Advancement in the treatment of Rheumatoid Arthritis using Nanoparticle based Drug Delivery

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***Abstract*- Nanotechnology has emerged as a viable tool for investigating new approaches to treating complex illnesses and detecting the development of numerous disease states. The fundamental goal of medication delivery is to use drugs only where they are needed, with as minimal side effects and off-target effects as feasible. Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes gradual bone and cartilage loss, resulting in acute disability, lower life expectancy, and higher mortality rates. Recent advances in treatment have greatly slowed disease progression and improved the lives of many RA patients. Some patients, on the other hand, achieve or maintain remission from their condition without needing to continue immunosuppressive medication. Furthermore, many patients may not react to existing medications or develop resistance to them. As a result, new drug alternatives for RA treatment are still required. Unlike traditional pharmaceuticals, Nano-carriers are designed to carry drugs specifically to the site of joint inflammation, avoiding systemic and unpleasant side effects. This article provides an overview of current nanotechnology-based treatments for rheumatoid arthritis as well as how the Nano-therapeutic regimen could be improved in the future.**

Keywords: **Rheumatoid Arthritis, Nanomedicine, Biomimetic Nano-carriers, Limitations.**

INTRODUCTION

Rheumatoid arthritis (RA) is long term autoimmune disease that causes significant synovial joint inflammation as well as osteocyte and cartilage destruction. This causes long-term impairment, an inability to interact effectively in social life and daily employment, and an increase in death rates, all of which have a significant impact on the patient's quality of life (1). RA is a group of joint diseases characterized by chronic joint inflammation of the hands and feet's smaller joints, such as the wrists, fingers, and toes (2). Despite significant advances in understanding and experience in RA treatment in recent years, effective RA therapy remains a challenge (3). The primary goals of pharmacological therapy are currently to relieve RA symptoms and reduce disease activity. Certolizumab- pegol encapsulated in nano-carriers with PEGylation shortens the time required to reach half of its concentration to fourteen days and show results in promising RA patients. (4)

Rheumatoid Arthritis pharmacological therapy causes a number of complications. Prolonged use of DMARDs, NSAIDs (non-steroidal anti-inflammatory drugs), and glucocorticoids has been linked to adverse effects on the gastrointestinal tract, hepatic, cardiac, and renal function. While treating RA, it is necessary to overcome the limitations of these therapeutic agents. (5,6,7). Recently, many nanoparticles have been found capable of delivering drugs for rheumatoid arthritis by influencing immune cells such as macrophages in inflamed joints (8,9). This method enhances drug solubility and allows more drug to dissolve. Targeted drug delivery systems are pharmaceuticals constructs that help achieve specific drug delivery or bioactive molecules within cells or tissues that express tissue-specific molecular markers that distinguish them from healthy cells tissues in the body (10, 11). Better drug delivery strategies and effective drugs are bioavailable at the site of interest (12). Target site concentrations should be within the therapeutic range. The therapeutic range is the range between drug concentrations (minimum effective) and Dangerous Concentration (13). The medical application of nanoparticles and the spread of nano-medicine are progressing rapidly. It has the ability for specific targeting and effective delivery of drug. It addresses the limitations of conventional treatment, which is confirmed by a number of preclinical and clinical studies drug dose to a certain point, side effects decrease and treatment results improves (14). Cell-specific and regulated transport of small molecules Macromolecules in therapy helps to establish the stable interactions with ligands, changes in size and shape, the ability to combine hydrophilic and hydrophobic materials, and increased carrier capacity (15). Nano-systems enable site-specific work targeted drug delivery while reducing drug use, reduces risk of off-target side effects. Long-term use of these systems (NSAIDS and GCs) may be approved in high-risk individuals. Inhibitors of signaling pathways Janus kinase (JAK), which regulates inflammation such as the spleen tyrosine kinase and activated B-cell nuclear factor k-light chain booster was recently added to the pool of targeted drug therapy. (16) . Anti-rheumatoid effect of nanoparticles in the treatment of rheumatoid arthritis and schemes for modulating the proinflammatory system and an overview of some clinically relevant findings the application will be discussed in this review article.

