directly [72].

4. Bionic Nanomaterials

Bionics is the study of biologically inspired engineering-based materials and their applications [73]. The application of bionics in nano drug delivery systems has revolutionized the field of biomaterials. Despite successful PEGylation and phospholipid modification, synthetic nanoparticulate systems that persist in living animals quickly elicit an immunological response, followed by fast immune system eradication. Thus, the application of bionics for the bio interfacing strategy to enable prolonged circulation time has gained much importance. Cell membrane-coated and exosomes-encapsulated nanoparticulate systems have found a prominent place in novel drug delivery systems.

4.1. Cell Membrane-Based Nanoparticulate Systems. The nanoparticulate systems have grown in popularity in recent years, in part due to the similarity they have with real biological systems. An endogenous cell membrane (e.g., macrophage) is used as a functional material on the surface of the nanoparticulate systems to minimize immunogenicity and extend blood circulation duration [74]. These systems certainly inherit the antigenic surface and associated membrane functions, such as chemotaxis to inflamed regions and cytokine neutralization, from their source cells. Macrophages and neutrophils are important innate immune cells in the human body. These cells are involved in the body's inflammatory response. These can cause synovial hyperplasia i.e., the release of a variety of degrading enzymes, cartilage degradation, and the production of inflammatory factors [75]. Immune cells are widely used to synthesize biomimetic nano particulates with anti-inflammatory properties. Biohybrid delivery systems can be constructed using a range of natural cells, including red blood cells, platelets, immune cells, malignant cells, and even *E. coli*, as the membrane source [76]. As a result, immune cells are frequently employed to synthesize biomimetic nanoparticulate systems with anti-inflammation characteristics. Recently, a variety of natural cells, including red blood cells, platelets, immunological cells, malignant cells, and even *E. coli*, have been produced [77]. The nanoparticulate systems described above have also been reported with cell membrane coating to be utilized as biomaterials. Figure 6 represents the application of cell membranes to encapsulate the nanoparticles.

Macrophage cell membranes based on porous silicon nanoparticulate systems (Psi) have been described as composite platforms for the treatment of RA by Fontana et al. Macrophages (KG-1) were employed as model cells for the vesicles' membrane cytoplasmic membrane. The PSi@KG-1 nanoparticulate system did not activate the immune system in KG-1 macrophages, and covering UnTHCPSi particles with cell membranes decreased their immunostimulatory activity [79]. Similarly, nanoparticles coated with macrophage-derived microvesicles have been shown to target RA. The monocytes' intrinsic ability to target inflammation motivated the development of macrophage-derived microvesicle-coated nanoparticulate systems (MMV-coated nanoparticulate systems, MNP) for the treatment of RA. The MMV was generated through the application of a novel strategy. It was found that the application of cytochalasin B (CB)

increased MMV secretion by loosening the macrophages' cytoskeleton-to-membrane link. The MMV proteome profile was examined using iTRAQ (isobaric tags for relative and absolute quantitation). This suggests that MMV has similar bioactivity to RA-targeting macrophages, based on its membrane proteins. Microparticles were examined both in vitro and in vivo after being coated with MMV and poly (lactic-co-glycolic acid) (PLGA) nanoparticulate systems. In vitro, MNP bound to inflamed HUVECs much more strongly than the red blood cell membrane-coated nanoparticulate systems (RNP). In a CIA mouse model, MNP showed a much greater ability to target compared to bare NP and RNP. In a proteomic investigation, Mac-1 and CD44 were found to have a significant role in the MNP's unique capacity to target. T-RNP-encapsulated Tacrolimus (a model medicine) greatly slowed the progression of the disease in mice. As a potential and plentiful source of macrophage-mimicking material, MMV has been demonstrated in this study to be an effective biomimetic vehicle for RA targeting and treatment [80]. A platelet membrane is also applied to the nanoparticles to treat RA with them. For the treatment of RA, platelet-mimetic nanoparticulate systems (PNPs) were produced that mimic the structure of platelets. Poly(lactic-co-glycolic acid) nanoparticulate systems (PNPs) were coated with a whole platelet membrane by platelet receptor-mediated adhesion, resulting in PNPs having a wide range of functional receptors. The platelet membrane covering the nanoparticulate systems made them more stable and better suited for passive targeting. Using P-selectin and GVPI recognition, the authors were able to increase PNP binding to inflamed endothelium in vitro and accumulation in joints of a CIA animal model of RA. It was demonstrated that PNPs might have targeted RA tissues similar to natural platelets via several routes. As an added benefit, PNPs were implanted with the model drug FK506, which was then administered to patients with RA [81]. According to a study by Zhang et al., nanoparticulate systems coated with a neutrophil membrane were found to be effective in reducing joint damage and inflammation in patients with RA. Nanoparticulate systems are covered with neutrophil membranes by fusing the membranes to polymeric cores. The antigenic exterior and related membrane activities of the parent cells were carried over into these nanoparticulate systems, making them ideal decoys for biological agents that target neutrophils. Proinflammatory cytokines were neutralized, synovial inflammation was reduced, and the nanoparticulate systems penetrated deep into the cartilage matrix to give significant chondroprotection against joint damage. Human transgenic mice were used to study the efficiency of neutrophil membrane-coated nanoparticulate systems in treating arthritis, which was shown to lessen joint damage and the severity of arthritis in mice produced by collagen [82].