2.Limitations of Conventional Rheumatoid Arthritis Treatment and recent role of Nanoparticle based drug delivery system

Major drawbacks of conventional drug administration for rheumatoid arthritis are poor patient adherence, short half-life, poor bioavailability and poor solubility these all can be resolve by seeking new dosing approaches.(17) Microparticles,nanoparticles,nanodispersions,nanocapsules,nanoemulsions,nanosuspensions and other new delivery modes approach to rheumatoid arthritis treatment enhances drug efficacy through drug effects the drug is transported to its destination at a higher concentration. As shown in the Fig.2, As Nano-medicine is growing and has been used in the past 10-15 years to treat rheumatoid arthritis.

Gradually, several other nanomedicine such as MTX combine with nano emulsion were reported as potential candidates for RA treatment (18),Chitosan loaded with siRNA combined with Nano-emulsion (19), curcumin loaded Carboxyl methyl cellulose acetate with nanoparticles (CMCAB), (20) exosomes as biomimetic particles, (21) stimulus-responsive liposomes, 34 carbon nanotubes loaded with MTX and siRNA, (22)and mesoporous silica nanoparticles encapsulating dexamethasone (23) to deliver conventional drugs.

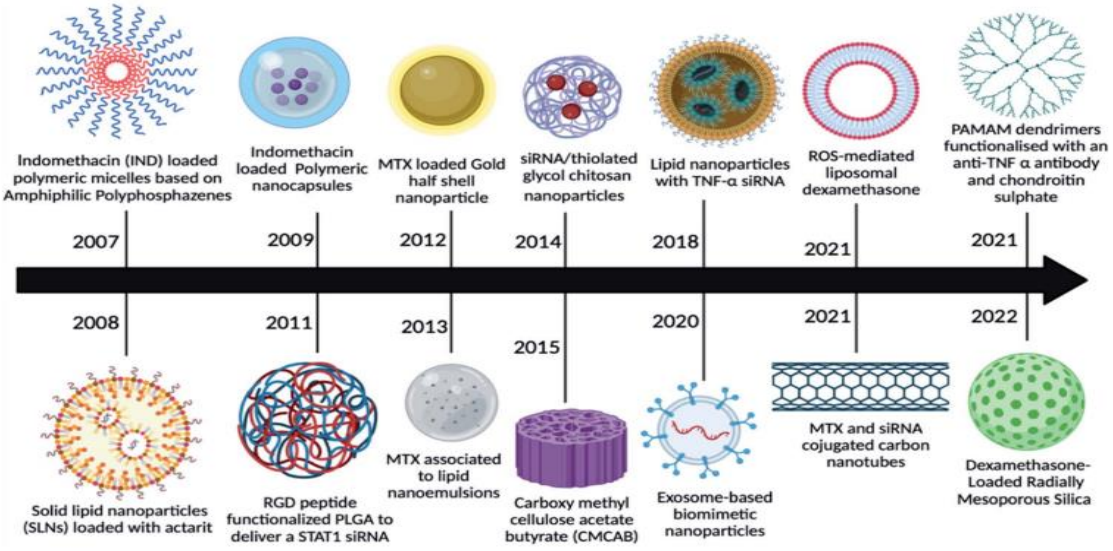

Fig. 2 Various nanoparticles used in the last decade for enhanced drug delivery

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3. Transport problems faced by Nano-medicines

Regardless of the benefits that nanoparticles bring, certain types of obstacles faced by drug during drug delivery systems and following are listed below (fig..3) (24)

(a) Nanoparticles that failed to target are identified by the mononuclear phagocyte system available in blood circulation, bone marrow, organs such as the spleen,lung and liver.(25) (b).Due to the hydrophobicity of the nanoparticles, Possibility of high adsorption of blood components onto the nanoparticle shell. (c) Extended circulation time of nanoparticles are a pre-requisite for in vivo injection until they arrive with respect to scope of targets and (d) drug targeting special cell placement may hinder permeability enhancement, the retention effect (EPR) reduces the effectiveness of drug internalization. protein corona, elimination by mononuclear cells phagocytic system (MPS), fluid dynamics, endothelial surface blood vessel, extracellular matrix, cell membrane, lysosomal degradation and efflux pumps are all biological in nature hurdles to overcome (26,27,28). To overcome the delivery obstacles that require manipulating nanoparticles functionalization by molecular targeting. As shown in the figure3.A broad category of transport processes includes transportation within different compartments such as between the cytoplasm and separate