4.2. Exosomes Encapsulated Nanoparticulate Systems. Exosomes are small intracellular membrane-based vesicles of varying compositions that participate in a variety of biological and pathological processes. Exosomes have significant advantages over other nanoparticulate drug delivery technologies such as liposomes and polymeric nanoparticulate systems in that they are nonimmunogenic due to their similar composition to the body's cells [83, 84]. Glucocorticoids (GCs) have a powerful antirheumatoid effect. However, their clinical applicability is limited due to nonspecific distribution after systemic administration, as well as significant adverse responses after long-term treatment. Exosomes are newly applied for the treatment of RA and much less research work is done yet.

Yan et al. reported exosome-derived biomimetic nanoparticulate systems targeted to inflamed joints for improved RA treatment. Glucocorticoids (GCs) are highly effective in the treatment of RA (RA). However, clinical applicability is constrained by their nonspecific distribution following systemic administration and the possibility of major adverse effects with long-term administration. To improve treatment and minimize side effects, the authors developed a biomimetic exosome (Exo) encapsulating dexamethasone sodium phosphate (Dex) nanoparticulate systems (Exo/Dex), the surface of which was modified with a folic acid (FA)-polyethylene glycol- (PEG-) cholesterol (Chol) compound to achieve an FPC-Exo/Dex active targeting drug delivery system. By inhibiting pro-inflammatory cytokines and enhancing anti-inflammatory cytokines, this approach demonstrated increased endocytosis and an effective anti-inflammatory impact against RAW264.7 cells in vitro. Further, biodistribution studies revealed that FPC-Exo/Dex fluorescence intensity was greater than that of other Dex formulations in joints, implying that it accumulates more readily at inflammatory sites. FPC-Exo/Dex preserved the bone and cartilage of CIA mice better and dramatically reduced inflammatory joints in an in vivo biodistribution trial. Following that, in vivo safety evaluations revealed that this biomimetic drug delivery system exhibited minimal hepatotoxicity and an acceptable level of biocompatibility [29].

5. Conclusions and Future Perspective

RA is an autoimmune musculoskeletal condition that has resulted in significant disability in individuals and has a global influence on people's life. Thus, efficient treatment of RA is critical for relieving patients' discomfort and increasing the cure rate. Nanotechnology has been applied for RA treatment. Nanoparticulate systems have significantly improved the targeted drug delivery and enhanced in vitro and in vivo effects of drugs with reduced side effects has been achieved successfully. Although nanotechnology is in its infancy, it has the potential to improve disease diagnoses, treatment, and research. The commercial and service industries' performance validates the idea that nanotechnology would someday play a substantial role in clinical practice. Nanotechnology can dramatically lower the cost of many existing therapies and enable a variety of creative applications and reduce the negative effects. Nanotechnology enables more precise treatment techniques, which may result in more effective and durable implants, lower infection rates, and enhanced bone and tendon healing. The theoretical benefits of nanomedicine are beginning to be realized,

particularly in the realm of immune disorders as well, because of massive fundamental scientific research efforts. However, additional research is necessary to fully understand the safety and usefulness of this innovative technology.

As the advances in medical understanding and technology could lead to new treatment options in the future, there are certain limitations as well. Even though NPS has demonstrated numerous advantages in drug delivery, some issues must be addressed before clinical application may proceed. As the liposomes have been utilized in clinical for drug delivery, most drug toxicities have been reduced when they are coated with liposomes; however, it is not the optimal vehicle for water-soluble medicines. As for metal carrier, many are not stable, which limit their application, e.g., zinc oxide. Similarly, CNT is a potential vehicle with outstanding biocompatibility, but it must be improved in its capacity to target specific cells. Therefore, reducing biological toxicity and maintaining their targeting and bioimaging ability are the future directions in drug delivery. A better understanding of anti-inflammatory disorders and focused usage of nanoparticulate systems for diverse diseases would significantly increase treatment effects and lessen the adverse effects.

Ethical Approval

This study does not involve any animals or humans studies.

Consent

All authors approved the final version of the manuscript.

Conflicts of Interest

All the authors declare that they have no financial or any other competing interests.

Authors' Contributions

Wenqing Liang, Hengguo Long, and Jiayi Zhao prepared the draft and wrote the manuscript. Yijun Yu and Zunyong Liu helped in preparing the figures. Wenyi Ming and Hongming Lin refined and arranged the contents of the manuscript. All authors approved the final manuscript. Wenqing Liang and Yijun Yu contributed equally to this work.

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