compartments. There are various biological barriers such as cell membrane, nuclear membrane and endosomal membrane serious obstacles to drug delivery. (1) Nanoparticles accumulate molecules on surfaces when in contact with biological material a liquid that develops a 'protein corona' that can affect the implementation of future treatment. By superimposing this-biomolecules, a specific identity of a nanoparticle that determines state the nanoparticle. It is recognized by and interacts with cells and contributes to their internalization and distribution. (2) Activated macrophages of the reticuloendothelial system aids in circulatory clearance pumps old blood cells and blood-borne substances into the RES organs. The main limitations of nano-therapeutic formulations are rapid phagocytosis and RES-based clearance, which decreases particles bioavailability.

(3) Nanoparticles are exposed to many environments complex fluid forces in the bloodstream as it passes through blood bends and branches, healthy or unhealthy blood vessels(29). (4) Extracellular matrix provides structural integrity to the tissue and contains high levels of collagen, provides stiffness and acts as a barrier for transport nanoparticles. (5) Once the particles have been removed from the blood vessels that need to connect to the site of infection as it damages cell membranes and causes particle endocytosis.

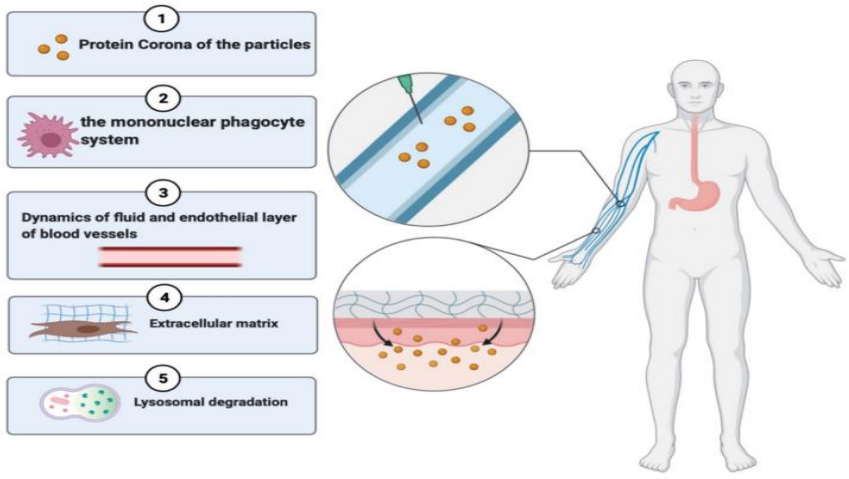

Fig. 3 Biological barriers faced by nanomedicines.

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4. Approaches to Combat Inflammation Synovial macrophages.

According to reported literature, this mechanism is tailored nanoparticles are said to carry drugs in the treatment of rheumatoid arthritis still mostly unknown (30).

Macrophages more common in inflamed joints, nano-carriers it is successfully taken up and phagocytosed by macrophages without surface modification. Therefore, it targets immune cells Macrophages using a nano-carrier system was one possibility. Parenteral delivery of nanoparticles system has been used successfully to combat macrophages. (31) These methods demonstrate that macrophages plays an important role in the progression of RA (through the production of pro-inflammatory cytokines) and nanoparticles may play an important role. It is taken up by macrophages via leaky and inflamed capillaries arthritis, and the phenomenon is known as increased permeability and retention (EPR). However, when injected into the whole body, nanoparticles are rapidly cleared by macrophages in the reticuloendothelial system "RES", reducing the number of drugs units available at sites of joints affected by rheumatoid arthritis (32,33). This modifies the nanoparticles in a way that retards RES interactions, target different organ systems, immune cells, or other systems specific pathways are constantly being researched.

4.1. Nanoparticles that passively fight macrophages

Increased vascular permeability and macrophage infiltration are two pathological features of rheumatoid arthritis, both of which provide a favorable context and potential target cells for nano-medicine delivery system. ELVIS effect (extravasation via leaky vasculature and inflammatory cell-mediated sequestration) nano-carriers can be preferentially concentrated, drug release in synovial tissue, comparable increased penetration and retention have been reported in treatment of tumors (34). Due to the large particle size of nano-drugs with size less than 200 nm and less than 10 nm, it can be removed by the Reticuloendothelial system. Therefore, the particle size is an important factor to consider when developing passive targeting techniques. (35).

4.1.1. Modification of nanoparticles with chitosan.

Chitosan is a natural-based amino-loaded polysaccharide chemicals widely used in biomedicine because it is biocompatible and bioactive. Non-toxic and biodegradable. investigation of the amphipathic properties of chitosan by-products has recently gained interest (36). Amphiphilic chitosan co-polymers such as glycol chitosan arises from the hydrophobic modification of chitosan can be tumbling in aqueous suspension. (37).

4.1.2. Biomimetic Nano-carriers in the Present Situation

Studies have shown that PEGylated polymer nanoparticles are potent an immune response that increases blood clearance. (38). The biomimetic drug delivery method based on natural nanoparticles has been developed using nanoparticles as camouflage self-elements reduce the ability to elicit strong responses of immune response, evasion of immune defenses, prolonged circulation period, enhanced aggregation at target sites .It enhances therapeutic efficacy and reduces toxicity and unwanted effects(39). L-aspartic acid is an essential amino acid an interesting feature for the functionalization of iron oxide nanoparticles. It is also affordable, biocompatible and also frequently used drugs and chemical synthesis, and of medical significance application. This work sets the framework for the efficient synthesis of: -Aspartic acid (AA) iron oxide nanoparticles (IONP) for the future. In vitro and in vivo studies of AAs-coated IONPs with drugs, drug candidates, and molecular probes. High zeta potential, hydro-dynamic size in addition to the low poly-dispersity index of these nanoparticles, Non-toxic effects greatly increase the potential for use .Those in-vitro and in vivo biomedical areas such as cells labeling, dosing and diagnostic delivery therapy(40).

5.Nanoparticles for actively targeting macrophages

Active medication represents a special form of communication between therapeutic agents and nano-carriers containing cells of the target information is often conveyed through specific ligand-receptor communication. The ligand-receptor interaction looks like this , if these components are in direct contact with each other.(41,42) .Carrier systems that deliver drugs, use surface modification to reach the target position that functionalizes on the surface and are not biologically taken up by the RES. Specific interaction of ligands on the outer side of nanoparticle and particular receptors present on target cells made intake of receptor- nanoparticle carrier complexes by receptor-based endocytosis and vesicle-based trafficking endosome.(43) . Active targeting approaches have been

established to overcome limitations and enhance nano-carrier accumulation in inflamed joints. The most important process of active targeting is achieved through surface modification, research on nano-pharmaceuticals using target ligand molecules. Rheumatoid arthritis-affected cells show increased membrane receptors or the outer surface protein level that enhances it appropriate internalization of nano-carriers via receptors entanglements that help nanoparticles penetrate inside cell. Nano-carriers loaded with active ingredients may enter the patient's body cells through such ligand- and receptor-mediated interactions. After that reaching the target tissue area, the nano-carriers causes cytosolic effects after or at the level of cellular uptake cell membrane (44). Release of drug from vehicle can occur on the cell surface, in extracellular matrix, or it is degraded by lytic and digestive enzymes present in lysosomal organelles. This ensures that drug can be delivered into cytosol with no attachment of colloidal carrier unit. Different targets are associated with key factors involved in synovial inflammation and it is being studied for the treatment of rheumatoid arthritis. One such target is folic acid (folate) receptor highly expressed in macrophages residing in synovium of joints affected by rheumatoid arthritis (45). The chemical complexes of folate to converts folate into various molecules via carboxyl groups permits the formation of internally absorbed folate conjugated receptor-assisted endocytosis. (46)

Liposomes actively target synovial macrophages.

Liposomes are composed of spherical nano-carriers bilayer membrane with outer surface made of phospholipids and the polar nucleus (47) Liposomes for treating rheumatoid arthritis is prevalent. PEG is a hydrophilic polymer that allows this recognition and uptake of liposomes by RES is reduced, resulting in prolongs liposomal circulation in the body (48).

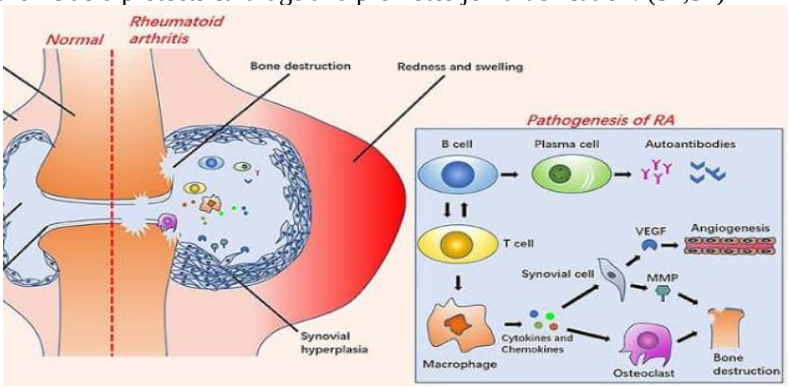
Therapeutic effect of dexamethasone in rheumatoid arthritis, a stealth polymer Liposomes can be used as nano-carriers. Liposomes are collected in inflamed joints, reduced inflammation and joint enlargement in arthritic animal. It shows that stealth polymer liposomes is used as modern medication deliver technology for different medicinal purposes.

4.2.2. Nano carrier based on Polymer used to actively combat synovial macrophages.

Polymer nano-carriers are biocompatible, can be targeted to specific tissues, and are widely used drug delivery. For rheumatoid arthritis, the pharmacological agents can binds to the surface or load in polymeric nanoparticles and deliver to the specific site for producing the action. The most common method is surface modification of nanoparticles with PEG (49). With this approach, it is possible nanodrugs are more stable, but sometimes they are less stable. It can decrease immunogenicity and excretion from the body. Polycaprolactone-polyethylene glycol-polycaprolactone (PCLPEG) micelles are intended for low dose delivery of Dexamethasone is used to treat arthritis. Micelle survived in the whole-body for a long period and aggregates in areas of inflamed joints. The delivery of Dexamethasone via micelles effectively reduce swelling, bone destruction, expression of inflammatory factors in blood and joints. (50)

4.2.3. Metal nanoparticles used for active targeting Synovial macrophages.

Metal nanoparticles can be used by modifying with various functional groups and used in biomedical applications. Currently, Au, Fe, and Ce nanoparticles are widely used to treat rheumatoid arthritis. RGD-bound Au half-shell Nano-carriers containing methotrexate synthesized for special chemical photo-thermal treatments and These peptides can target the inflammation site. Au half-shells are formed under NIR radiation (near-infrared) produces heat to increase the rate of drug release while simultaneously transferring heat and drug to inflamed joints. The NIR in combination with low-dose nano-carriers methotrexate shows collagen-induced improvement in arthritic mice than methotrexate alone. Complex of hyaluronate-gold nanoparticles/tocilizumab has been investigated in collagen induced arthritic mice. Tioconazole is an IL-6 receptor inhibitor that can disrupt IL-6 function in the blood progression of RA and hyaluronic acid protects cartilage and promotes joint lubrication. (51,52)



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CONCLUSION:

Rheumatoid arthritis is a highly variable disease with unpredictable response to treatment. Early treatment has shown reduction in structural damage and improves the incapacity for a long-term. Conventional treatments such as NSAIDs can reduce the severity of rheumatoid arthritis, but they can lead to persistent remissions and can have side effects, so they cannot be used long-term. Targeted therapy is generally considered from a molecular point of view, it can target specific cell populations by changing the way drugs are transported in the body. More over designing nanocarriers that represent priming strategies.It is a promising approach for improving drug delivery. Despite the fact that targeted drugs are therapeutically beneficial for RA, different target carriers have many drawbacks. It also includes a poor security profile. Toxicity can occur if the carrier spreads to non-target tissues. Surface PEGylation of Nano-drugs may help to prevent Nano-drug detection RES, thereby prolonging its bioavailability in the bloodstream,increase aggregation at sites of inflammation .This facilitates the tissue penetration and uptake of Nano-carriers.

Majority of processes are used to make nanoparticles for treatment of rheumatoid arthritis is complex and associated with high clinical costs. New research could address these deficiencies in RA medication delivery system and trying to overcome them. This review study focused on advances in Nano-carrier research in rheumatoid arthritis treatment, shortcomings of current drugs versus advantages of Nano-medicine and methods of Nanoparticles will give us better knowledge for the future.

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